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Review article

Technical aspects of neurostimulation: Focus on equipment, electric field modeling, and stimulation protocols

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ABSTRACT

Neuromodulation is a field of science, medicine, and bioengineering that encompasses implantable and non-implantable technologies for the purpose of improving quality of life and functioning of humans. Brain neuromodulation involves different neurostimulation techniques: transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), vagus nerve stimulation (VNS), and deep brain stimulation (DBS), which are being used both to study their effects on cognitive brain functions and to treat neuropsychiatric disorders. The mechanisms of action of neurostimulation remain incompletely understood. Insight into the technical basis of neurostimulation might be a first step towards a more profound understanding of these mechanisms, which might lead to improved clinical outcome and therapeutic potential. This review provides an overview of the technical basis of neurostimulation focusing on the equipment, the present understanding of induced electric fields, and the stimulation protocols. The review is written from a technical perspective aimed at supporting the use of neurostimulation in clinical practice.

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1. Introduction

Neuromodulation is defined as a field of science, medicine, and bioengineering that encompasses implantable and non-implantable technologies, electrical or chemical, for the purpose of improving quality of life and functioning of humans, by the international neuromodulation society (Krames et al., 2009). Brain neuromodulation involves different neurostimulation techniques that can activate parts of the nervous system. Neurostimulation can be applied invasively by means of deep brain stimulation (DBS) or non-invasively by transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS). Vagus nerve stimulation (VNS) allows both invasive and non-invasive stimulation. Stimulation techniques can be used as therapeutic tool in psychiatry and neurology and are also applied in cognitive neuroscience to study the functioning of the brain.

Various studies have demonstrated successful clinical outcomes of neurostimulation in multiple disorders. Relief of tremor in patients with Parkinson's disease is the most common and long-standing indication for DBS. However, not all patients respond optimally to a neurostimulation therapy. In clinical practice, neither the type of neurostimulation that is most suitable for an individual patient, nor the optimal stimulation parameters, such as the frequency, intensity, pulse shape, and electrode combinations are evidence-based. Also, the optimal target within the nervous system for various disorders remains to be identified.

The clinical application of neurostimulation has preceded the elucidation of the different mechanisms of action. Improved understanding of these mechanisms is crucial to ameliorate the outcome of neurostimulation therapies in clinical practice and expand their therapeutic potential. Understanding the technical basis of neurostimulation is a prerequisite to elucidate the effects of neurostimulation on neuronal tissue.

In this review we focus on the technical basis of the currently available stimulation techniques in clinical practice: TMS, tDCS, VNS, and DBS. The stimulation equipment, the current knowledge of electric field modeling, and the effects of stimulation protocols will be described. The last part of the review will elaborate on alternative stimulation methods, that are not standardized in clinical practice or that are under development and might be used in the future. Finally, future perspectives will be described.

The review is written from a technical perspective and aimed to support the use of neurostimulation in clinical practice. The review can be read to retrieve a more global overview of neurostimulation techniques but more importantly, it will give clinicians ideas what protocols can be used in certain cases and how the stimulation parameters can be chosen. Moreover, an increased insight in the technical background will increase the insight in the interpretation of the results of different neurostimulation studies.

2. Non-invasive neurostimulation

In this section, TMS and tDCS are extensively described whereas external trigeminal nerve stimulation (eTNS) and transcutaneous vagus nerve stimulation (tVNS) will be described briefly, later in this review. The stimulation coil used for TMS and the electrodes used for tDCS, eTNS, or tVNS are located outside the brain on the patient's head. This means that neuronal tissue is reached via several additional tissue layers. Fig. 1 gives an overview of the non-invasive neurostimulation techniques.

2.1. Transcranial magnetic stimulation (TMS)

TMS is a non-invasive stimulation method based on magnetic induction. A coil is placed over the head to locally apply a rapidly fluctuating magnetic field that generates electric current in the underlying brain tissue (Hallett, 2000; Kobayashi and Pascual-leone, 2003). Since the currents fall off rapidly with the distance to the magnetic stimulator coil, stimulation seems to be restricted to the cortex (Barker, 1999, 1991).

TMS can be applied as single pulse stimulation (spTMS) to depolarize neurons and evoke measurable effects, such as motor evoked potentials (MEPs) after stimulating the motor cortex or phosphenes (visual sensations) after stimulating the visual cortex. Paired pulse

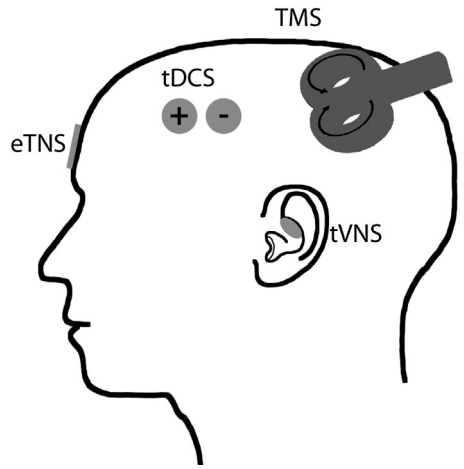

Fig 1. Non-invasive brain stimulation.
Overview of non-invasive stimulation techniques: TMS, tDCS, tVNS and eTNS.

Table 1
Different paired pulse TMS protocols.

Protocol	What is examined?	Intensity	Inhibition ISI	Facilitation ISI
Two equal suprathreshold stimuli at long ISI (10–250 ms)	Paired pulse facilitation and inhibition which are primarily due to intracortical facilitatory and inhibitory mechanisms operating at long ISI	120–160% RMT	10–30 ms	50–200 ms
Subthreshold CS and suprathreshold TS at short ISI (1–20 ms)	Excitability of separate inhibitory and excitatory neural circuits of the motor cortex	CS 80% RMT, TS should be adjusted to produce reasonable MEP	1–5 ms	8–25 ms
Suprathreshold CS and subthreshold TS at very short ISI (0.5–6 ms)	Excitability of motor cortical circuits	CS should produce MEP of about 1 mV, TS should be 90% RMT		1.1–1.5 ms, 2.3–2.9 ms, 4.1–4.4 ms

(ISI = inter stimulus interval, CS = conditioning stimulus, TS = test stimulus).

stimulation (ppTMS), a combination of a so-called conditioning stimulus (CS) and test stimulus (TS), with varying inter stimulus intervals to the same or different brain regions, is mainly used to assess cortical excitability. Table 1 provides an overview of the different ppTMS protocols (Pascual-Leone et al., 2002).

Repetitive TMS (rTMS) consists of trains of stimuli with a certain frequency and intensity. In contrast to spTMS and ppTMS, the effects of rTMS exceed the duration of the stimulation. rTMS might therefore be useful as a therapeutic tool for a broad spectrum of neurological and psychiatric disorders (Lefaucheur et al., 2014). Repetitive stimulation is nowadays approved by the Food and Drug Administration (FDA) for the treatment of migraine and depression.

The mechanism of action by which TMS deploys a long-lasting therapeutic effect is thought to originate from changes in synaptic plasticity. Long-term potentiation (LTP) is a long-lasting increase in synaptic strength whereas long-term depression (LTD) means a long-lasting decrease. Post-synaptic *N*-methyl-D-aspartate (NMDA) plays an important role in LTP and LTD. TMS has also shown to have effect on neurotransmitter γ-aminobutyric acid (GABA), as show in a magnetic resonance spectroscopy study by Stagg et al. (2009). Even though it is strongly suggested that synaptic plasticity is involved in the therapeutic effect, there has not been a clear direct link up to date (Hoogendam et al., 2010).

In general, TMS is considered to be a safe technique, when it is performed according to the TMS guidelines (Rossi et al., 2012). The most serious concern when applying TMS, is the possible induction of epileptic seizures. Schrader et al. (2004) showed that the crude risk of seizure induction is 0.0–2.8% after spTMS and 0.0–3.6% after ppTMS in epilepsy patients. Bae et al. (2007) showed a crude-risk of 1.4% for epilepsy subjects undergoing rTMS. Important to note is that because of the random occurrence of seizures, no direct causal relation between TMS and seizures was proven (Bae et al., 2007; Krishnan et al., 2015; Oberman et al., 2011; Schrader et al., 2004). The application of TMS in non-epilepsy patients induced seizure in few subjects (see Rossi et al. (2009) for overview of these cases to 2009), of whom some had a pre-existing neurological disorder and in some cases the stimulation protocol was not according to the guidelines (Loo et al., 2008). None of these seizures induced long-term sequelae and they all ended spontaneously. Pre-screening of potential risk-factors is very important.

Even though in general, adverse events related to rTMS were reported to be mild, the exact numbers differ between treatments of various pathologies. Overall, 17.1% of the epilepsy patients included in the review of Bae et al. (2007) reported on adverse events of which headache was most often found (9.6%). In the sham-controlled rTMS studies in depression, reviewed by Loo et al. (2008), approximately 28% of the patients experienced headache and 39% reported about pain or discomfort during stimulation. These numbers were higher compared to sham-stimulation (16% and 15% respectively).

2.1.1. Equipment: TMS coils

TMS equipment consists of two main components: a high-current charge-discharge system and a magnetic stimulation coil. In the charge-discharge system, a capacitor is charged to a high voltage and discharged into the stimulating coil (Walsch and Pascual-Leone, 2003). The TMS stimulation coil is the key component of the equipment since it transfers the magnetic energy to the neuronal tissue and it determines the shape of the induced electric field.

TMS coils are constructed from tightly wound copper wires, which are adequately insulated and housed in plastic covers (Wagner et al., 2007). The induced electric field, and thus the site of stimulation, depends largely on the shape of the TMS coil used. A circular coil induces a non-focal ring-shaped electric field. With a figure-of-eight coil, consisting of a pair of adjacent loops, with the current flowing in opposite directions, a relatively focal electric field is generated at the point where the two circles meet (Deng et al., 2013; Liu and Guan, 2003; Roth et al., 2013). Using figure-of-eight coils, negative stimulation is induced under the twain edges of the coil (Liu and Guan, 2003).

Besides the circular and figure-of-eight coils, also the use of double-cone coils and H-coils, aiming at stimulation of deeper targets in the brain, has been investigated (Fadini et al., 2009; Roth et al., 2014, 2010, 2007, 2002). In general it was concluded that both double-cone coils and H-coils indeed can effectively stimulate deeper targets, with the H-coil being most efficient (Roth et al., 2002). Deeper stimulation comes at the cost of a wider electric field distribution, so less focality. Deng et al. (2013) investigated the depth-focality trade-off in fifty TMS coils with different geometries. In all coils, a trade-off between depth and focality of the stimulation was shown. Rotem et al. (2014) introduced a coil that superimposes the electric fields from two figure-of-eight coils, orthogonal to each other, that operate with relative phase shift in time, to overcome the directional sensitivity of TMS (see Section 2.1.2). This coil may be useful to target brain regions in which the optimal coil orientation cannot be determined.

Since only $1/10^8$ of the magnetic energy in the coil is efficiently transmitted to the nervous tissue (Ravazzani et al., 2002), the power requirement of TMS is high. High frequency TMS protocols with conventional coils can quickly result in coil heating. Coil heating depends on the geometry of the TMS coil, the current and the pulse width (Ruohonen et al., 1998, 1997). Cooling systems for TMS coils have been developed in which moving air or liquid is transferred along the coil to prevent heating. Most coils contain a heat sensor that automatically blocks the stimulation coil when the temperature exceeds approximately 41 °C (Wassermann et al., 2008). The optimal coil design depends greatly on the application and there is no globally optimal solution (Ravazzani et al., 2002).

2.1.2. Electric field modeling

As stated before in this review, the mechanisms of action of neurostimulation techniques are not yet fully understood. Since it remains impossible to visualize the current distribution in the brain in situ, multiple studies have been performed to model the electric fields induced by stimulation. Firstly, knowledge of the electric field distribution in the brain can provide a link with the induced physiological stimulation effects. Secondly, modeling the fields as a function of different stimulation parameters (see Section 2.1.3) will increase the knowledge about the effect of these parameters. Here, a short introduction on electric field modeling is given, followed by an overview of previous modeling studies. The TMS modeling studies in this review cover three main topics: the importance of incorporating tissue anisotropies in the model; the effect of incorporating coil geometry in the model; and the spatial distribution of the electric field as a function of coil orientation.

The first models that were used to assess the stimulation induced electric fields were simple, spherical head models assuming homogeneity in the brain and isotropic conductivity. Conductivity is a measure of the ability of a material to conduct electric current. Different tissue types in the brain have different conductivity values, and will therefore cause the electric field to propagate differently. So these simple spherical head models needed to be extended into models taking into account the anisotropic and heterogeneous properties of the brain. The head can be segmented into different layers: white matter (WM), gray matter (GM), cerebrospinal fluid (CSF), skull, and scalp, each with its own conductivity value (Fig. 2a–e). Nowadays, also patient-specific models are used incorporating anatomical information derived from magnetic resonance imaging (MRI) data. Mathematically, the electric field resulting from TMS can be described as the sum of two terms: the primary electric field and the secondary electric field. The primary field is a direct result of the coil's rapidly changing current. A secondary field exists because of charge accumulations at surfaces with different electrical conductivities (Salinas et al., 2009). From the numerical side, several methods can be used to solve the mathematical equations for the electric field inside the brain. For most of these methods, the brain is first discretized into small elements. Next, a solution technique is applied such as the finite element method (FEM) (Laakso and Hirata, 2012; Miranda et al., 2003; Opitz et al., 2013, 2011; Pu et al., 2010; Thielscher et al., 2011; Windhoff et al., 2013; Zheng et al., 2005), finite difference method (FDM) (Roth et al., 1991), the boundary element method (BEM) (Salinas et al., 2009) or the impedance method (Tachas and Samaras, 2014; De Geeter et al., 2012, 2011a,b). An example of the discretization can be seen in Fig. 2f and g shows an example of the resulting electric field calculation.

The effect of incorporating specific conductivities within the brain was investigated. On the one hand, Davey et al. (2003) assumed a homogeneous brain since no large differences were found between the calculated electric fields using models with different conductivities versus homogeneous models. On the other hand, Miranda et al. (2003) showed a significantly increased electric field in the outer low conductivity region when using a concentric two layer model, with high and low conductivity. The latter study stated that detailed models provide better insight of the location of possible stimulation sites in the brain.

Conductivity values can be derived for every tissue type. Nowadays, it is possible to derive accurate conductivity values, as a function of position and direction within a tissue type. A geometrically accurate model of an individual head to calculate the electric field, based on high-resolution diffusion tensor imaging (DTI) for conductivity mapping, was used by Opitz et al. (2011) and Thielscher et al. (2011). In DTI, the fact that diffusion of water molecules primarily takes place along the direction of the white matter tracts is used to visualize these tracts. It is assumed that the motion of water molecules is linearly dependent on the ionic movement in membranes (Schmidt and van Rienen, 2012a). This allows the position- and direction-specific conductivities to be derived by solving a linear transformation of the DTI tensor (Tuch et al., 2001, 1999). It was assumed that the gyral folding patterns and the anisotropy of the brain tissue can have a strong effect on the field. Using position- and direction-specific conductivity values, more reliable calculations could be made for the induced electric fields in the GM and WM.

