

**DOPAMINERGIC IMPACT ON EXTERNAL BRAIN
STIMULATION-INDUCED NEUROPLASTICITY IN HUMAN
MOTOR CORTEX**

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ABSTRACT

Dopamine (DA) is involved in learning and memory formation, which are thought to depend on synaptic modifications like long-term potentiation (LTP) and long-term depression (LTD). Despite huge efforts to unravel the dopaminergic impact on these functions, the respective knowledge is still far from being complete. This might especially be due to the neuromodulatory impact of DA on cortical function, i.e. DA might affect cortical excitability and plasticity differently, dependent on DA dosage, DA sub-receptors, and the focality of plasticity induced, amongst others. The aim of the present thesis, which contains three studies, was to explore the impact of DA on cortical plasticity in healthy humans into larger detail. Specifically, we sought to determine if the multiple modes of action of DA on neuroplasticity depend on sub-receptor specificity, concentration level and type of plasticity. In all experiments the primary motor cortex served as a model system, and plasticity was monitored by motor evoked potential (MEP) amplitudes via transcranial magnetic stimulation (TMS). Focal plasticity was induced non-invasively by paired associative stimulation (PAS), while non-focal plasticity was generated by transcranial direct current stimulation (tDCS). In the first study we explored the impact of D1 receptor activity on plasticity. Here, shifting the balance of DA activation in direction of D1 by D2 block abolished non-focal plasticity and focal inhibition. Further enhancing D1 activity by adding L-dopa under D2 block re-established all kinds of plasticity. In concordance with animal experiments, the results favor an important impact of D1 receptor activity on neuroplasticity in humans. In the second study, in order to reveal if DA receptor activation exerts a non-linear dose-dependent effect on cortical plasticity, we explored the impact of different dosages of L-dopa on tDCS-induced plasticity. In accordance, the results show a nonlinear dosage-effect relation of dopamine receptor activation on plasticity, resulting in a 'U'-shaped dose-response curve for anodal tDCS and in an inverted 'U'-shaped dose-response curve for cathodal tDCS. The results are pinpointing to the importance of a specific dosage of dopamine optimally suited to improve plasticity. In the third study, we combined different doses of the D2/D3 dopamine agonist ropinirole (RP) with focal and non-focal plasticity induction in order to determine if the nonlinear effect of DA on plasticity depends on sub-receptor specificity and the kind of plasticity induced. D2-like receptor activation produced an inverted 'U'-shaped dose response curve on plasticity for facilitatory tDCS and PAS and for inhibitory tDCS. However, no dose-dependent response effect of D2-like receptor activation was evident for iPAS. The results of this study support the assumption that modulation of D2-like receptors exerts a dose-dependent non-linear effect on neuroplasticity in the human motor cortex, which differs for the type of plasticity induced. In summary, our results demonstrate that the dopaminergic influence on cortical plasticity (a) is specific for DA sub-receptors, and (b) is dosage-dependent. They furthermore demonstrate that (c) the effect differs for the specific kind of plasticity induced, and (d) suggest that the focusing effect and the stabilizing effect of DA on plasticity depends on the interaction of dopaminergic subreceptors. These results might be important for the therapeutic application of dopaminergic agents, especially for rehabilitative purposes, and explain some opposing results of former studies.

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LIST OF ABBREVIATIONS

AADC	L-amino acid decarboxylase
AMPA	α -amino-3-hydroxy- 5-methyl-4-isoxazolepropionic acid
cAMP	Cyclic adenosine monophosphate
CNS	Central nervous system
DA	Dopamine
DC	Direct current
ePAS	Excitatory paired associative stimulation
iPAS	Inhibitory paired associative stimulation
ISI	Inter-stimulus intervals
GABA	Gamma-aminobutyric acid
L-dopa	3,4, dihydroxyphenylamine
LTD	Long-term depression
LTP	Long-term potentiation
MEP	Motor evoked potentials
NMDA	N- methyl d-aspartate, a glutamate receptor subtype
PAS	Paired associative stimulation
PLC	Placebo
RP	Ropinirole
rTMS	Repetitive transcranial magnetic stimulation
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
TH	Tyrosine hydroxylase

INTRODUCTION

One of the most fascinating properties of the mammalian brain is its ability to react dynamically to environmental demands, i.e. to learn and memorize appropriate reactions. The neurophysiological foundation for this ability is called neuroplasticity, which refers to the property of neuronal networks to re-organize structurally and functionally by strengthening or weakening synaptic connections, or growing new or removing spines (for a review, see Citri and Malenka, 2008). Through these neuroplastic modulations, the brain is able to compensate for injuries and diseases and to adjust its activities in response to new situations or changes in its environment. Therefore, over the last decades, the topic of neuroplasticity has been the subject of great interest to neuroscientists for offering insights into the function of brain networks. The synaptic modifications underlying the most models of learning and memory, long-term potentiation (LTP) and depression (LTD), have been the main focus of plasticity research. LTP and LTD-like plasticity has been studied in a variety of animal models to learn more about the neuronal basis of learning and memory, and to ultimately link neuroplasticity to cognition on the macroscopic level. Moreover, direct studies of such long-term plastic changes in humans are now possible by means of advanced non-invasive technologies, such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS) and paired associative stimulation (PAS) (for a review, see Cooke and Bliss, 2006). These techniques have been demonstrated to be effective to induce plasticity in the human cortex, and therefore offer the opportunity to improve our understanding of cortical plasticity in humans.

Dopamine (DA) is known as one of the major factors regulating cortical excitability and plasticity in animals and humans. However, despite considerable advances in the understanding of the physiology, biochemistry, molecular biology, and anatomy of the DA system, the complex interaction of DA activity on synaptic plasticity is far from being completely understood. Opposing effects of DA modulation on synaptic activity at the cellular level and on cognition in both animal and human experiments (Chen *et al.*, 1996; Jay, 2003; Seamans and Yang, 2004) demonstrate the complex action of DA on central nervous system (CNS) function. The multiple modes of action of DA on neuroplasticity depend on various factors, such as sub-receptor specificity, concentration level, basal brain activity, kind of plasticity induced, amongst others (Millan *et al.* 2002; Centonze *et al.*, 2003; Seamans and Yang, 2004; Collins *et al.*, 2005; Nitsche *et al.*, 2006; Kuo *et al.*, 2008), making it difficult to foresee DA effects. Also, clinically, DAergic pharmacotherapy on neuropsychiatric disorders encounters limitations such as unexpected adverse effect or inconsistent outcome, which is probably associated with the heterogeneous pattern of DA action on CNS function (Kulisevsky, 2000; Obeso *et al.*, 2000; Kaiser *et al.*, 2002; Paulus and Trencwelder, 2006).

A more complete understanding of DA action on neuroplasticity might have important implications for the future treatment of patients with dopaminergic dysfunction, accompanied by cognitive disturbances, e.g., patients with Parkinson's disease or schizophrenia. Despite extensive contribution of animal and slice experiments to the knowledge of the relationship of DA and plasticity, its extrapolation to humans is limited because of the multitude of influences which determine the effects of DA on CNS function. In the present thesis, we aimed to enhance our understanding about the impact of the DA system on neuroplasticity directly in humans. Prior studies have already shown an important contribution of dopamine on plasticity in humans. It was demonstrated that

L-dopa prolongs focal facilitatory plasticity, but turns non-focal facilitatory plasticity into inhibition, and thus has a focusing effect on facilitatory plasticity (Kuo *et al.*, 2008).

Moreover it was shown that D2-receptor activity is essential for stabilizing non-focal inhibitory plasticity (Nitsche *et al.*, 2006). The specific aim of the current thesis was to explore further the impact of DA on cortical plasticity in humans, with a special emphasis on (a) dopaminergic sub-receptors, and (b) dosage-related effects.

The current thesis contains three chapters. In chapter 1, we give a brief introduction of the background of research. Chapter 2 represents the main component of the thesis, consisting of published or submitted manuscripts of which the specific objectives will be briefly introduced below. Finally, the last chapter gives a summary of the present PhD study, concluding remarks and an outlook to the intended future research.

CHAPTER 1

1. Central nervous system plasticity

1.1 Overview and plasticity in animals

Over the past decades, an enormous amount of research has revealed that the brain never stops changing and adapting. This revolutionary discovery, encompassing neuroplasticity, overthrew the centuries-old notion which hold the statement that brain structure and function is fixed in two ways: 1) no new neurons can appear after birth and 2) the functions of the structures of nervous system are permanently stable (for review see Doidge, 2007). Nowadays it is known that the brain is a plastic organ that can change its structure and function adjusting to new experiences or environmental alterations. These changes in the cerebral cortex have mainly been studied (1) as modifications of sensory or motor cortical representation of body parts (representational or map plasticity); and (2) as changes in the efficacy of existing synapses or generation of new synapses (neuronal or synaptic plasticity) (Boroojerdi *et al.*, 2001).

Representational plasticity is expressed as change of cortical areas following peripheral or central alteration of inputs and in response to behavioral relevant experience. For example, in the motor system, this form of plasticity has been observed following amputation, lesion in the motor cortex, training of a task, etc.

Synaptic plasticity encompassing modifications of synaptic transmission, which will be the focus of the present thesis, is one of the major mechanisms by which neural activity generated by an experience modifies brain function (Citri and Malenka, 2008).

Synaptic transmission can be either enhanced or depressed by cortical activity depending on correlation between pre- and postsynaptic firing. The most prominent long-lasting forms of plasticity observed at synapses are: LTP and LTD. LTP and LTD represent, respectively, a durable increase or decrease of synaptic strength involving several molecular regulating processes such as the expression of glutamatergic receptors. LTP and LTD have been suggested to represent neurophysiological correlates of learning and memory as well as many other forms of experience-dependent plasticity (Malenka and Bear, 2004). Both forms of synaptic plasticity have been studied in a variety of species, ranging from mice (Nosten-Bertrand *et al.*, 1996) to monkeys (Urban *et al.*, 1996), and at a number of different synapses throughout the CNS, from the cerebral neocortex (Fox, 2002) to the spinal cord (Ji *et al.*, 2003).

Understanding the factors which may influence brain reorganization has been the goal of considerable research. A large number of experimental studies have shown that the activation of N-methyl-D-aspartate (NMDA)-type glutamate receptors is an important prerequisite for plasticity (for a review see Yashiro and Philpot, 2008). A classical model of long-term synaptic plasticity assigns a regulatory role to NMDA receptors. During synaptic activity, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor-mediated depolarization of the postsynaptic membrane facilitates activation of NMDA receptors, which initiate Ca^{2+} -dependent signaling pathways that modulate the surface insertion and activity of AMPA receptors. These changes of AMPA receptors at the postsynaptic membrane cause changes in synaptic strength, i.e. LTP and LTD, which depend on the amount of the postsynaptic increase of calcium concentration. Whereas a relatively low enhancement of calcium concentration results in a weakening of synaptic connections, i.e. LTD, a large calcium increase generates LTP (Lisman, 2003; Rao and Finkbeiner, 2007). Thus, NMDA receptors are an essential part of the cellular

mechanisms required for the induction of LP and LTD. Consequently, these have also shown to be involved in learning and memory formation (Morris, 2003; Malenka and Bear, 2004; Rioult-Pedotti *et al.*, 2000; 2007). It has also been shown that neuromodulators can affect NMDA receptor-dependent plasticity (Gu, 2002). Several transmitter systems, such as acetylcholine, noradrenaline, serotonin, histamine and dopamine have so far been identified as playing an important role in neuroplastic changes. Available evidence suggests that neuromodulators affect plasticity via modification of the excitability of cortical neurons, enhancement of the signal-to-noise ratio of cortical responses, and modulation of the threshold of activity-dependent synaptic modifications (Gu, 2002). Below, we will give a brief overview of the involvement of the neuromodulator dopamine in neuroplasticity.

1.2 Neuroplasticity in humans

In recent years, neuroplasticity and its mechanism have been explored in some detail in humans. Here, plasticity has been shown to play a key role not just in the normal process of learning, memory and adaptation, but also in response to CNS injuries or disease (for a review, see Boller 2004). Thus, elucidating the details of functional relevance and mechanisms of plasticity is critical for understanding many aspects of normal and pathological brain function and terminally might support the development of efficient strategies for treatment of several brain disorders. Therefore, the underlying basis of cortical plasticity has been extensively investigated in animals and humans. Animal studies have provided insights into the cellular and molecular events essential to plastic processes, while in humans, insights into neuroplastic mechanisms have largely been at the physiological or behavioral level. However, until some years ago, it was a

challenging task to study the functional role of synaptic plasticity and its mechanisms in humans. Two main branches of research can be identified:

Pharmacological studies have provided insights into neuroplastic mechanisms in humans by using CNS active drugs that interfere with specific mechanisms of plasticity. For example, it was shown that use-dependent plasticity is substantially reduced by the NMDA receptor antagonist dextrometorphan and the gamma-aminobutyric acid (GABA) agonist lorazepam (Buonomano and Merzenich, 1998; Bütefisch *et al.*, 2000) suggesting that NMDA receptor activation and GABAergic inhibition are involved in this kind of plasticity, confirming previous evidence *in vitro* (Hess and Donoghue, 1994; Hess *et al.*, 1996).