The fact that the patient-specific gyral folding patterns influence the electric field can be linked to the finding that the orientation of the coil has an influence on the primary electric field (Jung et al., 2012; Kaneko et al., 1996; Thielscher et al., 2011). Thielscher et al. (2011) found the highest field strength occurring at the parts of the gyral crowns that are oriented perpendicularly to the induced field. Opitz et al. (2013) showed that rotating the coil has a larger effect on the calculated field compared to tilting the coil. The preferred coil orientation was different among people. This study furthermore focused on the impact of the gyral folding on the induced electric field. An effect of the current direction on the electric field distribution in the GM was found, with higher field strengths when the induced currents were perpendicular to the local gyrus orientation.

Orientation selectivity of TMS was investigated in more detail by Fox et al. (2004). Since most of the times TMS coils are flat and placed tangential to the scalp during stimulation, the resulting current in the brain is also tangential to the scalp. Day et al. (1989) hypothesized that TMS must be exciting the tangentially oriented neural elements at the gyral crown, such as horizontal interneurons or horizontal collaterals of pyramidal track axons. However, since horizontal fibers are isotropic, this cannot explain the preferred orientation for TMS. Mills et al. (1992) also found a clear orientation preference in TMS. In this study, it was speculated that horizontal fibers might have an anatomic orientation preference which tends to lie at right angles to the central sulcus. Laakso et al. (2014) showed the importance of the coil orientation on the electric field, both the strength and the depth of the penetration, when stimulating the hand motor area. The study of Fox et al. (2004) also showed excitation of the sulcal cortical surface, not on the gyral crown, in contrast to the hypothesis of Day et al.

The shape of the TMS coil has a major influence on the electric field distribution. Salinas et al. (2007) incorporated the coil geometry in the model. It was shown that modeling the electric field induced by TMS based on the wire width, height, shape and number of turns of the coil, clearly improved the fit of calculated-to-measured field near the coil body. Later (Salinas et al., 2009), the BEM was used to emphasize the importance of the secondary electric field, and it was shown that the direction of the secondary field was generally opposite to the primary field.

2.1.3. TMS stimulation protocol

A stimulation protocol has several parameters: the stimulation frequency, and its intensity, pulse shape, and duty cycle. Also the stimulation position is of major importance. A schematic overview is provided in Fig. 3. This section elaborates on the different parameters that influence the outcome of TMS. Furthermore, the differences between sp, pp, and rTMS are described, as well as the possibility to extend the TMS protocol by priming.

TMS can be applied according to different protocols: sp, pp, and rTMS. Different TMS protocols, and variations of these protocols, have been compared by Mochizuki et al. (2005), Thomson et al. (2011), Hamada et al. (2007), and Sacco et al. (2009). By comparison of reaction times resulting from ppTMS and theta burst stimulation (TBS) (Huang et al., 2005), Mochizuki et al. (2005) revealed that TBS leads to widespread changes in activity and more complex effects on behavior than pp sequences. Thomson et al. (2011) used near

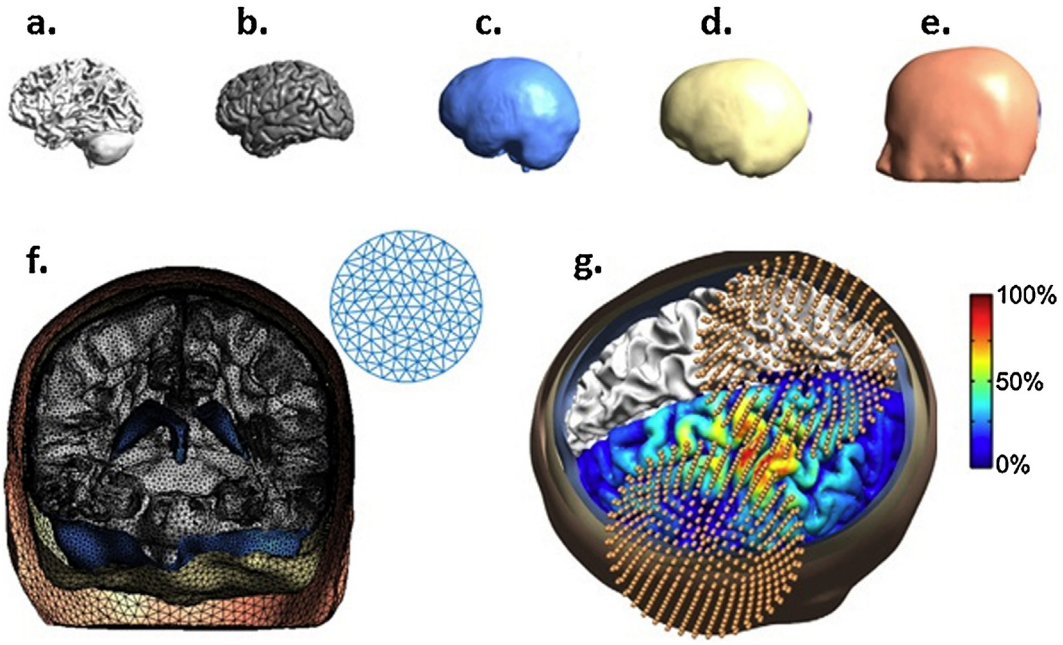

Fig. 2. Electric field modeling.
The head can be segmented into different layers (SimNIBS software, www.simnibs.de): white matter (a), gray matter (b), CSF (c), skull (d) and scalp (e) based on information obtained from MRI. These various tissue types have different properties concerning electric field propagation. By using models, such as for example FEM, BEM, the brain is split into small elements (f). Giving every area specific parameters, the electric field can be determined mathematically. An example is shown in (g) (Opitz et al., 2011; with permission). Here, the yellow dots represent the TMS coil, positioned above the left motor area. The modeled electric field is depicted in color (in the online version), scaled to the maximum.

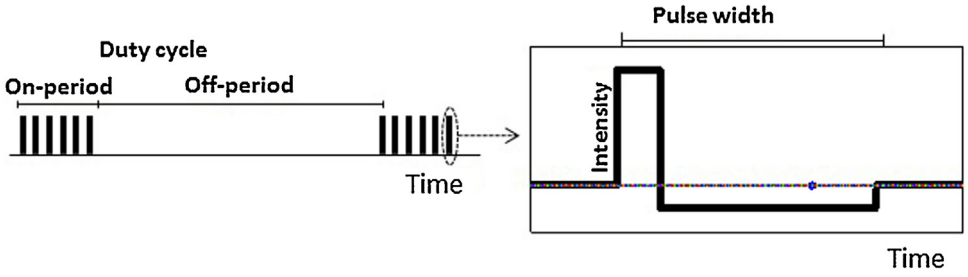

Fig. 3. Stimulation protocol.
Overview of a stimulation protocol with the different stimulation parameters; the duty cycle determined by the on- and off-period, the amplitude and the width of the pulse, and the frequency.

infra-red spectroscopy to compare the hemoglobin concentration after sp- and ppTMS over the left prefrontal cortex. The significant, initial, drop in hemoglobin level was not significantly different in different protocols. However, the pp protocol with inter stimulus interval of 15 ms showed significant shorter time for hemoglobin levels to return back to baseline values. Sewerin et al. (2011) furthermore showed that the efficiency of ppTMS paradigms can be optimized by using patient-specific values of the inter stimulus interval, derived from the response to single pulse stimulation.

Variations of the pp paradigms, triple pulse (Sacco et al., 2009) and quadro pulse stimulation (Hamada et al., 2007), have shown promising for enhancing motor cortical excitability. Triple pulse stimulation showed larger MEP responses than ppTMS (Sacco et al., 2009) and repetitive quadro pulse stimulation led to an even greater enhancement of motor cortical excitability (Hamada et al., 2007), suggesting a summation effect of additional pulses. However, because the inter stimulus intervals of the two studies differ (ms versus s), it cannot be concluded that the addition of a pulse in a pp protocol further enhances cortical excitability.

Stimulation protocols can be extended by priming. Priming is the application of brief pre-treatment stimulation that might increase the effect of the subsequent stimulation. Silvanto and Pascual-Leone (2008) stated that external stimulation interacts with the ongoing cortical excitability state so the rationale of priming is to optimize this state before stimulation. The cortical excitability state at the particular moment of stimulation will have an effect on, or even determine, the response to stimulation. The outcomes of different priming studies are ambiguous. On the one hand, significant improvements of the clinical effects on depression, after priming, were reported by Fitzgerald et al. (2008) and Iyer et al. (2003). On the other hand, 6 Hz priming before low-frequency (1 Hz) rTMS in a tinnitus population did not show clinical improvements (Langguth et al., 2008) neither did priming of an inhibitory continuous TBS (cTBS) protocol lead to significant changes in MEP sizes in healthy subjects (Todd et al., 2009). Priming cTBS protocols with intermittent TBS (iTBS) showed further inhibition of the cTBS protocol (Doeltgen and Ridding, 2011; Todd et al., 2009). The above mentioned priming studies all use a subthreshold intensity (90% rMT), but the number of stimuli differs (600–1200 pulses), and different outcome measures are used. Appropriate priming protocols still have to be determined and might depend on the pathology. 6 Hz priming seems to work to improve rTMS

treatment for depression patients but not for tinnitus and no effect is seen in healthy subjects. To improve and extend the use of priming in clinical practice, more knowledge should be gained about the mechanism of action. To date, this mechanism of priming is believed to be closely related to a phenomenon called metaplasticity: the response of a synapse, the induction of LTP or LTD by for example TMS, depends on the history of the synapse, also sometimes referred to as activity-dependent plasticity (Abraham and Bear, 1996; Todd et al., 2009).

Garry and Thomson (2009) compared the effect of pp paradigms during different excitability states: rest and isometric abduction of the left or right index finger. Effects were shown to depend on the intensity of the TS, but not on the excitability state. Conte et al. (2008) furthermore showed the lack of effect of attention in pp protocols. These findings contradict with the earlier mentioned, general, phenomenon that the outcome of TMS depends on the excitability state. A more refined definition of the excitability state might help to interpret these findings.

Transcranial magnetic stimulators can produce two types of pulses: monophasic and biphasic. Monophasic TMS pulses peak at around 100 μs and decay within approximately 1 ms. Biphasic pulses consist of two phases, together lasting for approximately 300 μs in which the current of the second pulse flows in opposite direction. Biphasic pulses are energy-efficient compared to monophasic pulses, since up to 60% of the energy needed to produce the pulse can be restored in the stimulator, for example for a next pulse (Barker, 1999). Arai et al. (2007, 2005) investigated the differences in after-effects between monophasic and biphasic high-frequency rTMS. The main finding of the latter study was that monophasic subthreshold rTMS has stronger, and longer-lasting (in the order of minutes), after-effects on MEPs than biphasic stimulation. This is probably because monophasic pulses preferentially activate one population of neurons oriented in the same direction, causing summation of the effect. This phenomenon only holds for rTMS. In case of single pulses, biphasic pulses are thought to be more powerful because the higher peak-to-peak amplitude between the two phases of the pulse and the longer duration (Arai et al., 2005). Antal et al. (2002) compared static contrast sensitivities before, during and ten minutes after monophasic and biphasic low frequency (1 Hz) rTMS applied to the occipital cortex at an intensity of the phosphene threshold (PT). Significant loss of contrast was found during, and after 10 min of monophasic stimulation, while biphasic stimulation resulted in no significant effect. The effect of stimulation significantly depended on the current waveform and direction. Niehaus et al. (2000) added that current direction has a higher influence in monophasic stimulation. Delvendahl et al. (2014) furthermore showed a stronger influence of current orientation for monophasic compared to half-sine shaped pulses.

An effective treatment should have long-lasting effects. Thut and Pascual-Leone (2010) reviewed combined TMS-EEG studies to characterize these lasting effects. They suggested that TBS protocols (Huang et al., 2005) show longer after-effects compared to conventional low and high frequency repetitive stimulation protocols (70 min versus 31 and 28 min). Several factors were suggested to extend the duration of the after-effects such as repeating sessions over days. A recent study by Quan et al. (2015) for example, showed a significant improvement of the negative symptoms in schizophrenia patients six weeks after applying rTMS sessions over a two week period. However, the exact relation between the number of stimulation days and the extension of the after-effects in time, is not known.

Stimulation intensity in TMS protocols is usually defined as a percentage of a subject's individual motor threshold (MT). An international committee defined the MT as the minimal stimulation intensity that induces a reliable MEP of minimal amplitude in the targeted muscle (Rossini et al., 2015). Often, MEPs are recorded from the first dorsal interosseous (FDI) or the abductor pollicis brevis (APB), since these muscles are well represented in the motor hand knob and can be easily stimulated. Thresholds can be determined while the muscle is at rest (resting motor threshold, RMT) or when the muscle is contracted (active motor threshold, AMT). The AMT is lower than the RMT. Besides the MT, the PT is often used in protocols investigating visual responses with TMS (Fierro et al., 2005). A study that assessed the variability in peak intensities of the stimulator, showed that after intensity change, the first stimulus induces a higher peak intensity (Reutens et al., 1993). This might slightly influence the determination of the MT.

MTs vary between and also within subjects (Conforto et al., 2004; Thordstein et al., 2013). Danner et al. (2008) showed that this variation can be reduced by using neuronavigation during stimulation, since neuronavigation can guarantee stimulation of a specific position. Julkunen et al. (2012) mentioned that the MT is highly dependent on the distance between the coil and the cortex. The distance between the scalp and the cortex was not found to have a significant influence (Danner et al., 2012). Janssen et al. (2014) confirmed this finding and stated that the use of MT might be suboptimal when stimulating other areas than the motor areas in the brain because of the large intra-individual differences in coil-target distance and target site anatomy. For this reason, some studies have used a percentage of the maximum stimulation output as stimulation intensity measure (Sparing et al., 2001). Others proposed the use of an adjusted threshold, with a correction for the distance between the motor area and the stimulation location (Stokes et al., 2013). Additionally, Kozel et al. (2000) showed that the distance from the stimulation coil to the cortex in the prefrontal cortex was greater than in the motor cortex in most subjects, with the difference increasing with age. Nahas et al. (2001b) showed that subjects with the smallest distance from the coil to the outer cortex showed greater increase in brain activity under the TMS coil.

Tables 2–4 provide an overview of the studies that have been performed to investigate the influence of different stimulation parameters in TMS research: frequency, stimulation position and intensity. Tables 5 and 6 show an overview of the studies performed to investigate pp paradigms and combinations of parameters.