In addition, recently, with technological advances such as non-invasive stimulation techniques, LTP and LTD-like synaptic modifications can be directly induced in the human cerebral cortex and thus have driven important discoveries for the understanding of brain function. Non-invasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS), tDCS and PAS, enable us to modulate brain functions in awake human subjects in a painless and reversible manner. In the past decades, these techniques have been increasingly applied to improve our understanding of motor cortex physiology and plasticity (for a review, see Wagner *et al.*, 2007). In the current thesis, we performed TMS to monitor motor cortex excitability and tDCS and PAS to selectively induce plasticity in the human brain.

1.2.1 Transcranial magnetic stimulation (TMS)

Since its introduction in 1986 by Anthony Barker, TMS has been a valuable tool in modern neurophysiology research because it can be applied (1) to monitor various

aspects of cortical excitability with different stimulation protocols, and (2) to interfere actively with brain function inducing neuroplastic changes in specific brain regions (Pascual-Leone *et al.*, 2000; Terao and Ugawa, 2002; Rossini and Rossi, 2007).

TMS is a painless and non-invasive technique and is considered of low risk for research in humans. TMS uses the basic principle that electrical current can excite excitable cells like neurons. Its application involves a short strong electrical current that when delivered through an insulated coil of wire placed over the scalp, induces a magnetic field that generates an electrical current in the tissue of sufficient magnitude to depolarize neurons. In basic and clinical neurophysiology, depending on aim, TMS can be used for the induction of single stimuli, pairs of stimuli separated by different intervals (to the same or to several brain areas), or trains of repetitive stimuli at various frequencies to investigate and modulate cortical plasticity. By single-pulse TMS, as used in the current thesis, it is possible to study the function of motor pathways in healthy subjects and in patients with neurologic disorders. When a single stimulus is applied to the motor cortex at appropriate stimulation intensity, motor evoked potentials (MEP) are elicited. Given that the peripheral nervous system is functioning normal, MEP amplitude and latency reflect the integrity of the corticospinal tract. Specifically MEP latency indicates CNS conduction velocity, while MEP amplitude serves as index of corticospinal excitability (Rothwell, 1993). In addition, specific TMS protocols such as paired-pulse TMS for eliciting intracortical facilitation, inhibition, and I-wave facilitation, as well as input-output curves (Ziemann and Rothwell, 2000) provide sophisticated recordings of cortical circuits and are used to specify the functional state of cortical sub-systems. Moreover, TMS is also able to induce cortical plasticity in humans. When applied repetitively—repetitive transcranial magnetic stimulation (rTMS)—TMS can generate plastic modifications of cortical excitability. Depending on stimulation parameters, rTMS

decreases or increases excitability of neural structures under the stimulating coil (Pascual-Leone *et al.*, 1998).

1.2.2 *Transcranial direct current stimulation (tDCS)*

In recent years, a technique of brain stimulation that seemed long forgotten has received renewed attention, that is transcranial direct current stimulation. In animal experiments, the capability of direct current (DC) stimulation to elicit cortical excitability and activity changes has been known for some time (Terzuolo and Bullock, 1956; Creutzfeldt *et al.*, 1962; Bindman *et al.*, 1964; Purpura and McMurtry, 1965). Here, depending on DC polarity, neuronal firing rates increase or decrease, presumably due to DC induced changes of the resting membrane potential: Anodal stimulation of the rat sensorimotor cortex induced long-lasting increases in the negative wave amplitude of sensory-evoked potentials and spontaneous discharge rates, while cathodal stimulation resulted in reverse effects (Bindman *et al.*, 1964). These shifts were stable at least for some hours after the end of stimulation. Further animal experiments revealed some of the mechanisms that lead to these effects. In histological studies, anodal stimulation modified intracellular cAMP level dependent on noradrenaline and increased the intracellular calcium level as well as early gene expression, the latter was suggested to be NMDA receptor-dependent (Hattori *et al.*, 1990; Islam *et al.*, 1995).

Recently, by application of weak direct currents through the scalp, DC stimulation has also been successfully applied in humans to elicit cortical excitability and activity shifts during, and after the end of stimulation in a painless and reversible way (Nitsche and Paulus, 2000; Nitsche *et al.*, 2007). Here, in accordance with previous animal experiments, anodal stimulation of the motor cortex enhances excitability, while

cathodal stimulation reduces it (Nitsche and Paulus, 2000, 2001; Nitsche *et al.*, 2003b, 2004b). The amplitude and endurance of stimulation effects are current intensity and stimulation duration dependent. DC can cause excitability changes for a short time during stimulation, but if applied sufficiently long, it induces after-effects stable for several minutes or hours after the end of stimulation. In humans, the minimal duration of tDCS to induce after-effects is 3 min (Nitsche and Paulus, 2000). Prolongation of stimulation duration proportionally increases after-effect duration (Nitsche and Paulus, 2000, 2001; Nitsche *et al.*, 2003a). The efficacy of tDCS in eliciting after-effects is not restricted to the human motor cortex. Effective alterations of somatosensory and visual systems (Matsunaga *et al.*, 2004; Antal *et al.*, 2006), as well as prefrontal functions (Nitsche *et al.*, 2003c; Kincses *et al.*, 2004; Fregni *et al.*, 2005) can also to be elicited by tDCS over the respective areas.

As suggested by pharmacological studies, the effects during a short-lasting tDCS, which elicits no after-effects, are probably solely due to shifts in neuronal resting membrane potential. Indeed, the primary effect of anodal tDCS during stimulation was prevented by blocking sodium or calcium channels (Nitsche *et al.* 2003b). In contrast, synaptic mechanisms seem not to contribute to the during-tDCS effects, since application of the NMDA receptor-antagonist dextromethorphan, the GABA-agonist lorazepam and the monoaminergic reuptake-blocker amfetaminil did not influence the tDCS-induced excitability shift (Nitsche *et al.*, 2003b; 2004a; c). However, the endurance for minutes beyond the end of stimulation critically depends on membrane potential changes, but has been demonstrated to involve also modulations of NMDA receptor efficacy, since blocking NMDA receptors by dextromethorphan abolishes any after-effects of stimulation (Liebetanz *et al.*, 2002; Nitsche *et al.* 2003b).

1.2.3 Paired associative stimulation (PAS)

Paired associative stimulation (PAS) is another non-invasive neuroplasticity-inducing stimulation tool. It produces plasticity in the sensorimotor cortex by combining peripheral nerve stimulation with motor cortex TMS (Stefan *et al.*, 2000). It was shown that the direction of plastic effects induced by PAS specifically depends on the inter-stimulus interval (ISI). With an ISI of 25 ms, the sensory input elicited by peripheral stimulation reaches the motor cortex simultaneously with the TMS stimulus delivered directly to the motor cortex, and elicits a long-lasting cortical excitability enhancement (Stefan *et al.*, 2000). The resulting simultaneous activation of a postsynaptic neuron delivered by conjoint afferent inputs has been shown to induce LTP also in animals (Baranyi *et al.*, 1991; Hess and Donoghue, 1994). In the case of 10 ms ISI, however, the afferent stimulus reaches the respective motor cortical neurons relevantly later than the TMS stimulus. This a-synchronous activation has been shown to induce LTD-like effects (Wolters *et al.*, 2003), similar to a-synchronous stimulation in animals (Zhang *et al.*, 1998). Thus PAS shares some features with spike-timing-dependent synaptic plasticity. This kind of plasticity may reflect neurophysiological foundations of learning processes. Indeed, a close relationship between motor learning and the amount of PAS-induced excitability-enhancing plasticity has been demonstrated (Ziemann *et al.*, 2004; Stefan *et al.*, 2006).

1.2.4 Similarities and differences between PAS and tDCS

In recent years, tDCS and PAS have been proposed as LTP and LTD-like plasticity-inducing protocols for use in human experimentation (Stefan *et al.*, 2000; Paulus and Nitsche, 2001; Nitsche *et al.*, 2003a; Wolters *et al.*, 2003). Both protocols

accomplish long-lasting, NMDA receptor- and calcium-channel-dependent excitability changes (Liebetanz *et al.*, 2002; Stefan *et al.*, 2002; Nitsche *et al.*, 2003b). The main difference between these tools lies in the synapse-specific focal effects of PAS, whereas the plasticity induced by tDCS is relatively nonfocal and not synapse-specific. DC stimulation has been shown to modify cortical excitability under the whole area covered by the stimulation electrode, and is not restricted to sub-sets of synapses (Purpura and McMurtry 1965; Nitsche *et al.*, 2007). In contrast, the plasticity induced by PAS is thought to be restricted to the intercortical connections between the somatosensory and motor cortex (Stefan *et al.*, 2000)

2. The dopamine system

Since its discovery as a neuromodulator by Arvid Carlsson approximately 50 years ago (Carlsson, 1959), dopamine is a subject of great interest to neuroscientists for being involved in (1) cognitive functions such as learning and memory formation, which likely depend on neuroplastic processes such as LTP and LTD; and (2) in the pathophysiology and treatment of several neuropsychiatric disorders (for a review, see Iversen and Iversen, 2007).

DA is synthesized from tyrosine, an amino acid, in DA neurons where it is stored in vesicles and protected from oxidation. Tyrosine crosses the blood brain barrier and is converted into 3, 4-dihydroxyphenylalanine (L-dopa) by the enzyme tyrosine hydroxylase (TH) in catecholaminergic neurons, the L-amino acid decarboxylase (AADC) converts L-dopa into dopamine (Molinoff and Axelrod, 1971). In response to an action potential, DA is released into the synaptic cleft and extracellular space. Once

release, DA interacts with two classes of dopamine receptors, D1- (D1 and D5) and D2-like (D2, D3 and D4) receptors, localized at the postsynaptic neuron as well as with autoreceptors at the presynaptic neuron (Missale *et al.*, 1998; Vallone *et al.*, 2000). It has been postulated that dopamine can have opposing functional effects depending on the activated receptor type.

Despite huge efforts to unravel the dopaminergic impact on cortical activity and plasticity, knowledge is still far from being complete. This might especially be caused by its neuromodulatory function. Dopamine has been shown to influence cortical excitability, plasticity, and cognitive functions antagonistically, dependent on not only sub-receptor activation, but also on concentration level, cortical area under study, and type of cognitive function, amongst others (for an overview see Seamans and Yang 2004).

3. Dopamine and plasticity

3.1 Dopaminergic effects on plasticity - animal data

DA is closely linked to various CNS functions (Seamans and Yang, 2004). Functionally, dopamine plays a key role in working memory performance and in the acquisition, stabilization and retrieval of long-term memory (Brozoski *et al.* 1979, Seamans *et al.* 1998). Hereby, dopaminergic stimulation can either facilitate or inhibit cognitive performance (Floresco and Phillips 2001).

The physiological basis of these functional DA effects is complex. For its impact on cortical activity, and excitability, it was shown that dopamine might elicit

opposing effects. In cortical neurons, a prominent effect of iontophoretic application of DA is to depress neuronal activity (Krnjević and Phillis, 1963; Bevan *et al.*, 1978). Also, in the visual cortex, iontophoretic application of dopamine reduced the firing of a majority of neurons stimulated by flashes of light (Reader, 1978). However, dopamine-induced excitation of cortical neurons has also been reported (Bevan *et al.*, 1978). It is now clear that dopamine cannot be thought of as simply excitatory or inhibitory in CNS, but rather as a neuromodulator of excitatory corticostriatal responses, at both presynaptic and postsynaptic levels. It is postulated that DA effects are dependent on the membrane potential of a neuron, i.e. DA might have opposite effects at high and low activity levels of neuronal networks (Surmeier and Kitai, 1997). DA is hypothesized to be suppressive at hyperpolarized membrane potentials and facilitatory and positive membrane potentials (for review see Seamans and Yang, 2004).