A general finding is that stimulation above a frequency of 5 Hz increases the excitability whereas stimulation below 1 Hz causes a decreased excitability (Gorsler et al., 2003; Hallett, 2000; Knoch et al., 2005; Loo et al., 2003; Sparing et al., 2001). However, this does not always hold since Lin et al. (2014) showed an increase in anticonvulsant properties when frequency increases from 1 to 5 Hz, followed by a decreased effect after increasing the frequency to 10 Hz. A comparable trend in the effect of frequency, however in different frequency ranges, was found by Yadollahpour et al. (2014) in a rat study and by Luber et al. (2007) in healthy subjects. Speer et al. (2000) reported increases in regional cerebral blood flow (rCBF) when stimulating at 20 Hz. In contrast, a decrease in rCBF was found at 10 Hz. The application of high frequency left rTMS and low frequency right rTMS has comparable anti-depressive effects which might suggest that the effect of frequency depends on the stimulation position (Fitzgerald et al., 2009a,b; Isenberg et al., 2005; Rossini et al., 2010; Stern et al., 2007). However, when the knowledge about the pathology, in this case depression, is taken into account, this effect might also be explained by the imbalance between left and right hemispheres in patients with depression (Grimm et al., 2008). The effect of frequency might also be patient-specific, as shown by Jin et al. (2006).

The direction of the effect of TMS, inhibitory or excitatory, might also depend on the number of stimuli and the spacing, the period between stimulation trains, as was shown in TBS studies performed at intensities derived from the AMT (Gamboa et al., 2011, 2010). Conventional inhibitory cTBS and excitatory iTBS protocols (Huang

Table 2
Overview of rTMS-studies investigating the influence of stimulation parameter: frequency.

Pathology	Animal/ human	Position	Investigate effect on	Frequencies [Hz]	Parameter of interest	Outcome	Source
Depression	Human	Left and right DLPFC	Treatment of major depression (HF left rTMS versus LF right rTMS)	Low, high	HAMD	No significant difference in responder rate was found	Rossini et al. (2010)
	Human	Prefrontal cortex (left and right)	Treatment of major depression (HF left rTMS versus LF right rTMS)	Low, high	MADRS, BDI, HAMD, BPRS, CORE, GAF	HF left rTMS is as effective as LF right rTMS	Fitzgerald et al. (2009a)
	Human	Left and right DLPFC	Anti-depressant effects	1, 10	HAMD	Left 10 Hz and right 1 Hz showed similar significant anti-depressant effects	Stern et al. (2007)
	Human	Left and right DLPFC	Treatment of major depression	1, 20	HAMD, BDI, CGIC	rTMS given at LF over the right frontal cortex appears to be as effective as HF treatment of the left frontal cortex for treatment of depression	Isenberg et al. (2005)
	Human	Left prefrontal cortex	Mechanisms of action	1, 15	rCBF extracted from SPECT	HF rTMS led to an overall increase, whereas LF rTMS produced a slight decrease in the mean relative rCBF in the left DLPFC	Loo et al. (2003)
	Human	Left prefrontal cortex	Anti-depressant effect of daily rTMS	1, 20	rCBF extracted from PET	20 Hz rTMS over the left prefrontal cortex was only associated with increases in rCBF, recorded 72 h after the last treatment session. 1 Hz rTMS showed only decreases in rCBF	Speer et al. (2000)
Epilepsy	Rats	Right motor cortex	Penicillin-induced seizures	1, 5, 10	Density spectral array trendgraphs, iEEG parameters	1 and 5 Hz showed anti-convulsive properties in iEEG seizure profiles. 5 Hz outperformed 1 Hz in seizure suppression. Data from 10 Hz rTMS suggested facilitative characteristics	Lin et al. (2014)
HV	Human	M1	Modulation induced on M1	1, 5	Amplitude of CNV, motor reaction time	Inhibition of motor cortex due to 1 Hz rTMS stimulation, resulted in an amplitude increase of early and late components of CNV, and a slight reducing effect on motor reaction times, while 5 Hz stimulation did not change CNV amplitude	De Tommaso et al. (2012)
	Human	M1	ISP	3, 5, 10	ISP derived from EMG of FDI	rTMS of 10 Hz increased the area of ISP. At 3 and 5 Hz, the ISP remained unchanged	Cincotta et al. (2006)
	Human	Left or right DLPFC	Inhibition of well-learned routines, relying on frontal lobe functioning	1, 10	RNG performance	Counting bias was significantly reduced after the 1 Hz stimulation compared with baseline, but significantly exaggerated after 10 Hz stimulation	Knoch et al. (2005)
	Human	Right motor cortex	Excitability of the unstimulated left motor cortex by stimulating right site	0.5, 5	MEP induced by single pulse TMS	HF right motor rTMS can increase left motor cortex excitability whereas LF right motor rTMS can decrease it	Gorsler et al. (2003)
Schizophrenia	Human	DLPFC	Schizophrenia outcome	Patient specific peak alpha frequency, 3, 20	PANSS	Individual alpha-TMS demonstrated a significantly larger therapeutic effect than the other conditions	Jin et al. (2006)

BDI = Beck Depression Inventory, BPRS = Brief Psychiatric Rating Scale, CGIC = clinical global impression of change, CNV = contingent negative variation, CORE = rating of psychomotor disturbance, DLPFC = dorsolateral prefrontal cortex, EMG = electromyography, FDI = first dorsal interosseous, GAF = global assessment of function, HAMD = Hamilton Depression Rating Scale, HF = high frequency, HV = healthy volunteers, iEEG = intracranial EEG, ISP = ipsilateral silent period, LF = low frequency, MADRS = Montgomery-Åsberg Depression Rating Scale, MEP = motor evoked potential, PANSS = positive and negative syndrome scale, PET = positron emission tomography, rCBF = regional cerebral blood flow, RNG = random number generation, SPECT = single photon emission computed tomography.

et al., 2005) were compared to prolonged protocols, containing twice as many pulses. The prolonged continuous protocols showed excitatory effects and the prolonged intermittent protocol showed inhibitory effects (Gamboa et al., 2010). A later study showed that different spacing might enhance or decrease the effect of a single stimulation train (Gamboa et al., 2011). Voluntary motor activation, necessary for AMT determination, has also been shown to influence the effect of TBS (Gentner et al., 2008).

Table 3
Overview of rTMS-studies investigating the influence of stimulation parameter: stimulation position.

Pathology	Position	To investigate the effect of	Parameter of interest	Outcome	Source
Depression	Left and right DLPFC	A single rTMS session on an go/no-go task	Task performance	Performance significantly improved after right DLPFC rTMS	Bermpohl et al. (2006)
HV	Primary motor cortex and primary visual cortex	Stimulation on the TEPs in different locations	TEPs	1 Hz rTMS over the motor cortex appears to increase the amount of inhibition following a TMS pulse. No effect was found after stimulation of visual cortex	Casula et al. (2014)
	DLPFC and MPFC	Prefrontal 1 Hz rTMS by stimulating the generators of ERPs in the prefrontal cortex	N2 amplitude in a go/no-go task	After 1 Hz rTMS of the left DLPFC (but not of the MPFC) an inhibitory effect on the N2 amplitude was observed. After 1 Hz rTMS of the MPFC, a trend towards an increased P3 amplitude was found	Grossheinrich et al. (2013)

DLPFC = dorsolateral prefrontal cortex, ERP = event related potential, HV = healthy volunteers, MPFC = medial prefrontal cortex, TEP = TMS evoked potential.

Table 4
Overview of TMS studies in healthy volunteers investigating the influence of stimulation parameter: stimulation intensity.

TMS	Animal/ human	Position	Investigate effect on	Intensity	Parameter of interest	Outcome	Source
sp	Human	Hotspot for ADM MEP	TEPs	60, 80, 100, 120% RMT	TEPs in the EEG (GMFA and peak amplitudes)	Also low intensities (60% RMT) were able to induce TMS evoked brain responses. The peak amplitudes depend nonlinearly on the intensity	Komssi et al. (2004)
r	Human	Primary motor cortex (M1)	Local and distant effects on brain activity	80, 90, 100, 110 and 120% of twitch threshold	rCBF extracted from PET	1 Hz rTMS delivered to the primary motor cortex (M1) produces intensity-dependent increases in brain activity locally and has associated effects in distant sites with known connections to M1	Speer et al. (2003b)
r	Human	Left PFC	Intensity-related changes in brain	80, 90, 100, 110 and 120% of twitch threshold	rCBF extracted from PET	Stimulation intensity was found to be inversely correlated with the rCBF in the stimulated and contralateral PFC and other areas	Speer et al. (2003a)
r	Rats	Rat's head	LTP in the rat hippocampal CA1	0.75 T (<RMT) and 1.00 T (>RMT)	LTP recorded after stimulating brain slices	LTP was enhanced only in the 0.75 T rTMS group, while no change was observed in the 1.00 T rTMS group	Ogiue-Ikeda et al. (2003)
r	Human	Hotspot for APB muscle activation	Inhibitory function and cortical excitability	85, 115% RMT	Inhibitory function, RMT and MEP size	rTMS at both intensities produced an increase in the RMT but only 115% stimulation reduced the size of MEPs. rTMS had no effects on the cortical silent period or cortical inhibition measured with pp TMS	Fitzgerald et al. (2002)
r	Human	Left prefrontal cortex	Bilateral effects as measured by interleaved BOLD fMRI	80, 100, 120% RMT	BOLD fMRI activation maps	All intensities activated auditory cortex, with 80% RMT having no other area of significant activation. 100% MT showed contralateral activation and 120% MT showed bilateral prefrontal activation	Nahas et al. (2001a)

APB = abductor pollicis brevis, ADM = abductor digiti minimi, BOLD = blood oxygen level dependent, GMFA = global mean field amplitude, LTP = long-term potentiation, MEP = motor evoked potential, PET = positron emission tomography, PFC = prefrontal cortex, rCBF = regional cerebral blood flow, RMT = resting motor threshold, TEP = TMS evoked potential.

The choice of the stimulation target and positioning of the TMS coil on the scalp depends on knowledge of the pathology to be treated. For example in depression, the left dorsolateral prefrontal cortex (DLPFC) is known to be hypoactive (Koenigs and Grafman, 2009). Therefore, a facilitating TMS protocol targeted at this position is deemed relevant to improve depression symptoms. Compared to depression, the variability of the expression of epilepsy is larger: in case of focal epilepsy, the focus can be located in different parts of the brain resulting in various patient-specific stimulation positions. Superficial foci, such as for example in epilepsy patients with focal cortical dysplasia, can be stimulated directly. The hyperexcitable characteristics of epilepsy aim for an inhibiting, low frequency, stimulation protocol (Sun et al., 2012). Deeper foci might be stimulated indirectly, by stimulating cortical areas that are known to be functionally connected to the foci or by the use of coils designed to stimulate deeper structures. Table 3 lists some findings about the influence of the stimulation position on the outcome of TMS. For example, the performance of a go/no-go task improved after rTMS of the right DLPFC, but not after stimulation of the left DLPFC (Bermpohl et al., 2006). Also, differences between stimulation of the DLPFC and the medial prefrontal cortex (Grossheinrich et al., 2013) and the primary visual cortex were listed (Casula et al., 2014).

The effects of the stimulation position might be linked to the effect of the stimulation intensity. The two studies by Speer et al. (2003a,b) showed opposite intensity-dependent effects of the stimulation when stimulating the primary motor cortex and the left prefrontal cortex using the same stimulation protocol. Komssi et al.

Table 5
Overview of research into stimulation parameters for paired-pulse TMS studies in healthy volunteers.

Position	Goal	Parameter of interest	Outcome	Source
Hotspot of tongue motor cortex	To investigate the influence of multiple parameters on SICI and ICF	1. Body position (recline and supine), inter-stimulus intervals (ISI, 2, 10, 15 ms) between the TS (120, 140, 160% RMT) and CS (80% RMT) 2. ppTMS ISI (2, 2.5, 3 ms), CS (70, 80% RMT), TS (120% RMT)	1. Significant effect of body position, TS intensities and ISIs and interaction between intensity and ISIs 2. Significant effect of ISI but not CS intensity on MEP amplitude	Kothari et al. (2014)
APB hotspot	To investigate SICI at three different CS intensities (40, 70, 90% of RMT)	CMCT	Maximum SICI developed with CS set to 70% RMT	Vucic et al. (2009)
Motor cortex	To investigate the variability in cortical excitability by comparing sub- and suprathreshold intensity of CS (80% versus 120% of individual RMT)	EMG response in ADM	Reductions in EMG response in the ADM after CS in one hemisphere and TS in the opposite hemisphere (in a range of 12 ms) were found after CS of 120%	De Gennaro et al. (2004)
Vertex	To investigate the influence of the intensity of the CS on ICI and ICF with different ISI (3 versus 13 ms)	Latencies and areas of motor evoked potentials in right extensor carpi radialis muscle	MEP areas of 3 ms and 13 ms showed a different dependency on the intensity of the CS. Changes in MEP latencies were comparable	Kossev et al. (2003)
Left motor cortex	To investigate the influence of stimulus parameters (intensity of the CS varying from 0 to 100% RMT and ISI of 1, 3, and 5 ms)	CMAP	Maximal reduction of the amplitude of the MEPs was found at a CS intensity of 65% RMT and ISI of 1 ms	Schäfer et al. (1997)

ADM = abductor digiti minimi, APB = abductor pollicis brevis, CMAP = compound muscle action potential, CMCT = central motor conduction time, ICF = intracortical facilation, ICI = intracortical inhibition, ISI = inter-stimulus interval, MEP = motor evoked potential, RMT = resting motor threshold, SICI = short-interval intracortical inhibition.

(2004) found a non-linear relation between the peak amplitudes of TMS evoked brain responses and the intensity. Imaging studies showed that higher intensity TMS in general produced more activity under the coil as well as in contralateral brain regions (Fitzgerald et al., 2002). Also intensities below the MT were able to induce brain responses (Table 4).

In pp studies, Vucic et al. (2009) and Schäfer et al. (1997) found maximum short-interval intracortical inhibition (SICI) and maximum MEP reduction at 70% and 65% of RMT respectively. Both studies investigated a range of intensities for the CS, suggesting that the intensities below around 70% RMT cause an increase in inhibiting effect and higher intensities attenuate the effect. A contrasting finding was reported by De Gennaro et al. (2004), who only showed a reduction in EMG response, measured in the abductor digiti minimi in the hand, using a CS of 120% RMT.

When investigating rTMS as treatment option for epilepsy, the anti-epileptic effect was more pronounced when a figure-of-eight coil was used, and was shown to depend on the frequency of the stimulation and the duration of the protocol (Joo et al., 2007; Yadollahpour et al., 2014). Studies in healthy animals show a relation between the duration of the protocol and the frequency: higher frequencies require shorter protocols (Aydin-Abidin et al., 2006; Zyss et al., 1999).

According to Nojima et al. (2013) the combination of long protocols and high intensities can also emphasize the effect of TMS: a larger decrease in MEP amplitude was found with increasing intensities and duration of a 1 Hz stimulation protocol. An extensive review by Pell et al. (2011) stated that there is quite some dependency among the different stimulation parameters.

2.2. Transcranial direct current stimulation (tDCS)

tDCS is another non-invasive brain stimulation method in which a weak current is applied to the brain via a pair of large, spongy, electrodes. Generally, positioning the positively charged electrode (the anode) over the stimulation target causes enhancement of neu-

Summary of the technical aspects of TMS

In clinical practice, figure-of-eight coils are mostly used to perform relatively focal TMS. Single- and paired-pulse protocols can be used if one wants to study the functioning of the brain whereas repetitive stimulation protocols are necessary to obtain a long-lasting, therapeutic effect. In rTMS studies, monophasic pulses have shown to have longer-lasting effects on MEPs compared to biphasic pulses. However, because of efficient energy consumption in the stimulator, biphasic pulses are mostly used in rTMS protocols. In single pulse protocols, biphasic pulses are more effective.

The transfer from simple head models, assuming homogeneous and isotropic brain properties, to more complex models including position- and direction-specific properties probably leads to more accurate calculations of the electric field induced by TMS. The shape of the TMS coil, the position, and the orientation have a major influence on the electric field distribution. The preferred coil orientation differs between people, indicating the importance of incorporating patient-specific anatomical information in the models.

Various pathologies require different stimulation protocols. For example, the hyperexcitable characteristics of epilepsy make inhibiting protocols, so low frequency protocols or continuous TBS protocols, suitable. Depression requires facilitating, high frequency or intermittent TBS protocols when stimulating the left DLPFC.

The stimulation intensities are often defined as a percentage of a subject's individual motor threshold. It is not sure if this percentage is also representative for stimulation outside the motor cortex. Correction methods, e.g. for the distance between stimulation position and motor cortex, can be used.

Higher stimulation intensities and longer protocols have been suggested to enhance the strength and duration of the therapeutic outcome. The effect of TMS might be reversed after extending protocols beyond a certain duration. In determining the final stimulation protocol, the burden on the patient should also be taken into account. The guidelines for the use of TMS are published (Rossi et al., 2012).

Table 6
Overview of research into combination of parameters in rTMS studies.

Pathology	Animal/ human	Position	Investigate	Parameters and values	Parameter of interest	Outcome	Source
Depression	Human	Prefrontal cortex	The regional blood flow after SPECT	Frequency (5, 20 Hz) and coil-cortex distance	rCBF	20 Hz rTMS caused more relative flow below the TMS coil, compared to 5 Hz rTMS. Patients with smallest distance from coil to outer cortex showed greatest increase in brain activity at the site of stimulation	Nahas et al. (2001b)
	Human	Left prefrontal cortex	Response rate of left sided stimulation (at 5 and 10 Hz) after failed response on right sided stimulation	Frequency (5 and 10 Hz) and position (left versus right prefrontal cortex)	HAMD, MADRS	Small but significant response was found to left sided stimulation, independent of the frequency	Fitzgerald et al. (2009b)
Epilepsy	Rats	Spot with the maximum resultant electric field in kindling focus	The anti-epileptic effect	Frequency (0.5, 1, 2 Hz) and coil shape (figure-of-eight versus round)	ADD, progression of kindling (cumulated)	rTMS had anti-epileptogenic effects at all frequencies. The inhibitory, anti-epileptic, effect was higher at 1 Hz compared to 0.5 and 2 Hz. Application of rTMS 1 Hz by circular coil imposed a weaker inhibitory action compared with the figure-of-eight coil	Yadollahpour et al. (2014)
	Human	Epileptic focus or central vertex (in case nonfocal/multifocal epilepsy)	The anti-epileptic effect	Stimulation duration (3000 versus 1500 pulses) and position (see position)	Seizure frequency	Longer stimulation subgroup tended to have fewer seizures (not statistically significant). TMS stimulation site and structural brain lesions did not influence seizure outcome. Interictal spikes decreased significantly	Joo et al. (2007)
HV	Human (and model)	Primary motor cortex	MEP sizes	Stimulation intensity (85%, 100% and 115% RMT) and number of pulses (up to 1800)	MEPs	Results showed that more pulses and stronger intensities lead to a larger decrease in MEP amplitude at 1 Hz stimulation	Nojima et al. (2013)
	Human	V5/MT	To test the effects on MAE	Intensity (20% versus 90% PT), stimulation hemisphere	MAE	No main effects were reported. No effect of motion direction, stimulation location, stimulation intensity or side was found	Murd et al. (2012)
	Human	SMG	P300 latencies of the ERP	Frequency (0.25, 0.5, 0.75, 1 Hz) and hemisphere	P300 latency	P300 is only altered when stimulating left SMG at 1 Hz (lengthened 15 ms) or 0.75 Hz (shortened 15 ms).	Torii et al. (2012a,b)
	Human	M1/PMC	Excitability of the FDI corticospinal pathway	Frequency (1, 20 Hz) and intensity (90, 115% RMT)	Input-output curve (intensity versus MEP threshold)	LF115 over M1 increased the slope of the FDI input-output curve but did not change the S50 and plateau value. HF90 led to a more complex effect with an increase in the slope and a decrease in the S50 and plateau value	Houdayer et al. (2008)
	Human	Precuneus	On working memory	Frequency (1, 5, 20 Hz) and timing (presentation versus retention phase)	RT	Only 5 Hz stimulation to the parietal site resulted in a significant decrease in RT. Significant speeding of RT occurred in the retention phase but not the probe phase	Luber et al. (2007)
	Human	Left primary motor cortex (M1)	On inhibitory after-effects	Stimulation intensity (10% below or 15% above RMT), two different figure-of-eight shape coils	TMS induced MEPs from FDI	Suprathreshold 1 Hz rTMS has bigger effect on suppression of corticospinal excitability. Coil manufacturer also has influence	Lang et al. (2006)
	Cats	Occipital cortex	On VEPs and EEG	Stimulation frequency (1, 3, and 10 Hz) and duration of the protocol (1, 5, 20 min)	VEP and EEG recordings	Short high-frequency trains seem to be more effective than longer trains, and low-frequency rTMS requires longer application. Changes in the spectral composition of the EEG were not correlated to changes in VEP size	Aydin-Abidin et al. (2006)
	Human	Left or right DLPFC	Lateralized and frequency-dependent effects	Frequency (1, 10 Hz) and hemisphere	rCBF changes recorded by PET	Right prefrontal rTMS induces a different pattern of rCBF changes than left prefrontal rTMS	Knoch et al. (2006)
	Human	Wernicke's area	Picture naming	Frequency (1, 20 Hz), intensity (35, 45, 55% MSO)	Naming latency	Naming latency could be facilitated only immediately after Wernicke's area stimulation at a frequency of 20 Hz and at an intensity of 55% MSO, which is more than the motor threshold	Sparing et al. (2001)
	Rats	Rat's head	Effect of TMS compared to those produced by other anti-depressant treatments, in particular to repeated ECS	Stimulation frequency (20 versus 30 Hz) and number of sessions (9 versus 18 days)	Porsolt's forced swimming test	Standard ECS reduced the immobility by 50%, effects of rTMS were smaller (significant though). The stimulation at 20 Hz required 18 treatment sessions to produce a significant effect, while only 9 sessions with stimulation at 30 Hz were necessary	Zyss et al. (1999)
	Human	APB hotspot	MEP size	Intensity, coil orientation (360° in steps of 45°), 2 different coils	MEP size	Orientation of maximum MEP size depend on coil type. Influence of the stimulation frequency also depends on coil type	Brasil-Neto et al. (1992)

ADD = after-discharge duration, APB = abductor pollicis brevis, DLPFC = dorsolateral prefrontal cortex, ECS = electroconvulsive shock, ERP = event related potential, FDI = first dorsal interosseus, HAMD = Hamilton Depression Rating Scale, HF = high frequency, HV = healthy volunteers, LF = low frequency, MEP = motor evoked potential, MADRS = Montgomery-Åsberg Depression Rating Scale, MAE = motor after-effects, MSO = maximum stimulator output, MT = motor threshold, PET = positron emission tomography, PMC = premotor cortex, PT = phosphene threshold, rCBF = regional cerebral blood flow, RMT = resting motor threshold, RT = reaction time, SMG = supramarginal gyrus, SPECT = single photon emission computed tomography, VEP = visual evoked potential.

ral activity, whereas positioning the negatively charged electrode (the cathode) over the target reduces excitability (motor cortex stimulation at 1 mA) (Nitsche et al., 2008; Paulus, 2011).

An important difference between tDCS and other brain stimulation techniques is that tDCS does not induce direct activation by neural action potentials because the tDCS static fields, in the range of approximately 0.5–2 mA, are not strong enough (Nitsche et al., 2008). It is believed that tDCS modifies the transmembrane neural potential and thus influences the level of excitability (Wagner et al., 2007). tDCS is therefore often referred to as a brain modulation technique instead of a brain stimulation technique (Parazzini et al., 2011).

Common adverse events of tDCS were reviewed by Brunoni et al. (2011). The occurrence of adverse events was compared between an active stimulation group and a sham group. Itching was the most commonly reported adverse event (39.3% versus 32.9%), followed by tingling (22.2% versus 18.3%), headache (14.8% versus 16.2%), burning sensation (8.7% versus 10%), and discomfort (10.4% versus 13.4%). Although tDCS is presently not approved for any indication, the FDA has cleared some tDCS devices as having a non-significant risk. The rules for using tDCS vary from country to country (Fregni et al., 2014). tDCS is currently being investigated in clinical trials to treat depression, anxiety, attention deficit hyperactivity disorder (ADHD), epilepsy, and tinnitus (Brunoni et al., 2013).

Besides tDCS, also transcranial alternating current stimulation (tACS) or transcranial random noise stimulation (tRNS) are investigated to modulate cortical excitability. An oscillating electric field with either a specific frequency, or white noise in the range of 0.1–640 Hz, is used for tACS and tRNS respectively (Antal and Paulus, 2013; Paulus, 2011; Terney et al., 2008). Where tDCS used a constant field to induce membrane polarization to change the spiking rate of neurons, tACS uses an oscillating field aiming to induce network synchrony and changes in the phases of the spiking (Antal and Paulus, 2013; Zaghi et al., 2010). Brain oscillations are closely related to multiple cognitive functions (Herrmann et al., 2013). With these techniques directional sensitivity of standard tDCS can be avoided. The main characteristics of tDCS, tACS, and tRNS are shown in Table 7 (adapted from Kadosh (2014)). However, the remainder of the review will focus on tDCS.

2.2.1. Equipment: tDCS electrodes

In tDCS, constant currents are applied via patch electrodes with surface areas ranging from 16–100 cm^2 (e.g. Kuo et al., 2013; Martin et al., 2014). In its simplest form, the DC source is placed in series with the scalp electrodes and a potentiometer, which is used to adjust the constant current. The configuration and the shape of the tDCS electrodes determine which part of the brain is actually stimulated.

Datta et al. (2009, 2008) investigated the influence of different tDCS electrode configurations. The degree of shunting, the loss of effective current through the scalp because of the relatively high resistivity of the skull, depends on the configuration of the electrodes. Decreasing the distance between the electrodes results in an increased amount of shunting and more current is necessary to obtain an equivalent peak cortical electric field.

In case the reference electrode is placed over the scalp, anodal stimulation of one cortical area is combined with cathodal stimulation and vice versa. Increasing the size of the reference electrode was shown to result in a decreased effect of the functionally efficient reference electrode (Nitsche and Doemkes, 2007). To prevent unwanted excitability changes under the reference electrode, the efficacy of various montages using cranial and extracranial reference electrode positions for tDCS was investigated (Moliadze et al., 2010). The distance between the electrodes correlated negatively with the duration and size of the induced after-effects suggesting that stimulation intensity should be adapted to compensate for the inter electrode distance, which is relatively large when using an extracranial reference electrode.

The low spatial focality is considered to be a limitation of tDCS. Focality can be increased by reducing the size of the stimulation electrode (Nitsche and Doemkes, 2007) or by using ring electrode configurations, containing a cathodal ring electrode surrounding an anodal inner disc electrode. In this case, the focality also depends on the distance between the anodal and cathodal part of the electrode. Increasing the ring diameter decreases the fraction of shunting but also decreases focality (Datta et al., 2009, 2008).

2.2.2. Electric field modeling

The electric field in the brain after tDCS is comparable to the secondary field induced by TMS (see Section 2.1.2) because there is no rapidly changing current in case of tDCS. The skull strongly affects the electric field resulting from tDCS because of its high resistivity to electrical current. Studies modeling the electric field have been performed (Eaton, 1992; Kim et al., 2014; Metwally et al., 2012; Parazzini et al., 2014, 2012, 2011; Ravazzani et al., 1996; Roth et al., 1990; Ruohonen, 1995; Salvador et al., 2010, 2012; Shahid et al., 2013; Tofts and Branston, 1991) and showed that the induced electric field is not restricted to the area close to the stimulation electrodes. This section describes the electric field distributions resulting from models that incorporate between five and forty tissue types. Also the effects of skull composition and different electrode configurations are mentioned.

Salvador et al. (2010) discovered, by using high resolution FEM in a five-layer head model, that the maxima of the current densities do not appear on the gyri under the electrodes but in localized hotspots at the bottom of the sulci. In a later study, Salvador et al. (2012) further emphasized the importance of the conductivity values in the modeling studies. In isotropic models, it was shown that decreasing the conductivity of the skin resulted in increased maximum values of all field components, on both the CSF-GM and the GM-WM interface. The distribution of the electric field, however, remained almost unaltered. Decreasing the conductivity of the skull led to an expected decrease of electric field values. In this case, also the distribution of the field was affected significantly. According to Salvador, the skull is the tissue whose conductivity mostly influences the electric field distribution.

Parazzini et al. (2014, 2012, 2011) used 40 different tissue types for the head models. It was shown that the region with the maximum induced field is usually below or close to the anode. Variations in the size of the anodal or cathodal electrodes resulted in different electric field distributions. It was furthermore shown that variations in the injected current are linearly correlated with the field amplitudes.

Shahid et al. (2013) and Wagner et al. (2014) explicitly investigated the effect of adding more compartment to electric field models. Shahid et al. (2013) focused on the estimation of the contribution of regional anisotropic conductivity to the spatial distribution of an electric field across GM, WM, and subcortical regions. Four models were analyzed in this study. The first model contained average isotropic conductivity values assigned to 19 segmented tissues. Three additional models were derived from the base model by assigning different conductivity values to the cortical and subcortical regions and taking into account the anisotropies. By comparing the different models, it was shown that anisotropy causes variations in the strength of electric field hotspots across the cortex. The formation of active zones away from regions directly under the electrodes is attributed to the location of electrodes, geometry of the cortex, and a highly conductive CSF layer, which also acted as a region of high current density.