With regards to the dopaminergic impact on neuroplasticity, animal experiments have appointed to its influence on synaptic plasticity in various parts of the brain such as the striatum (Kreitzer and Malenka, 2005; Kung *et al.*, 2007), hippocampus (O'Carroll *et al.*, 2006) and prefrontal cortex (Otani *et al.*, 1998; 2003; Seamans and Yang, 2004). In rat prefrontal cortex, the induction of LTD and LTP of glutamatergic synapses is powerfully modulated by dopamine (Otani *et al.*, 1998, 2003). This finding supports the possibility that dopamine may, like other neuromodulatory transmitters, be able to promote neuronal plasticity in the cerebral cortex. The specific dopaminergic impact on neuroplasticity seems to depend on sub-receptor specificity: animal experiments revealed that the D1-receptor activation prolongs LTP and LTD (Bailey *et al.*, 2000; Gurden *et al.*, 2000; Huang *et al.*, 2004), while D2 receptors have been described to have positive as well as negative effects on both kinds of plasticity (Frey *et al.*, 1989; Chen *et al.*, 1996; Otani *et al.*, 1998; Gurden *et al.*, 2000; Spencer and Murphy, 2000; Manahan- Vaughan

and Kulla, 2003). Whereas the positive impact of D1 receptors on LTP and LTD might be caused by its enhancing effect on NMDA receptor activity, the mixed effect of D2 receptors on plasticity might be due to its reducing effect on NMDA as well as GABAergic activation (Tseng and O'Donnell 2004). Dependent on the balance of NMDA and GABAergic activation, plasticity might be prevented by reduced NMDA receptor activity, or enhanced by reduced GABAergic inhibition.

Additionally, the concentration levels of dopamine seem also to determine the impact of DA on brain functions. Animal studies have demonstrated that either insufficient or excessive dopamine impairs cognitive functions (Cai and Arnsten, 1997; Goldman-Rakic *et al.*, 2000; Seamans and Yang, 2004). This non-linear dopaminergic dose-response curve has been observed in mice (Lidow *et al.*, 2003), rats (Stewart and Plenz, 2006), monkeys (Vijayraghavan *et al.*, 2007) performing cognitive tasks. Not only can DA act at different concentrations on different subreceptors to exert opposing physiological actions, but strong versus weak D1 receptor activation alone can produce opposing actions. Substantial literature points to an inverted 'U'-shaped relation between cognitive performance and D1 stimulation levels (Williams and Goldman-Rakic, 1995; Zahrt *et al.*, 1997; Floresco and Phillips, 2001; Seamans and Yang, 2004). Studies exploring the relationship between D2-like receptor activity and cortical function are rare. However, D2/D3 agonists have shown non-linear effects on yawning behavior in rats (Collins *et al.*, 2005). This suggests that not only DA, and D1-like receptor agonists, but also D2-like activation elicit dose-dependently non-linear functional effects.

3.2 Dopaminergic effects on plasticity and cognitive performance- human data

In comparison to animal studies, for humans the number of investigations exploring the impact of the dopaminergic system and particularly the role of DA sub-receptors on cortical functions are limited.

For the impact of DA on cortical excitability, it was demonstrated that L-dopa prolongs the cortical silent period, (Priori *et al.* 1994). This inhibitory effect of dopamine on cortical excitability might at least in part be caused by D2 receptors, because it has been shown that D2 agonists strengthen intracortical inhibition, and diminish facilitation, while these effects are reversed by D2 antagonist haloperidol (Ziemann, 2003). In line with these findings, intracortical inhibition is reduced in Parkinson's patients, but restored by dopaminergic medication (Lefaucheur, 2005). These results are at least partly in accordance with animal findings, in which D2 receptor activation decreases excitability (Seamans and Yang, 2004).

With regard to the dopaminergic impact on neuroplasticity, it was shown that in Parkinson's patients, in contrast to healthy volunteers, PAS-induced facilitatory plasticity was abolished, but re-established by administration of L-dopa (Ueki *et al.* 2006), suggesting an important impact of the dopaminergic systems also on plasticity in humans. In healthy subjects, the impact of dopamine on plasticity was explored to a larger extent. Here activation of the dopaminergic system by L-dopa stabilized inhibitory plasticity, as induced by tDCS. Interestingly, for facilitatory plasticity, only focal, PAS-induced plasticity was enhanced and prolonged, but non-focal, tDCS-induced facilitatory plasticity turned into inhibition (Kuo *et al.* 2008). The stabilization of inhibitory plasticity might be at least partly due to D2 receptor activity, since the D2- antagonist sulpiride

eliminates tDCS-induced plasticity, whereas D2-agonism prolongs the inhibitory effect of cathodal tDCS (Nitsche *et al.*, 2006). This pattern of results is in accordance with an important influence of the D2 receptor on inhibitory plasticity, as already shown for LTD in animals (Otani *et al.*, 1998; Spencer and Murphy, 2000). The impact of D1 receptors on plasticity in humans was not explored so far. Also nothing is known about the dose-dependent effect of dopaminergic activation on plasticity in humans.

According to its effect on plasticity, it seems plausible that DA affects cognitive performance. Indeed, positive effects of dopamine on motor and verbal memory in healthy subjects (Floel *et al.*, 2005; Knecht *et al.*, 2004) and in patients after stroke (Floel *et al.*, 2005) are reported. Among the studies investigating the effects of dopaminergic subreceptors on cognition in humans, D2 receptors were explored in more detail than D1 receptors. In a recent study, Mehta and collaborators (2004) showed that D2 receptor antagonism impaired performance of healthy subjects in a working memory task, which requires flexible information processing. Interestingly, in the same study the D2 antagonist sulpiride improved the performance of well-learned working memory tasks, which affords stability of processing. These results are in accordance with a hypothesized de-focusing effect of D2-receptors on network activity, which might be accomplished by its NMDA receptor activity-reducing effect (Seamans and Yang 2004). An improvement of cognition by a focusing effect of D1 activity on neuronal networks, which is accomplished by the enhancement of activity of already active NMDA receptors, is suggested by another study: here the D1/D2 agonist pergolide improved performance in a well-learned working memory task, while bromocriptine, a selective D2 agonist, had no effects (Müller *et al.*, 1998). Also here, dose-dependent effects of dopaminergic activation were not explored.

The findings cited above are consistent with the hypothesis that the dopaminergic impact on neuroplasticity is dependent on sub-receptor specificity, and might differ for the kind of plasticity induced. Moreover, animal experiments are in favor for a non-linear dose-dependent effect of dopaminergic activation on plasticity. In the present thesis, we have further investigated this issue to understand better the complex effects of dopaminergic sub-receptors on human plasticity.

4. AIMS

In general, the main aim of the present thesis was to explore the impact of DA on cortical plasticity in healthy humans. Specifically, we sought to determine if the multiple modes of action of DA on neuroplasticity, in accordance with previous animal and human evidences, depend on sub-receptor specificity, DA concentration level and the kind of plasticity induced.

These goals are investigated by the following studies:

- Study I- to investigate the specific impact of D1 on cortical plasticity in humans;
- Study II- to reveal whether global DA activation exerts a non-linear dose-dependent effect on cortical plasticity in humans;
- Study III- to determine whether the dose-dependent effects of DA are dependent on D2-like receptor specificity and the kind of plasticity induced.

CHAPTER 2

In the following chapter, the three studies incorporated in the thesis will be presented. In the first study (Study I), we explored the relevance of D1-receptor activation for focal and non-focal plasticity in humans. Here, two experiments were performed: a) the balance of D1/D2 receptor activation was shifted towards the D1 receptor by blocking D2 receptors via sulpiride; b) D1 activation was further enhanced by combining L-dopa with sulpiride. The remaining studies are dedicated to the dose-dependency of DA effects on plasticity. In study II, we combined different dosages of L-dopa, which results in a not subreceptor-specific activation of the dopaminergic system, on tDCS-induced plasticity. In the third study (Study III), we aimed to explore if the nonlinear effect of DA observed in study II depend on sub-receptor specificity and the kind of plasticity induced, as previously suggested (Nitsche *et al.*, 2006; Kuo *et al.*, 2008). Therefore, we explored the impact of different dosages of the D2-like agonist ropinirole (RP) on focal and non-focal plasticity, as induced by tDCS and PAS.

1. Original articles and manuscripts

- Nitsche MA; Kuo M; Grosch J, Bergner C, **Monte-Silva KK**; Paulus W D1-
Receptor Impact on Neuroplasticity in Humans. *The Journal of Neuroscience*,
February 25, 2009 29(8):2648 –2653
- **Monte-Silva KK**; Liebetanz D; Grundey J; Paulus W; Nitsche MA. Dosage-
dependent non-linear effect of L-dopa on human motor cortex plasticity.
Submitted to Biological Psychiatry
- **Monte-Silva KK**; Kuo M; Thirugnanasambandam N; Liebetanz D; Paulus W;
Nitsche MA. Dose-dependent inverted U-shaped effect of dopamine (D2-like)
receptor activation on focal and non-focal plasticity in humans. *Journal of
Neuroscience* (in press)

1.1 Study I: D1-receptor impact on neuroplasticity in humans

It is proposed that DA improves cognitive functions by focusing information processing (Mehta *et al.*, 1999; Bartholomeusz *et al.*, 2003; Knecht *et al.*, 2004; Floel *et al.*, 2005). This focusing effect of dopamine was confirmed for the human primary motor cortex for global DA activation. Since the D1 receptor has been shown to be specifically involved in such a DA focusing effect in animals, the specific impact of D1 on plasticity in humans was explored. In the first experiment, the balance of D1/D2 receptor activation was shifted toward the D1 receptor by blocking D2 receptors with sulpiride. We explored the impact of this drug solely on focal, PAS-induced plasticity, because its effect on non-focal, tDCS-induced plasticity was already tested (Nitsche *et al.*, 2006). In the second experiment, D1 activation was enhanced by combining L-dopa with sulpiride. The effects of this drug combination on plasticity were explored for PAS- and tDCS-induced plasticity. Here, sulpiride alone abolished inhibitory paired associative stimulation (iPAS)-induced inhibition, but not excitatory paired associative stimulation (ePAS)-generated facilitation, underlining the importance of D1-receptor activity for focal facilitatory neuroplasticity. Combining sulpiride with L-dopa reestablished iPAS-induced inhibition, but did not affect ePAS-induced plasticity. tDCS-induced plasticity, which was abolished by sulpiride in a former study, also recovered. Thus enhancing D1 activity further relative to D2 activity is relevant for facilitatory and inhibitory plasticity. In summary, in comparison with former results show that an appropriate balance of D1 and D2 activity seems necessary to (1) consolidate the respective excitability modifications and (2) to elicit a focusing effect.

1.2 Study II: Dosage-dependent non-linear effect of L-dopa on human motor cortex plasticity

It has been demonstrated that either insufficient or excessive dopamine impairs cognitive functions, producing an inverted ‘U’-shaped effect (Seamans and Yang, 2004). This finding suggests an optimal range for DA concentration to maintain normal CNS functions (Cai and Arnsten, 1997). Direct neurophysiological evidence for such dose-dependent effects of DA receptor activation in humans is still missing. In order to reveal such a non-linear dose-dependent effect of dopamine on cortical plasticity in humans, the impact of 25, 100, and 200 mg of the dopamine precursor L-dopa on tDCS –induced plasticity was explored. The results show a nonlinear dosage-effect relation of dopamine receptor activation by L-dopa on motor cortex plasticity in humans, resulting in a ‘U’-shaped dose-response curve for anodal tDCS and in an inverted ‘U’-shaped dose-response curve for cathodal tDCS. In accordance with previous findings, the results are pinpointing to the importance of a specific dosage of dopamine optimally suited to improve plasticity.

1.3 Study III: Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and non-focal plasticity in humans

In the third study of the thesis, we combined different doses of a D2/D3 dopamine agonist with non-focal and focal plasticity-inducing stimulation tools in order to determine if the nonlinear effect of DA, as observed in the study II, depends on sub-receptor specificity and the kind of plasticity induced. Low (0.125 mg or 0.25 mg), medium (0.5 mg) or high (1.0 mg) dose ropinirole (RP- D2-like dopamine agonist) or equivalent placebo medication were administered orally 1 hour before the start of tDCS and PAS. D2-like receptor activation produced an inverted ‘U’-shaped dose response curve on plasticity for facilitatory tDCS and PAS and for inhibitory tDCS. However, no dose-dependent response effect of D2-like receptor activation was evident for inhibitory PAS. This study adds evidence to the importance of D2-like receptors for most types of plasticity and support the hypothesis that dopaminergic modulation of D2-like receptor on neuroplasticity differs depending on the level of receptor activation and the kind of plasticity induced.