Wagner et al. (2014) started with a three compartment model and extended this model to six compartments in a step by step process. A new method was used to model the anisotropy in

Table 7
Overview of the main characteristics of tDCS, tACS, and tRNS (rCBF = regional cerebral blood flow, adapted from Kadosh (2014)).

	tDCS	tACS	tRNS
Current delivered	Small direct, constant current (0.5–2 mA)	Bidirectional, biphasic current in sinusoidal waves (0.25–1 mA), frequency 1, 10, 15, 30, 45 Hz, voltage 5–15 mV	Alternating current with random amplitude and frequency (0.1–640 Hz), intensity between −500 and 500 μA, sampling rate 1280 Hz, current of 1 mA
Typical stimulation time	20 min	2 and 5 min	10 min
Effect on cortical excitability	Increased excitability with anodal stimulation, decreased excitability with cathodal stimulation	No effects found	Unambiguous findings: tRNS might enhance cortical excitability, potentially with reduction of rCBF without affecting regional cerebral metabolic rate of oxygen consumption
Mechanism of action	Membrane polarization	Interfere with ongoing brain oscillations by entraining or synchronizing neuronal networks	Not known

white matter conductivity, based on a reversed gradient approach. Incorporation of the specific conductivity values for spongiosa and compacta bone in the skull (conductivity of the spongiosa areas being approximately 3.5 times higher) resulted in a change in electric field, depending on the position of the electrodes. The closer the electrodes are to the spongiosa, the more current is shunted trough the spongiosa resulting in decreased brain current density. Incorporation of the CSF in the model also leads to a more inhomogeneous current distribution in the brain, mainly because of the high conductivity of CSF. Modeling the white matter regions turned out to be mostly important when considering deeper target regions in the brain. Also, Metwally et al. (2012) emphasized the importance of incorporating the anisotropic characteristics of the skull and white matter in the brain models used for electric field modeling in tDCS. Incorporation of tissue anisotropies resulted in more diffused electric field in the white matter.

The impact of skull thickness and composition was recently investigated by Opitz et al. (2015). Different correlations were found between the electric field strengths resulting from the full model, including the distinction between spongiosa and compacta areas in the skull, and from the reduced model, in which the conductivity values of spongiosa and compacta areas were modelled equally. In general, thinner skull regions lead to higher electric field strengths. However, this is not a linear effect since the thicker parts of the skull contain more spongiosa areas with higher conductivities.

Besides the different models used by Shahid et al. (2013), four different electrode configurations were investigated. Different configurations resulted in distinct field patterns with noticeable variations in their strengths. The hotspots across the cortex were mostly located between and in the proximity of electrodes. Generally, it is expected that an increase in the distance between the electrodes would enhance the strength of the electric field in the brain. But it appeared that the distance between the electrodes is not as important as their relative locations. The skull thickness and composition also affect the electric field distribution in the brain (Opitz et al., 2015). FEM can be used to derive the optimal electrode position for tDCS (Im et al., 2008; Rampersad et al., 2013). By simulating the electric fields induced by tDCS for different electrode configurations, it was shown that the optimized configurations do not coincide with the configurations that are commonly used (Rampersad et al., 2013).

2.2.3. tDCS stimulation protocol

Positioning of the electrode patches, the distance between the patches, stimulation duration, and stimulation intensity are the most important parameters in a tDCS stimulation protocol. Studies investigating the effect of these parameters on the outcome of tDCS studies are described in this section.

Batsikadze et al. (2013) investigated the effect of stimulation intensity after applying tDCS to healthy volunteers. Whereas both anodal and cathodal 2 mA stimulation of the left primary motor cortex were found to induce a significant increase in MEP amplitudes, as recorded from the FDI, 1 mA cathodal tDCS decreased the corticospinal excitability, suggesting an intensity-dependent effect on polarity. Shekhawat et al. (2013) investigated the influence of stimulation intensity and duration on the response effect for suppression of tinnitus. Twenty minutes of 2 mA stimulation was found to be most effective. An interaction was found between duration and intensity of the stimulus on the change in rated loudness of tinnitus and clinical global improvement score. The general tendency, that longer stimulation induces longer after-effects (in the order of minutes and sometimes even hours), is expected to hold only for cathodal tDCS (Paulus, 2011). An anodal tDCS study has shown that the excitatory after-effects finally resulted in inhibition after applying 26 min of anodal tDCS, suggesting an upper limit for excitatory after-effects (Monte-Silva et al., 2013; Paulus, 2011). Dieckhöfer et al. (2006) compared anodal with cathodal stimulation by recording low and high frequency components of somatosensory evoked potentials. Cathodal tDCS induces a significant reduction of the N20 (the negative evoked potential after 20 ms) component while there was no effect after anodal stimulation. No changes in source activity were found for the N30 (the negative evoked potential after 30 ms) component or high frequency oscillations, suggesting distinct generators of the low and high frequency sources.

Two different montages were furthermore compared in a patient with tinnitus (Parazzini et al., 2012). It was shown that tDCS of the left temporoparietal cortex resulted in a widespread distribution of the electric field whereas tDCS of the DLPFC showed a concentrated field.

3. Invasive neurostimulation

In invasive neurostimulation techniques, electrodes are placed in direct contact with excitable tissue during a surgical procedure. Fig. 4 provides an overview of the positioning of the electrodes and pulse generators for VNS, DBS and responsive neurostimulation (RNS).

3.1. Vagus nerve stimulation (VNS)

VNS is a stimulation technique in which the vagus nerve, the tenth cranial nerve, is stimulated. The technique was developed in the eighties and was approved for the treatment of partial-onset epilepsy by the European Union in 1994 (Ben-menachem, 2002)

Summary of the technical aspects of tDCS
In tDCS, low current is applied via patch electrodes. Generally, anodal stimulation causes neuronal excitation whereas cathodal stimulation causes inhibition. However, the direction of the effect also depends on the stimulation intensity and the stimulus duration: excitatory effects might become inhibitory when the duration of stimulation is extended beyond approximately 20 minutes. The stimulation intensity depends on the distance between the electrodes. The distance between the electrode patches affects the electric field strength, because decreasing the distance results in an increased amount of shunting and more current is necessary to obtain an effect. Positioning of the tDCS electrodes highly depends on the stimulation target. The electric field is not confined to the proximity of the stimulation electrodes, but also occurs distant from regions under the electrodes. One of the possible causes is the highly conductive layer of CSF. The anisotropic properties and even also the composition of the skull affect the electric field distribution. Incorporation of the white matter properties is most important when the focus is on the electric fields deeper in the brain.

and by the FDA in 1997. For depression, VNS gained CE approval in 2001, and FDA approval in 2005 (Amar et al., 2008). Over 100,000 patients have been implanted with the Neurocybernetic Prosthesis System (Cyberonics Inc., Houston, Texas), a device that is implanted under the skin in the left pectoral area and delivers stimulation through a bipolar lead that is wound around the vagus nerve in the cervical region.

Stimulation is performed on the left vagus nerve, since the right vagus nerve has more dense projections to the atria of the heart which could theoretically result in negative adverse events

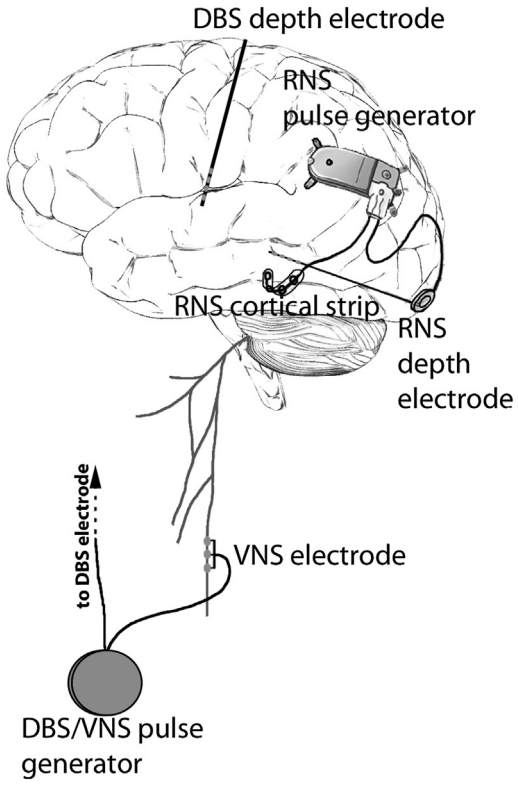

Fig. 4. Invasive brain stimulation.
Overview of invasive stimulation techniques. An example of the positioning of the electrodes of DBS and RNS within the brain and the VNS electrodes in the cervical region. Also the position of the pulse generators are shown for the different stimulation modalities.

during stimulation. The most prevailing side effect of VNS is hoarseness with or without voice alterations (55% (Sackeim et al., 2001), 60–62% (Ben-Menachem, 2001)). Also, the occurrence of dyspnea (16%, 23%), pain (17%, 27%), headache (20%, 30%), and infection (4%, 3%) was reported in an epilepsy study (Handforth et al., 1998) and a depression study (Rush et al., 2000) respectively. The side effects are usually related to periods in which the stimulation is on and seemed to diminish over time (Ben-Menachem, 2001; Boon et al., 2001a, 2007a; Vonck et al., 2001, 2012).

Important structures in the mechanism of action of VNS are the locus coeruleus (LC), the nucleus tractus solitaries (NTS), the thalamus, and the limbic structures (Krahl and Clark, 2012; Woodbury and Woodbury, 1990). The NTS, located in the brainstem, is bilaterally innervated by afferents of the vagus nerve during unilateral stimulation. So unilateral VNS can influence both hemispheres. Neurotransmitter release possibly plays a role in the mechanism of VNS. The LC is a noradrenergic nucleus which is known to have for example anti-epileptic effects (Boon et al., 2001a; Vonck et al., 2008, 2003, 2001).

Typically, the stimulation is automatically provided according to a certain duty cycle which does not require any intervention from the patient. In addition, the VNS device can be triggered to deliver one stimulation train by means of a handheld magnet when patients experience an aura or by caregivers who witness seizures. Boon et al. (2001b) and Tatum and Helmers (2009) investigated the efficacy of the magnet. Even though, in most cases, an intervention from caregivers was required, the magnet was considered an added value in controlling seizures (Boon et al., 2001b).

Based on the promising results obtained with the magnet, responsive VNS (rVNS) is being investigated for epilepsy. Responsive stimulation means that stimulation is only provided after a trigger is detected. In case of rVNS, the trigger can be extracted from the patient's electrocardiogram. Seizure-related cardiac changes, such as ictal tachycardia or increase in heartrate, occur in over 70% of the epileptic seizures. A case study using this novel VNS device reported a decreased seizure duration in a patient with refractory epilepsy (Hampel et al., 2015). A large prospective randomized trial has been performed in the European Union, demonstrating that the cardiac based seizure detection algorithm, incorporated in the device, has a high sensitivity. Long-term results on seizure duration and severity are pending (Boon et al., 2014).

Even though this review focuses on invasive VNS, recently also non-invasive transcutaneous VNS (tVNS) has been developed which involves unilateral external transcutaneous stimulation of the auricular branch of the vagus nerve using an external pulse generator (Stefan et al., 2012) (see Fig. 1). tVNS has demonstrated initial efficacy in epilepsy (Ellrich, 2011; He et al., 2013; Stefan et al., 2012) and depression (Rong et al., 2012). These results should be interpreted with caution since they were obtained in small pilot studies.

3.1.1. VNS electrodes

Per definition, so independent of the pathology, VNS stimulates the vagus nerve using a specially designed electrode that surrounds this nerve. Compared to other stimulation techniques, the variation of electrode position and shape of the electrode is limited.

The VNS lead contains helical cuffs that contain one positive and one negative electrode and one anchor tether that surround the vagus nerve. Two sizes are available for clinical practice, with a helical inner diameter of 2 or 3 mm. Materials typically used are platinum, iridium and stainless steel as conductors and silicone rubber, polytetrafluorethylene and polyimide as insulating carriers (Rodriguez et al., 2000). Cuff-electrodes may have several advantages compared to intramuscular, epymisial and surface electrodes. Firstly, these electrodes reduce the stimulus intensity required for nerve activation minimizing hazardous electro-chemical processes

secondary to charge delivery and diminishing the power consumption of the stimulator system. Secondly, cuff-electrodes are more flexible with respect to the positioning of the electrode which minimizes mechanical distortion and the probability of lead failure (Rodriguez et al., 2000).

3.1.2. Electric field modeling

The vagus nerve contains multiple fiber types of which some are known to be important for VNS to be effective (Krahl et al., 2001). Electric field modeling in VNS might be helpful in steering the field towards the important fibers.

To the best of our knowledge, only one study has been performed in which computational models were used to investigate the effect of stimulation parameters, output current and pulse width, and tissue encapsulation at the site of electrode placement, in VNS (Helmers et al., 2012). A 3D digital representation of the geometry of the vagus nerve and VNS electrodes was created and a FEM was constructed to determine the voltage distribution in the vagus nerve, as a function of output current and pulse width. Two cases, with and without encapsulation layer, were compared.

While the model showed activation in 99.5% of the fiber types that are important for vagus nerve activation without an encapsulation layer, this was reduced to 55% when the encapsulation layer was taken into account. In both cases, stimulation intensity was set to 1.5 mA and pulse width to 500 μs. The optimal combination of stimulation parameters was derived from strength-duration curves, illustrating the non-linear relation between output current and pulse width. The optimal intensity was concluded to be between 0.75 and 1.75 mA and the optimal pulse width between 250 and 500 μs.

3.1.3. VNS stimulation protocol

Even though there is hardly variation in the stimulation position and the electrode type used for VNS, the remaining stimulation parameters, such as the frequency, pulse width, the duty cycle, and the intensity, can still create various stimulation protocols. The stimulation parameters may influence the outcome of VNS. The choice of the duty cycle can for example determine whether a patient responds to VNS or not (Scherrmann et al., 2001).

Mu et al. (2004) and Lomarev et al. (2002) investigated the effects of respectively pulse width and frequency on functional MRI (fMRI) activation maps in patients with depression. Mu et al. (2004) showed that, compared to 250 and 500 μs, a pulse width of 130 μs produced significantly less overall activation and 500 μs produced more deactivation compared to 130 and 250 μs. Both regional overlap and differences in fMRI activation maps were seen with the various pulse widths. Moreover, Lomarev et al. (2002) showed that 20 Hz produced more acute activity changes compared to 5 Hz stimulation.

Besides the frequency of the stimuli, also the frequency of the stimulation trains: the duty cycle, can influence the outcome of VNS (Heck et al., 2002). A duty cycle of 30 s stimulation on, 180 min off, 1 Hz and 130 μs pulse width, is often considered to be the condition control. The standard therapeutic protocol, that is clinically used is 30 s stimulation on, 5 min off, 30 Hz, 500 μs pulse width (DeGiorgio et al., 2000), has shown to be significantly more effective than the control condition. DeGiorgio et al. (2005) investigated the influence of the duty cycle in patients with epilepsy. Neither the output current, nor the duty cycle turned out to correlate with the clinical outcome in terms of seizure reduction and responder rate. In case of initial non-responders to the standard protocol, increasing the current or the frequency of the duty cycle might improve the clinical outcome. However in general, the standard clinical stimulation protocol showed a better outcome compared to a protocol with a rapid duty cycle: 7 s on, 30 s off (Scherrmann et al., 2001).