CHAPTER 3

1. Summary of findings

- Study I demonstrates a distinctive contribution of D1 receptor activity to focal and non-focal plasticity in the human motor cortex. Enhancement of the relative activation of D1 by D2 receptor block resulted in an abolition of iPAS induced focal inhibitory, but not ePAS-induced focal facilitatory plasticity. Further enhancement of relative D1 activation by L-dopa under D2 block reestablished focal and non-focal inhibitory as well as excitatory plasticity. The results of our study show a nonlinear contribution of D1 receptor activity to focal and nonfocal plasticity in the human motor cortex. These results moreover deliver indirect evidence for the importance of balanced DA receptor activation for achieving a focusing dopaminergic effect on plasticity.
- Study II shows a non-linear dosage-dependent effect of dopamine receptor activation by L-dopa on motor cortex plasticity in humans, resulting in an inverted ‘U’-shaped dose-response curve for cathodal tDCS: low or excessive dopamine levels impaired the establishment of tDCS-induced inhibitory plasticity. For anodal tDCS, however, the relation between L-dopa dosage and effects on plasticity is ‘U’-shaped: low and high dosages of the drug reduced facilitatory effects of anodal tDCS, but the medium dosage converted them to inhibition. The identification of this non-linear effect contributes to the understanding of how an inappropriate increase of dopaminergic drug dosage does provide not only no added benefit, but leads to a functional impairment

- Study III suggests that the modulation of the D2-like receptor exerts a dose-dependent non-linear effect on neuroplasticity in the human motor cortex, which differs for the type of plasticity induced. D2-like receptor activation by RP produced an inverted ‘U’-shaped dose response curve on plasticity for facilitatory tDCS and PAS and for inhibitory tDCS. However, no dose-dependent response effect of D2-like receptor activation was evident for focal inhibitory plasticity. These results imply that the dose-dependent DA effect depend on sub-receptor specificity

2. Limitations, conclusions and future prospects

2.1 Limitations

In general, some potentially limiting aspects of the current thesis should be mentioned: (1) in principle, basal dopamine level might affect DA impact on plasticity, which could not be controlled here. However, the subjects included in the studies had no history of dopamine-related disease and represent a relatively homogenous population with small chance of selection bias; (2) Due to the difficulties to obtain real receptor-specific substances suited for use in humans, our results reflect indirect evidence for a selective D1 and D2 receptor activation; (3) tDCS and PAS do not only differ in the focality of plasticity stimulation, but also in aspects of timing. While tDCS induces plasticity via tonic stimulation of cortical neurons for several minutes, PAS is a phasic stimulation technique. Here associated single stimuli are applied, and timing of the stimuli is critical. (4) In all studies, in principle the subject blinding might have been somewhat compromised because of the different duration of monitoring the after-effects and systemic side-effects of medications (sulpiride, L-dopa and ropinirole) in the

different experimental sessions. However, because (a) only a minority of subjects experienced side-effects (b) the multitude of sessions per subject makes it difficult to identify the specific experimental condition, and (c) the participants were not aware of proposed results, we believe that blinding might be somewhat compromised, but would still be present.

2.2 Conclusions

These are the first systematic studies exploring (a) dose effects of the dopamine precursor L-dopa on different paradigms of induced neuroplasticity in human and (b) trying to differentiate between the influences of excitability increasing D1 and excitability decreasing D2 and D3 receptors. The studies included in this thesis address issues which are crucial for the understanding of non-uniform and complex effects of dopamine on synaptic plasticity and cognitive function in humans. In summary, the results of the current thesis favor the hypothesis that the DA impact on plasticity in the human motor cortex depends on sub-receptor specificity, concentration levels of dopamine and on the type of cortical plasticity, e.g. focal or non-focal plasticity.

Our results point out the importance of D1 sub-receptor activation for plasticity induction and the importance of a specific dosage of dopamine optimally suited to improve plasticity. Taken together, in connection with the results of former experiments of our group (Nitsche *et al.*, 2006; Kuo *et al.*, 2008), we show (1) the importance of balanced D1 and D2 receptor activation for achieving a focusing and consolidating dopaminergic effect on plasticity; and (2) the non-linear impact of DA on plasticity, resulting in U-shaped dose-effect curve depending on the kind of stimulation-induced plasticity.

As discussed above, DA can exert seemingly opposite effects, such as facilitation and inhibition, on synaptic activity (Seamans and Yang, 2004); and improve or impair cognitive performance (Floresco and Phillips 2001); etc. The results of the current thesis, which shows that the multiple effects of dopamine action are dependent on sub-receptor specificity, concentration level and the kind of plasticity, might help to understand the partially opposing effects of DA on synaptic activity and cognition in animals and humans and non-uniform effects of DAergic pharmacotherapy in neuropsychiatric disorders. The identification of the non-linear effect of DA contributes to the understanding of how an inappropriate increase of dopaminergic drug dosage does provide not only no added benefit, but leads to a functional impairment.

Moreover the knowledge about the relationships between drug concentration and its effects (therapeutic effectiveness and undesirable effects) is potentially important for the safe and effective use of drugs in clinical practice. This knowledge might be useful to develop tailor-made drugs and optimize individual of patients with a dopaminergic dysfunction, accompanied by cognitive disturbances, e.g., patients with Parkinson's disease and restless leg syndrome.

2.3 Future prospects

Some interesting aspects of importance for future studies should be mentioned.

(1) Studies are needed to discern the dependency of the observed effects from some other factors. For example, (a) L-dopa differs from other DA agonists because it does not affect neurons independent of neuronal activity, thus a non-selective agonist is needed to explore if the L-dopa effects are definitely caused by the unselective stimulation or by the differences in activation-dependency of stimulation; (b) ropinirole has higher affinity for

D3- than D2 receptors, thus studies exploring more specifically D2 effects on plasticity are needed, especially since D1 and RP do not explain the L-dopa effects completely; (2) Further studies are important for exploring the dependency of the effects of dopaminergic activation on cognitive performance from task characteristics, i.e. tasks affording stable or flexible information processing . According to our results, dopaminergic stimulation might not improve task performance in all instances; (3) Genetic factors influence stimulation-induced plasticity in humans (Cheeran *et al.*, 2008). Thus it is possible that individual genetic variants may influence the specific impact of dopaminergic activity on plasticity. (4) The impact of dopaminergic drugs on cognition is age-dependent. Increased age reduces dopaminergic signaling, and receptor density (Volkow *et al.*, 1994; Floel *et al.*, 2005). Thus, the effect of dopamine on plasticity, as accomplished in the present study, might be specific for young healthy subjects, and differ in older subjects. Further studies for clarifying these aspects are necessary; (5) in the present study, all DA dosages induced a “hyperdopaminergic state” in healthy subjects, limiting, therefore, the extrapolation of results to patients with a dopaminergic deficit. Thus, for obtaining therapeutic information, further studies are needed to explore directly if the non-linear effect of dopamine on cortical function is the same in patients as in the healthy subjects studied here.

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Academic Titles

- 2006 Ph.D. student in Neuroscience.
Georg-August University of Göttingen, Germany.
Supervisors: Uwe Mattler, Paulus Walter, Michael Nitsche.
Financial Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES, Brazil.
- 2005- 2006 Master in Nutrition
Federal University of Pernambuco, UFPE, Brazil.
Title: Nutrition, peripheral electrostimulation and brain development: electrophysiological and behavioural studies in rats
Supervisor: Rubem Guedes.
Financial Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, CAPES, Brazil.
- 2005 – 2006 Specialization in therapeutic resources (UFPE-Brazil)
- 2000 – 2004 Graduation in Physical Therapy (UFPE-Brazil)

Professional Experience

Company: Department of Clinical Neurophysiology. Georg August University of Göttingen/Germany
Function: Researcher
Periods: since March 2007.

Project Participations

Supervisor: PD Dr. Michael Nitsche

03/2007 - Anodal repeated tDCS for prolonging the after-effects of stimulation

- 03/2007 - Dose-dependent effects of D2-like receptor activation on focal non-focal plasticity in Parkinson patients
- 08/2008 – 12/2008 Dose-dependent effects of dopamine receptor activation by L-dopa on non-focal plasticity in humans
- 04/2008 - 12/2008 Cathodal repeated tDCS for prolonging the after-effects of stimulation
- 04/2008 - 08/2008 Impact of D1-like receptors on neuroplasticity in humans
- 10/2007 - 04/2008 Dose-dependent effects of D2-like receptor activation on focal and non-focal plasticity in humans
-

Company: Sobell Department of Motor Neuroscience and Movement Disorders- London
Function: Researcher
Periods: Feb, 2009- April, 2009.

Project Participations

Supervisor: Prof. Dr. John Rothwell

- 02/2009 – 04/2009 D2-like receptor impact on neuroplasticity induced by theta burst stimulation
-

Company: Deutsches Primaten Zentrum – DPZ- Göttingen/Germany
Function: Researcher
Periods: March, 2007 – October, 2007.

Project Participations

Supervisor: PD Dr. David Liebetanz

- 03/2007 - 10/2007 Functional effects of transcranial direct current stimulation in Rhesus monkeys
-

Company: Federal University of Pernambuco State, Department of Physical Therapy
Function: Temporary professor
Periods: May, 2006 – October, 2006.

Company: Federal University of Pernambuco State, Department of Nutrition
Function: Researcher
Periods: May, 2006 – October, 2006.

Project Participations

Supervisor: Prof. Dr. med Rubem Guedes

- 05/2001 – 11/2002 Nutrition, physical activity, brain development: effect on cortical spreading depression in rats.
- 11/2001 – 06/2002 Ambiental stimulation, malnutrition and nervous system development: a electrophysiologic study
- 07/2002 – 06/2003 Effect of peripheral electrostimulation on the cortical spreading depression in young rats
Financial Support: Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPQ, Brazil.
- 07/2003 – 06/2004 Effect of peripheral electrostimulation on cortical spreading depression in adult rats
Financial Support: Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPQ, Brazil.
- 06/2004 – 04/2005 Effect of the peripheral electrostimulation on the exploratory behavior in adult rats: influence of the nutritional state
Financial Support: Conselho Nacional de Desenvolvimento Científico e Tecnológico, CNPQ, Brazil.
- 04/2005 – 08/2005 The Effects of repetitive electrical stimulation on cortical spreading depression: potential implications for the treatment of depression
- 05/2005 – 06/2006 Transcranial direct-current stimulation: after-effects on cortical spreading depression in rats.
- 04/2006 – 05/2006 Cortical electrical stimulation effect on spreading depression in rat cortex
- 02/2006 – 09/2006 Effect of physical exercise on nervous system development in rats

AWARDS

2003 – First place with the study: “Efeito da eletroestimulação periférica precoce sobre a depressão alastrante cortical ” Galdino Loreto Premium- XI Symposium on the Brain - Recife/ PE.

PUBLICATIONS

1. **Monte-Silva KK**; Kuo M; Thirugnanasambandam N; Liebetanz D; Paulus W; Nitsche MA. Dose-dependent inverted U-shaped effect of dopamine (D2-like) receptor activation on focal and non-focal plasticity in humans. *Journal of Neuroscience* (in press)

2. Nitsche M, Kuo M, Grosch J, Bergner C, **Monte-Silva K**, Paulus W. D1-receptor impact on neuroplasticity in humans. *Journal of Neuroscience* 29(8):2648-53, 2009;
3. **Monte-Silva KK**, Assis LN, Leal GMA, Guedes RCA. Nutrition-dependent influence of peripheral electrical stimulation during brain development on cortical spreading depression in weaned rats. *Journal Nutritional Neuroscience* 10:187-194, 2007.
4. Fregni F, Liebetanz D, **Monte-Silva KK**, Oliveira MB, Santos AA, Nitsche MA, Pascual-Leone A, Guedes RCA. Effects of transcranial direct current stimulation coupled with repetitive electrical stimulation on cortical spreading depression. *Experimental Neurology* 204:462-466, 2007.
5. Liebetanz D, Fregni F, **Monte-Silva KK**, Oliveira MB, Santos AA, Guedes RCA. After-effects of transcranial direct current stimulation (tDCS) on cortical spreading depression. *Neuroscience Letters* 399:1-8, 2006.
6. Fregni F, **Monte-Silva KK**, Oliveira MB, Freedman SD, Pascual-Leone A, Guedes RCA. Lasting accelerative effects of 1 Hz and 20 Hz electrical stimulation on cortical spreading depression: relevance for clinical applications of brain stimulation. *European Journal of Neuroscience* 21(8):2278-2284, 2005.