Summary of the technical aspects of VNS

VNS on the left vagus nerve, is an approved treatment method for epilepsy and depression. The most common clinically used VNS protocol consists of 30 s stimulation, 5 min no stimulation, 30 Hz stimulation frequency, and a pulse width of 500 μs. Electric field modeling is not often performed for VNS but might be helpful to steer the electric field towards the important fibers and to investigate the effect of stimulation parameters. Initial non-responders might become responders after increasing the current or the frequency of the duty cycle.

Another study in an epileptic rat model (Mollet et al., 2013) showed that 0.25 mA is sufficient to decrease cortical excitability. This study also showed that VNS does not have a long-lasting effect since the MT one hour after stimulation did not differ from the baseline MT, before stimulation. The influence of the current intensity was investigated by Bunch et al. (2007) in a group of 61 patients. Higher output-currents are needed to generate vagus nerve action potentials when the pulse width is reduced to less than 200 μs. Koo et al. (2001) investigated the threshold current intensity to produce nerve action potentials as a function of pulse width and age. Also, the conduction velocity of the vagus nerve was investigated. Longer pulse widths required lower current intensities to produce action potentials. The necessary current to generate action potentials furthermore decreased with increasing age. This suggests age-related adjustments of the stimulation parameters. The conduction velocity was lower in children below age 12.

3.2. Deep brain stimulation (DBS)

In DBS, electricity is directly delivered to specific brain areas through stereotactically implanted electrodes. During an MRI-guided stereotactic procedure under local anesthesia (Villeger et al., 2006), DBS electrodes are implanted through burr holes (Gigante and Goodman, 2011; Pereira et al., 2012). The pulse generator is implanted under the left clavicle or in the abdominal cavity (Hassan and Al-Quliti, 2014).

DBS has gained FDA approval for the treatment of movement disorders such as essential tremor (ET), Parkinson's disease, dystonia, and obsessive compulsive disorder (OCD). In Europe, the method is also approved for movement disorders and refractory epilepsy (Al-Otaibi et al., 2011; Labar and Dean, 2002; Saillet et al., 2009; Sprengers et al., 2014; Vonck et al., 2012). Furthermore, DBS is investigated as a treatment option for depression, chronic pain, Tourette syndrome, Huntington's disease, Alzheimer's disease, obesity, addictions, and consciousness disorders (Chen et al., 2012). Depending on the pathology, different brain regions are targeted. The ventral intermediate nucleus of the thalamus (VIM) and the globus pallidus internus (GPi) are the most widely used targets for dystonia (Ostrem and Starr, 2008). In case of Parkinson's disease, the subthalamic nucleus (STN) and the GPi are the most commonly used targets (Benabid, 2003). For ET, besides the VIM, also the posterior subthalamic area (PSA) is now used as a target (Fytagoridis et al., 2013). Many targets have been investigated for OCD (Greenberg et al., 2006; Mallet et al., 2008; Sturm et al., 2003). The most widely used, and only approved, target for epilepsy is the anterior nucleus of the thalamus (ANT) (Fisher et al., 2010; Fisher and Velasco, 2014). Besides the ANT, also the centromedian nucleus of the thalamus (Velasco et al., 2001) and the cerebellum (Velasco et al., 2005), have been investigated as targets for epilepsy in randomized clinical trials (Sprengers et al., 2014). Moreover, promising results have been obtained when the hippocampus is targeted (Boon et al., 2007b; Vonck et al., 2005, 2002).

For a long time, it was hypothesized that DBS merely works either via functional ablation by suppressing or inhibiting the structure being stimulated or via activation of the stimulated structure (McIntyre et al., 2004c). Nowadays, the mechanism of action is thought to be more related to large neuronal networks in the brain since widespread changes in neuronal activity were found in networks comprising the DBS target (McIntyre and Hahn, 2010; Okun et al., 2013). These changes in firing patterns of neuronal activity are probably linked to mechanisms of synaptic plasticity (Ganguly and Poo, 2013; Okun et al., 2013; Van Hartevelt et al., 2014). The exact mechanism of DBS still remains to be elucidated.

Although DBS has provided remarkable therapeutic benefits for patients with several pathologies, side effects can occur related to surgery or the hardware. Zrinzo et al. (2012) showed that intracranial hemorrhage is the most prevalent side effect in DBS (0.9% in the study by Zrinzo et al. but overall literature suggested a prevalence of 5% (Zrinzo et al., 2012)). The occurrence of hemorrhage is a risk factor for the occurrence of seizures after DBS. According to Coley et al. (2009), the seizure risk after DBS is 2.4%. Most seizures occur within 48 h after the surgical implantation of the electrodes. Besides that, implant site infections, electrode migrations or misplacement, wire fractures, skin erosion or device malfunctions can occur. The exact number vary between different centers. In a meta-analysis, Appleby et al. (2007) showed some cases in which significant psychiatric side effects occurred. The rates of depression, cognitive impairment, and mania are low, but also a relatively high rate of suicide (0.16–0.32% in DBS versus 0.02% in the normal population in the United States) was found in patients treated with DBS, depending on the stimulation target. It was suggested that patients should be pre-screened for suicide risk-factors before DBS and should be closely monitored afterwards.

DBS can also be administered by means of RNS that only provides stimulation after a trigger is detected by a so-called closed-loop algorithm (Kent and Grill, 2014; Stanslaski et al., 2012). The RNS neurostimulator (NeuroPace, Inc., Mountain View, California) is cranially implanted under the skull and is connected to one or two depth leads and/or cortical strips. RNS can also be connected to cortical strips only. Strictly speaking, in that case it is cortical stimulation rather than DBS.

RNS has been studied extensively in epilepsy (Asconapé, 2013; Carrette et al., 2015; DeGiorgio and Krahl, 2013; Gigante and Goodman, 2011; Liu et al., 2013; Morrell, 2006; Raghunathan et al., 2009; Skarpaas and Morrell, 2009; Sun et al., 2008). In this case, the pulse generator continuously analyzes the electrocorticogram, recorded with a cortical strip lead, and automatically triggers electrical stimulation when specific characteristics are detected (Morrell, 2006). A recent study (Bergey et al., 2015) showed significant seizure reduction after long-term follow-up of RNS in patients with medically refractory epilepsy. Besides use in epilepsy, different triggers, such as the typical rhythms in the beta frequency band, are being investigated for use of RNS in Parkinson's disease (Basu et al., 2013; Beuter et al., 2014; Gorzelic et al., 2013; Modolo et al., 2012; Shukla et al., 2012).

3.2.1. Equipment: DBS electrodes

The electrodes used for DBS are surgically implanted in the brain. Depth electrodes contain multiple contact points such that the electric field can be steered to optimally stimulate the target. This section mentions the research that is performed to improve the electrode design, for example to diminish surgical complications or to perform directional steering.

Presently used DBS depth electrodes (Models 3387, 3389, Medtronic Inc., Minnesota, USA), as well as depth electrodes from the RNS system (NeuroPace, Inc., Mountain View, California), have a linear array of four cylindrical electrode contacts, consisting of platinum and iridium, that can be individually switched on or off depending on the placement of the electrode with respect to the target area in the brain (Wei and Grill, 2005). The depth electrodes have a diameter of 1.27 mm, ring-shaped contacts, and inter-contact distances ranging from 0.5 to 10 mm (Medtronic, 1998; Neuropace, 2013).

Lai et al. (2012) have worked on an improved design of the electrode probes used for DBS. Based on the rationale that a lower electrode impedance increases the signal-to-noise ratio, a probe was developed with a rough three-dimensional microstructure on the electrode surface. The electric field generated by the probe was experimentally validated, using a FEM.

Parittotokkaporn et al. (2012) and Ben-Haim et al. (2009) also focused on the electrode design but aimed at decreasing the risk of adverse effects during or after DBS. Lead migration is one of the possible risks of DBS. Parittotokkaporn et al. (2012) added microtextured features to DBS probes to reduce probe mobility and showed that the lead migration in ex-vivo porcine brain was reduced without additional tissue damage. It was not investigated whether this microtexture can be used in platinum iridium electrodes (Turner, 2012) or whether it changes the physical characteristics of the electrodes. Hemorrhage is another possible complication of DBS surgery. Ben-Haim et al. (2009) showed decreased occurrence of hemorrhages using a modified microelectrode, with a decreased diameter.

Martens et al. (2011) presented a novel design of a high-resolution DBS lead that enables directional steering of the electric field. The DBS-array lead carries 64 disc-shaped electrodes, which are arranged in 16 equally spaced rows, covering a total length equivalent to the state-of-the-art DBS electrode arrangements (Toader et al., 2010). By tracking the iso-fieldlines of the electric field and thresholding at a certain level, a volume of tissue activated (VTA) could be determined. It was shown that the new DBS array is capable of generating VTAs equivalent to currently used DBS electrodes but is also able to smoothly steer those in a preferential direction with 1–2 mm increments. Optimal overlap between the VTA and the stimulation target increase the effectiveness of the stimulation. Furthermore, the induction of adverse events by stimulating tissue beyond the stimulation target is diminished.

The VTA was also investigated by Butson and McIntyre (2006) as a function of electrode design. In this study, a FEM of the electrodes and surrounding medium was coupled to models of myelinated axons to predict the VTA. The relation between the aspect ratio (diameter/height) of the electrode, and the VTA was investigated. A low aspect ratio maximized the VTA by providing greater spread of the stimulation parallel to the electrode shaft without sacrificing lateral spread. The results of this study furthermore showed that modified electrode designs can be used to customize the VTA to specific target nuclei.

3.2.2. Electric field modeling

Because the brain consists of conductive media, it acts as a volume conductor: the electric fields from an electric source are transmitted through biological tissue. Volume conduction plays an important role in DBS. Knowledge of the anatomical distribution of the electric field is of paramount importance to maximize the therapeutic effect of neurostimulation and to get a deeper insight into the underlying mechanism of action of DBS. Multiple studies using the FDM (Vasques et al., 2009) or the FEM were performed to model the electric field induced in the brain during DBS (Aström et al., 2012; Butson et al., 2006; Chaturvedi et al., 2006; Grant and Lowery, 2009; McIntyre et al., 2004a,b; Miocinovic et al., 2009; Pedoto et al., 2012; Schmidt and van Rienen, 2012a,b; Wårdell et al., 2014; Wei and Grill, 2005). The main focus of these studies is the importance of incorporating specific conductivity values or encapsulation layers, and steering towards the stimulation target.

Butson et al. (2006) emphasized the importance of incorporating DTI information in the model, to derive position- and direction-specific conductivity values. This was confirmed by showing significant differences in VTAs between homogeneous, isotropic models and heterogeneous, anisotropic tissue models, during DBS of the STN for Parkinson's disease (Butson et al., 2006).

Schmidt and van Rienen (2012a,b) also investigated the influence of anisotropic conductivity on the field distribution in STN DBS. The maximum differences between the electric fields derived from the isotropic and anisotropic models occurred in the proximity of the active electrode contact in the unipolar stimulation cases and additionally in the proximity of the ground electrode in bipolar cases. Investigating the influence of the electrode position by moving the electrode around the primary position resulted in differences in the electric field distributions, mainly observable within the surroundings of the stimulating electrode contact.

The model used by Schmidt and van Rienen (2012a) was extended with an encapsulation layer surrounding the DBS electrode body. The influence of the encapsulation layer can be described in different stages after implantation. In the acute stage, the peri-electrode space is filled with extracellular fluid. Due to the high conductivity of extracellular fluid, a path of low resistance is created enabling the current to spread further. So neglecting the peri-electrode fluid layer may lead to an underestimation of the field strength during the acute stage. Approximately two weeks after implantation, giant cells with low conductivity start to occur at the electrode surface. The spread of current into the surrounding tissue is restricted, which may cause an overestimation of the actual electric field (Yousif and Liu, 2007).

The effect of the encapsulation layer was furthermore investigated by Chaturvedi et al. (2006). Clinical measurements of the corticospinal tract activation, MEPs of various muscles, were used to address the level of model complexity necessary to accurately predict neural activation generated by STN DBS. Based on the comparison of the electric fields with the anatomy of one dataset, it was suggested that estimation of the neural response to DBS requires a model that incorporates electrode capacitance, electrode impedance, electrode location and orientation in the brain and 3D tissue conductivity values.

Other studies have focused on spatially steering the electric field towards the morphology of the stimulation target, such as the STN or the GPi, based on iso-potential fieldlines or iso-electric fieldlines (Hemm et al., 2005; McIntyre et al., 2004b; Vasques et al., 2010, 2009; Wårdell et al., 2014). Wårdell et al. (2014) showed that incorporating patient-specific information, retrieved from DTI, can improve the electric field calculations in Tourette patients. McIntyre et al. (2004b) developed a quantitative understanding of the VTA by DBS of the STN. It was shown that the VTA extends beyond the actual borders of the STN, using clinically effective stimulation parameters. Furthermore, it was shown that slight (~1 mm) deviations of the electrode positions can substantially alter the VTA. Vasques et al. (2010, 2009) showed that, compared to state-of-the-art DBS electrodes, a double contact with a height of 2.5 mm, induced a more homogeneous field and less voltage was needed for GPi stimulation.

Miocinovic et al. (2009) performed a validation study of the methods used to model the electric fields by comparing the electric field induced by DBS electrodes implanted in a rhesus monkey in the thalamus and the STN to a theoretical field, calculated with microelectrodes positioned in a saline bath with a DBS electrode. Three important findings have been reported. Again, the importance of the inhomogeneities and anisotropies was emphasized. Furthermore, it was shown that DBS electrode impedance is primarily dictated by a voltage drop at the electrode-electrolyte interface and the conductivity of the tissue medium, and the stimulus waveform recorded in saline or brain tissue was modified from the stimulus waveform generated by the pulse generator.

Walckiers et al. (2010) investigated the influence of the neurostimulator when modeling the electric field after DBS with FEM. Using a model for the reference electrode, a reduction of VTA was shown. Grant and Lowery (2009) also showed that incorporating the reference electrode in the model changes the VTA.

3.2.3. DBS stimulation protocol

Even after implantation of the DBS electrode lead, electrical steering can be applied by selecting the electrodes that are actually used for stimulation. Multiple choices have to be made to obtain a DBS protocol: monopolar or bipolar, unilateral or bilateral, synchronous or asynchronous stimulation. This section describes the current knowledge about these options. Besides that, also the knowledge about the influence of different pulse shapes and frequencies are listed.

In DBS, stimulation must be delivered by at least one positive (anodal) or negative (cathodal) stimulation electrode. Cathodal stimulation causes positively charged ions to flow towards the electrode, causing depolarization in nearby neurons. The opposite holds for anodal stimulation. DBS can be performed in a monopolar or bipolar way. In monopolar DBS, the metal housing of the neurostimulator serves as the anode (Denys et al., 2012). In general, monopolar stimulation results in a larger current spread than bipolar stimulation for a given stimulation intensity. Hemm et al. (2005) showed, based on a simple model, that monopolar stimulation causes a more homogeneous electric field. The larger spread of the electric field causes a higher number of side effects in monopolar stimulation. During bipolar stimulation, higher stimulation intensities are necessary to obtain similar clinical effects as with monopolar stimulation (Deli et al., 2011).

Unilateral versus bilateral stimulation studies were performed by Hamani et al. (2010) and Van Nieuwenhuyse et al. (2015). Hamani et al. (2010) showed that left unilateral stimulation of the subcallosal cingulate gyrus was equally effective as bilateral DBS in treating major depression. In contrast, Van Nieuwenhuyse et al. (2015) found bilateral stimulation to be more effective in a DBS study in the hippocampus of rats, for the treatment of epilepsy.

In rats, Cymerblit-Sabba et al. (2013) compared synchronous stimulation, stimulation with two electrodes that were simultaneously activated, to asynchronous stimulation, using different stimulation frequencies. The asynchronous protocol was more efficient in terminating and shortening induced hippocampal seizures. Wyckhuys et al. (2010) investigated whether Poisson-distributed stimulation, stimulation with the interstimulus intervals varying according to a Poisson distribution, was more effective compared to standard high frequency stimulation in a kainate rat model. The Poisson-distribution stimulation showed a slightly increased number of rats with a significant reduction in seizure frequency. Also the reduction in seizure frequency was higher in rats treated with the Poisson protocol compared to high frequency stimulation (67% versus 50%).

Simulation studies have been performed aiming at modifying the stimulation pulse shape to optimize the efficiency of the stimulation (Grill and Mortimer, 1996; Hofmann et al., 2011; Wongsarnpigoon and Grill, 2011). The underlying thought is that the frequency of battery-replacement surgeries could be decreased by improving the energy efficiency of the stimulation. An older study by Grill and Mortimer (1996) determined the effect of rectangular stimulus pulse widths on the selectivity of peripheral nerve stimulation. Better spatially selective stimulation was observed when applying shorter pulses. Later, Wongsarnpigoon and Grill (2011) used a generic algorithm to determine the optimal waveform shape. The resulting waveforms resembled truncated Gauss-shaped pulses. The optimized waveforms turned out to be

more energy- and charge-efficient than several conventional waveforms used in neural stimulation. Hofmann et al. (2011) showed a further increase in efficiency with the introduction of a pause within a biphasic pulse, with specific and optimized duration. An evaluation to compare the actual waveforms from different manufacturers showed that the actual stimulation waveforms differed from the intended ones, as prescribed by the manufacturers (Butson and McIntyre, 2007).

Tables 8 and 9 provide an overview of the research that is performed to gain insight into the influence of stimulation frequency as well as studies that investigated the effect of combinations of parameters in DBS.

As can be seen in Table 8, the optimal stimulation frequency depends on the pathology. In dystonia and epilepsy, 130 Hz stimulation has shown to be an optimal frequency (Kupsch et al., 2003; Ostrem et al., 2014), whereas in ET, no additional benefit was found above 100 Hz (Ushe et al., 2004). In Parkinson's disease, the stimulation frequency is often set to 130 Hz. Some studies showed that stimulation at 60 Hz can decrease the number of freezing episodes, compared to 130 Hz stimulation (Moreau et al., 2008; Xie et al., 2012). However, Phibbs et al. (2013) could not confirm this finding and Brozova et al. (2009) commented that a decrease in freezing of gait (FOG) may be accompanied by worsening of other types of gait problems. Different phenotypes within a certain pathology seem to respond differently to stimulation. This was also confirmed by Yamamoto et al. (2004), who showed that stimulation parameters, such as the effective stimulation sites and intensities varied between different kinds of tremor.

An imaging study in animals, performed by Paek et al. (2014), showed that combinations of frequency and intensity influence the activated brain regions differently. A negative fMRI response was generated with 130 Hz stimulation while 10 Hz stimulation generated a positive response in the same area. Moreover, an increase of the stimulation intensity had an effect on the size of the affected brain areas.

Vercueil et al. (2007) investigated the effect of different pulse widths; 60, 120 and 450 μs, on the clinical improvement in primary generalized dystonia. No significant differences were found. Another study investigating the effect of different combinations of pulse widths and frequencies on the intensities required to measure a positive clinical outcome in patients with Parkinson's disease (Rizzone et al., 2001). A hyperbolic intensity-pulse width curve was obtained, indicating that at higher pulse widths, lower intensities are sufficient to induce a clinical effect. Furthermore, for a certain pulse width, increasing the frequency led to decreased intensity required to obtain any effect.

Liu et al. (2012), Pedrosa et al. (2013), and Earhart et al. (2007) investigated different protocols with and without prior high frequency stimulation respectively in intentional and postural tremor. The varying results suggest that the effect of neurostimulation might be enhanced or attenuated by the cortical excitability state. Based on this thought, Zhang et al. (2012) investigated the effect of timing of high frequency DBS in the ANT on amygdala-kindled seizures in rats and showed that bilateral post-kindling stimulation has a stronger effect compared to pre-kindling stimulation. This finding suggests that RNS is more appropriate for clinical antiepileptic treatment than scheduled stimulation.

It is not yet known whether neurostimulation induces a long-lasting effect. On the one hand, Cif et al. (2013) suggested the induction of long-lasting effects by showing that no difference between symptom evolution was found in dystonia patients during DBS administration and after DBS discontinuation. On the other hand, the study by Van Nieuwenhuyse et al. (2015) showed that after discontinuation of 10 days of unilateral or bilateral DBS, the electrographic seizure rate returned to baseline. Because stimulation in the study of Cif et al. (2013) was in the order of years, and the study of Van Nieuwenhuyse et al. (2015) in the order of days, these findings might suggest that a long-lasting effect might not occur before a certain amount of stimulation time is reached.

Summary of the technical aspects of DBS

In DBS, the cathode causes neuronal enhancement. In case of monopolar stimulation, the housing of the neurostimulator serves as the anode. Monopolar stimulation causes larger, more homogeneous current spread. This larger spread might also induce more side effects. Bipolar stimulation requires higher stimulation amplitudes to achieve equal effects.

Accurate models to perform electric field calculations should incorporate position- and direction-specific conductivity values and also the encapsulation layer needs to be modeled. Models can be used to predict the optimal stimulation position, such that the spatial overlap between the volume of tissue activated and the target is maximized.

The effectiveness of unilateral versus bilateral DBS probably depends on the pathology. In case of bilateral stimulation, the clinical effects might increase using an asynchronous or Poisson-distributed stimulation protocol.

Currently, a pulse with a pause between the two Gauss-shaped phases (one positive and one negative) is considered to be optimal. No direct effect of the pulse width was found, but there is a relation between pulse width and stimulation intensity. The optimal stimulation frequency for DBS might depend on the pathology.

4. Alternative stimulation techniques

Besides the techniques mentioned earlier in this review, other stimulation techniques exist that are not standardized in clinical practice or that are under development and might be used in the future. These stimulation techniques try to overcome drawbacks of the methods mentioned before, such as the invasiveness of DBS and VNS and the relative non-focality of non-invasive techniques. Although an extensive explanation of these techniques is beyond the scope of this review, we would like to briefly mention some of them.

In trigeminal nerve stimulation (TNS) one of the two upper branches of the trigeminal nerve, the fifth cranial nerve is stimulated (DeGiorgio et al., 2013, 2003; Fisher, 2011). TNS can be delivered either transcutaneously with external electrodes and an external pulse generator (eTNS, Monarch system by NeuroSigma or Cefaly system by Roxon) (see Fig. 1), or subcutaneously with implanted electrodes and an implanted generator (sTNS, Monarch system by NeuroSigma, under development). eTNS received CE mark in September 2012 and is approved for subjects aged 9 and above as an adjunctive therapy for either epilepsy (DeGiorgio and Krahl, 2013b; DeGiorgio et al., 2013, 2009, 2006, 2003; Moseley and DeGiorgio, 2014; Pop et al., 2011) or depression (Cook et al., 2013; Schrader et al., 2011). The system has further received a Humanitarian Use Device from the FDA for the treatment of Lennox-Gastaut syndrome in children. eTNS has also been shown to have a positive effect on mood (Schrader et al., 2011). A trial in ADHD has recently been published (McGough et al., 2014). The eTNS system by NeuroSigma contains a 1.25 inch disposable, hypoallergenic, silver-gel, self-adhesive stimulation electrode (DeGiorgio et al., 2006). To the best of our knowledge, no research on the optimization of equipment or stimulation parameters has been published and eTNS has not been used in routine clinical practice. The hypothesized mechanism of action seems to overlap with that of VNS: the trigeminal nerve projects towards important structures in the brain such as the NTS and the LC (Moseley and DeGiorgio, 2014).

Electroconvulsive therapy (ECT) and magnetic seizure therapy (MST) are both old stimulation techniques that are considered as

Table 8
Overview of studies investigating the effect of frequency in DBS studies in human.

Pathology	Position	Investigate effect on	Frequencies [Hz]	Parameter of interest	Outcome	Source
Dystonia	STN	Dystonia severity	60, 130	BFMDRS-M and TWSTRS-S	130 Hz stimulation is more effective than 60 Hz stimulation	Ostrem et al. (2014)
	GPi	Dystonia severity	0, 5, 50, 130, 180, 250	European Profile of QOL and BFMDRS	Original frequency of 130 Hz resulted in clinical improvement. At higher frequencies, higher improvements were found whereas at lower frequencies significant deterioration was found	Kupsch et al. (2003)
ET	VIM	Tremor suppression	0, 30, 45, 60, 75, 90, 100, 130, 145, 185	RMS of tremor (measured by accelerometer)	Highly significant inverse sigmoidal relationship between stimulation frequency and normalized tremor acceleration. Tremor acceleration had a nearly linear response to stimulation frequencies between 45 and 100 Hz, with little additional benefit above 100 Hz	Ushe et al. (2004)
PD	STN	Bradykinesia	All stimulation frequencies available to the subject's neurostimulator	Amplitude and frequency of hand opening-closing task	Multiple frequencies resulted in increased movement amplitudes. No clear relationship between stimulation frequency and movement frequency was discovered	Huang et al. (2014)
	STN	FOG	60, 130	Measure of stride length	Not able to demonstrate improved gait at either frequency	Phibbs et al. (2013)
	STN	FOG	60, 130	FOG measures	130 Hz stimulation induced severe FOG in 2 patients. Lower frequency (60 Hz) could improve FOG, without change in contacts, voltages and pulse widths	Xie et al. (2012)
	STN	Motor performance	0, 10, 20, 30	Voluntary tapping	20 Hz stimulation appeared to reduce the kinesia time relative to no stimulation compared to 10 and 30 Hz stimulation	Kühn et al. (2009)
	STN	Finger tapping task	0, 5, 10, 20	Repetitive depression of a keyboard task and extensions of the index finger	The range of frequencies investigated can slow distal upper limb movements in patients with PD. 5 and 20 Hz stimulation reduced the tapping rate and increased the coefficient of variation of tap intervals	Eusebio et al. (2008)
	STN	Kinesia time	0, 5, 10, 15, 20, 25, 30, 130	Kinesia time in a tapping task	The effects of stimulation do not simply increase with increasing frequencies. There are relative deteriorations in the 5-10 and 20–25 Hz range	Fogelson et al. (2005)

BFMDRS-M = Burke Fahn Marsden Dystonia Rating Scale Movement score, ET = essential tremor, FOG = freezing of gait, GPi = globus pallidus internus, PD = Parkinson's Disease, QOL = quality of life, RMS = root mean square, STN = subthalamic nucleus, TWSTRS-S = Toronto Western Spasmodic Torticollis Rating Scale severity, VIM = ventral intermediate nucleus of the thalamus.

a 'last resort' treatment possibility in severe clinical depression refractory to other treatments. During ECT and MST generalized seizures are induced under anaesthesia using high-intensity electrical stimulation or rTMS respectively. Both approaches are based on the idea that seizures might have a potential therapeutic effect: they might reset the brain by possible release of norepinephrine and other neurotransmitters (Deng et al., 2015; Keltner and Boschini, 2009). Compared to ECT, MST is not restricted by the high electrical impedance of the skull. Kayser et al. (2011) showed comparable anti-depressant effects of ECT and MST and did not report any side effects, even though cognitive side effects are often associated with the treatment. ECT is highly efficacious in treatment-resistant depression. A meta-analysis showed superior results of ECT compared to placebo stimulation, placebo medication, and different types of anti-depressants (Pagnin et al., 2004).

Even though propagation of ultrasound trough the skull is non-trivial, it is nowadays possible to direct ultrasound to focal areas deeper in the brain by using specially designed transducers. Two types of focused ultrasound (FUS) are nowadays investigated. High-intensity focused ultrasound (HIFU) has been used to irreversibly ablate tissue whereas low intensity focused ultrasound pulsations (LIFUP) can induce reversible neural excitation and inhibition. One of the major advantages of ultrasound is that it can be combined with fMRI, as ultrasound is MRI compatible. Combined with MR techniques, HIFU is increasingly used to treat various types of extracranial soft tissue tumors (Coluccia et al., 2014; Jagannathan et al., 2009) and LIFUP can be used as a neurostimulation device. The influence of stimulation parameters has been investigated (King et al., 2013), but the optimal settings are not known yet.

Another technique that can be used for neurostimulation: optogenetics, was reviewed by LaLumiere (2011). Optogenetics uses light to control the activity of neurons which have been modified to express light-sensitive proteins. Because the light influences only the neurons expressing light-sensitive ion channels, the non-specific effects of electrical stimulation or admission of medication can be overcome. The viral delivery of opsin genes, to generate the light-sensitive neurons, is a hurdle for this technique's clinical use. The light, with particular wavelength, is often administered employing laser techniques combined with a fiber-optic cable that is inserted in the brain region of interest. Optogenetics was defined as 'Method of the year 2010', by Nature Methods (Pastrana, 2011).

5. Discussion on neurostimulation

In this review, the technical aspects of different neurostimulation techniques, which are currently applied in clinical practice, were described with the focus on equipment, electric field modeling, and stimulation protocols. Also a short overview of alternative stimulation techniques was provided.

5.1. Comparison of the different stimulation methods

Neurostimulation techniques aim to become a treatment option for various neurological and psychiatric disorders. Fig. 5 shows a

Table 9
Overview of studies investigating the effects of combinations of stimulation parameters in DBS studies.

Pathology	Animal/human	Position	Investigate effect on	Parameters and values	Parameter of interest	Outcome	Source
PD	Human	STN	FOG	Voltage (3, 3.7 V) and frequency (60, 130 Hz)	Number of freezing episodes and UPDRS	Number of freezing episodes was significantly lower at 60 Hz and 3.7 V. Improvement in the UPDRS was not significant	Moreau et al. (2008)
	Human	STN	Clinical effectiveness in PD	Frequency (10, 50, 90, 130, 170 Hz) and pulse width (60, 120, 210, 450 μs)	Intensity necessary to obtain the disappearance of contralateral wrist rigidity and side effect threshold	Impossible to obtain required clinical effect at 10 and 50 Hz (no matter of the pulse width)	Rizzone et al. (2001)
						Intensity-pulse width curves showed a hyperbolic trend	
Depression	Rats	SCG	Anti-depressant response	Stimulation intensity (100, 200, 300, 400 μA), frequency (20, 130 Hz)	Forced swim test	Strongest response was observed with a current intensity of 200 μA, followed by 100 μA and 300 μA. 400 μA did not produce any effect. Using 200 μA, a frequency of 130 Hz was more effective than 20 Hz	Hamani et al. (2010)
Dystonia	Human	GPi	Neural firing with and without prior high frequency stimulation	Microstimulation frequencies (1–100 Hz) and train lengths (0.5–20 s)	Neural firing rate and evoked field potentials	Post-HFS, overall firing was reduced compared with pre-HFS and the firing and evoked field potential amplitudes were enhanced at low frequencies	Liu et al. (2012)
Epilepsy	Rats	Piriform cortex	Piriform cortex kindled seizures	Intensity (0.25, 1, 3 ADT), pulse width (0.01, 0.1, 1, 10 ms), train duration (1, 15 min), state of the rat (fully kindled, during kindling acquisition)	ADT	There is a complex relation between stimulation patterns and effect on kindled seizures	Ghorbani et al. (2007)
HV	Swine	thalamus	Neural network activation	Frequency (10, 130 Hz) and intensity (3, 5, 7 V)	BOLD activation maps	Stimulation frequency and voltage combinations modulated the brain network activity differently in the sensorimotor cortex, the basal ganglia and the cerebellum in a parameter dependent manner 130 Hz generated a negative BOLD response in the motor cortex, while 10 Hz increased the positive BOLD response	Paek et al. (2014)
Tremor	Human	Thalamus	Intentional tremor	Frequency (0, 10, 120–150 Hz), tremor type (intentional versus postural), electrode position	TRS and ultrasound-based tremor-amplitude measurements	Lowest scores for TRS were achieved under 120–150 Hz stimulation, while 10 Hz showed the highest scores	Pedrosa et al. (2013)
						Ratio of tremor amplitude between 0 and 10 Hz stimulation was lower for intentional tremor compared to postural tremor The more ventral the electrodes were placed, the higher the influence on the intentional tremor amplitude during 10 Hz stimulation. No influence was found on the postural tremor	
	Human	VIM	Tremor suppression	Frequency (0, 30, 45, 60, 75, 90, 100, 130, 145, 185 Hz) and tremor type (intentional versus postural)	Tremor frequency and amplitude	130 Hz is the optimal stimulation frequency	Earhart et al. (2007)
						Tremor frequency did not change with stimulation frequency. The amplitude however, decreased with increasing frequency (for postural tremor only until 130 Hz). The effect on postural tremor was bigger than on intentional tremor	

ADT = after discharge threshold, BOLD = blood oxygen level dependent, FOG = freezing of gait, GPi = globus pallidus internus, HFS = high-frequency stimulation, LFS = low-frequency stimulation, PD = Parkinson's disease, SCG = subcallosal cingulate gyrus, STN = subthalamic nucleus,TRS = tremor rating scale, UPDRS = Unified Parkinson's Disease Rating Scale, VIM = ventral intermediate nucleus of the thalamus.

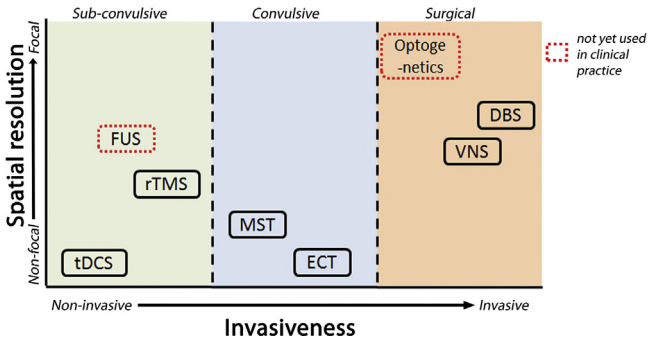

Fig. 5. Invasiveness versus spatial resolution of different neurostimulation techniques.
Invasiveness versus spatial resolution for the different stimulation techniques described in this review. The techniques in the red boxes are not yet used in clinical practice. This plot is adapted from Deng et al. (2015).

schematic overview of the invasiveness versus the focality of the different stimulation techniques treated in this review.

On the one hand, the non-invasiveness of TMS and tDCS might be beneficial, especially from a patient's perspective. On the other hand, invasive stimulation techniques require only a single surgical procedure, though with a relatively high burden, whereafter the stimulation will continue for the duration of the battery lifetime without additional interventions for the patient. A battery replacement surgery is necessary every couple of years. Battery lifetime depends on the type of neurostimulator and the stimulation protocol, with more stimuli and higher intensities decreasing the battery lifetime. The average battery life for VNS is now 8-10 years (Ben-Menachem, 2012) and for DBS in for example epilepsy approximately 2.5 years. RNS will be even more battery efficient, since in this case stimuli are only applied if necessary (Vonck and Boon, 2015).

The invasive neurostimulation techniques DBS and VNS outperform the less invasive techniques in terms of spatial resolution. New stimulation techniques, such as FUS and optogenetics are investigated to improve the focality of the stimulation even further.

VNS is the technique that is performed with the least variability when it comes to choices of stimulation parameters: the position of stimulation is fixed and a standard protocol is often used. TMS, tDCS, and DBS are performed along a broader range of stimulation parameters. Table 10 gives an overview of the characteristics of the neurostimulation techniques TMS, tDCS, DBS, and VNS.

An extensive description of the current knowledge of the mechanisms of action was beyond the scope of this review. Although the mechanisms of action differ, there is overlap in the clinical effects of different stimulation techniques. Both DBS and VNS are used as a treatment for epilepsy and nowadays also TMS and tDCS are investigated for that pathology. Fox et al. (2014) investigated diseases treated with both invasive and non-invasive neurostimulation techniques. An important finding was that sites where DBS was effective were functionally connected to sites where non-invasive brain stimulation was effective. This suggests that the effect of non-invasive stimulation extends in the brain along the functional network comprising the stimulation position. In this way, it should in principle be possible to also, indirectly, target deeper brain regions with non-invasive stimulation techniques. Whether it is possible to achieve similar results with invasive and non-invasive stimulation techniques in the future remains to be resolved.

In line with the abovementioned findings, it might be possible to predict the outcome of invasive neurostimulation with non-invasive stimulation techniques. However, to be able to quantify this prediction, more information about the individual mechanisms should be available.

5.2. Current clinical practice

As can be seen in Tables concerning the stimulation parameters (Tables 2–6, 8 and 9), a lot of research is dedicated towards pathologies such as Parkinson's disease, depression, migraine and epilepsy. Not only the information about the type of neurostimulation is important, but also the information about the pathology to be treated. Connectivity analysis can provide insight into networks that might be disturbed in certain pathologies (Besseling et al., 2013; Vaessen et al., 2012; Veer et al., 2010). Also, combined TMS-EEG recordings can provide additional information about pathologies and the cortical excitability (e.g. Shafi et al., 2015). The optimal stimulation position can be determined by the location in the brain that is affected, for example the DLPFC in depression, or as a position that is involved in a specific pathology, such as the ANT in epilepsy. Because the effect of the different stimulation parameters are not known yet, optimization of the stimulation protocol per patient is currently performed based on trial-and-error (McIntyre et al., 2004a).

If a patient is eligible for neurostimulation, the first choice is the neurostimulation method: for example TMS, tDCS, VNS, or DBS. The type of neurostimulation that fits best to an individual patient is not known. Important to emphasize is that there is not a single neurostimulation method that is optimal. The optimal method depends on the specific factors, such as the patient's pathology. The choice of neurostimulation method is currently often driven by the treating hospital, which is often specialized in certain techniques.

In TMS, the exact positioning of the stimulation coil can be determined during the performance of the protocol by means of neuronavigation (Bashir et al., 2011). It is, however, important, that clinicians are able to interpret the depicted fields by neuronavigation systems correctly. The current navigation systems show the electric field induced by the TMS coil overlaid on the patient's MRI using simple models. No patient-specific geometry is taken into account, so the neuronavigation only provides a global idea of the real stimulation position. Another important point that needs attention is that neuronavigation only shows the estimated electric fields in the brain. Due to the fact that the orientation of neurons with respect to the electric field plays an important role for stimulation, the modeled electric field is not necessarily the same as the region of the brain that is really activated. A recent study by De Geeter et al. (2015) embedded realistic models of neuron tracts in the model, computed from DTI. Moreover, activation of axons during extracellular stimulation is rather complex. The threshold for activation varies with axon diameter, orientation and curvature, and it is not known what sizes of axons are responsible for therapeutic effects and side effects during stimulation (Aström et al., 2015). So at this point, the use of neuronavigation is mostly important to get a global idea of the affected location in the brain and to guarantee stimulation of a particular position during a long or longitudinal stimulation protocol.

5.3. The future of neurostimulation

It can be concluded that much research is going on in all directions within the field of neuromodulation. To really make a big step forward into the clinical implementation of neurostimulation, the research focus should be on exploring the mechanisms of action, the effect of the different stimulation parameters, and the effect of external factors such as the cortical excitability state. There is a lot of debate about which scale is the most appropriate to investigate this issue. Some state that a very small, neuron-size, resolution should be used. Patch clamp techniques can be used to

Table 10
Overview of the characteristics of TMS, tDCS, DBS, and VNS.

	TMS	tDCS	DBS	VNS
Invasiveness	Non-invasive	Non-invasive	Invasive	Non-invasive or invasive
Administration	In hospital/healthcare center	Mostly in hospital/healthcare center Portable tDCS devices are currently available	Implantation in hospital, then via duty cycle	Implantation in hospital, then via duty cycle
Patient-interference possibility	No	No	No	Yes, with a magnet
Device	Coil	Electrode patches	Depth electrode	Cuff-electrode
Device position	Depends on pathology	Depends on pathology	Depends on pathology	Surrounding vagus nerve
Stimulation types	spTMS and ppTMS to study brain behavior, rTMS for therapeutics	tDCS, tACS, tRNS (see Table 7)	Not applicable	Not applicable
Stimulation frequency	Depends on pathology: —<1 Hz: inhibitory stimulation —>5 Hz: excitatory stimulation	Not applicable, constant current for approximately 20 min	Most often 130 Hz but also sometimes 60 Hz	20–50 Hz
Duty cycle	Not applicable	Not applicable	Standard 5 min off, 30 s on	Standard 5 min off, 30 s on
Duration of the stimulation protocol	Multiple days, optimal number of sessions per day and duration per session not known	Multiple days, optimal number of sessions per day not known, duration of session approximately 20 min	Battery lifetime	Battery lifetime
Sustainability therapeutic effect	Not known	Not known	Battery lifetime, might extend beyond the battery lifetime	Battery lifetime
Stimulation intensity	Percentage of patient specific MT	0.5–2 mA	1–5 V	0.25-3.5 mA
Mechanism of action	Neuroplasticity	tDCS, tACS, tRNS (see Table 7)	Neuroplasticity	Branches of vagus nerve project to important brain structures

measure neurophysiology on single cell level (Beurrier et al., 2014; Loddenkemper et al., 2001). Patching of connected pairs can nowadays also be used to investigate synaptic behavior. Others state that brain function is not encoded in single neurons and propose the use of larger scale analyses. The concept that the brain is organized in networks is nowadays generally accepted (Bassett and Bullmore, 2009; Bullmore and Sporns, 2009).

More detailed knowledge about the mechanisms of action might be helpful to predict best candidates for specific types of neurostimulation and to predict their responses (Vonck and Boon, 2015). Even though neurostimulation is only offered in case of medication resistivity, it might be possible that a combination of pharmacological interventions with neurostimulation will become able to treat various patients (Vonck and Boon, 2015).

Up till now, electric field modeling is used for research purposes to gain a better understanding of the mechanisms of action. In the future, modeling might become helpful in determining the optimal stimulation parameters. For example now, the intensity in TMS protocols is most commonly derived from the patient's specific MT. In the future, it might become possible to delineate a target in the brain and derive the appropriate stimulation intensity, and the coil position, more accurately from subject-specific simulations.

SimNIBS (simulation of non-invasive brain stimulation, www.simnibs.org, (Thielscher et al., 2015)), is an example of an easy to use, linux-based, free downloadable tool to simulate electric fields induced by TMS and tDCS. Many coil types that are often used in clinical practice are included in SimNIBS, such that the user only needs the MR images, the coil position and orientation, and the stimulation intensity as input. The accurate calculation of the electric field is time consuming, with the longest step being the calculation of the patient-specific head mesh. To our knowledge, there are no existing easy to use toolboxes that can be used to simulate the electric fields induced by DBS. FEMLAB (Comsol, Inc., Burlington, MA) might be used to perform finite element calculations. However, the implementation of the electric field calculations require detailed knowledge about the stimulation device and the brain and is a highly challenging technical task.

Modeling studies are hard to validate since it is impossible to measure the electric fields in situ so a gold standard is not available. One way to quantify the accuracy of the models is to stimulate parts of the brain that evoke a response that can directly be measured, such as the corticospinal tract. Presumably, the addition of the position- and direction-specific conductivity values to the models will improve the spatial resolution of the electric field in the brain. However, there are still uncertainties in the models for example concerning the exact values of the conductivity and permittivity of different brain regions, and also their dependence on the stimulation frequency (Thielscher et al., 2015). Important to note is that the electric field models are currently only used for research purposes. So even though electric field models can improve the insights of brain stimulation, they cannot be used in clinical practice yet.

The sustainability of the therapeutic effects of TMS and tDCS need further exploration. Since these two types of neurostimulation are mainly applied in hospitals or healthcare environments, it is important that the therapeutic effects are long-lasting. In the future, self-delivery of non-invasive stimulation by the patient in a home environment, ideally according to a patient-specific stimulation protocol, may be a crucial step to really use TMS or tDCS as a therapeutic tool. Even if there is a sustainable effect of TMS or tDCS, these effects will not last forever so in both cases repeated sessions are necessary to keep the therapeutic outcome. A home-based, portable, device should incorporate features that make sure the stimulation is applied to the right position in the brain, for example a patient-specific cap positioning the TMS coil to the right position,

or including the tDCS electrodes at the right spot (Wagner et al., 2007). In migraine, a portable TMS system has already been tested with positive results (Lipton and Pearlman, 2010). tDCS equipment is simpler and smaller compared to TMS equipment. Portable tDCS equipment is commercially available (for example by Magstim Company Limited, Wales, UK).

So in conclusion, it is challenging to predict the future of neurostimulation. The answers to many remaining questions will eventually determine what different stimulation techniques will mean in a couple of years and how they will be implemented in clinical practice. The positive outcome of neurostimulation in some cases is actually a major motivation to investigate stimulation in more detail to hopefully increase the knowledge about what is really happening after neurostimulation, to fine-tune the protocols, and to increase the number of positive outcomes.

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