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Titel der Diplomarbeit

„COMPARING LASTING EFFECTS AFTER TMS AND TDCS OF THE LEFT DLPFC

A STUDY ON RESTING EEG POWER SPECTRUM IN NICOTINE ADDICTED SUBJECTS“

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Abbreviations

A/m²**/**mA/cm² = ampere per square meter**/** milliampere per square centimeter (electrical current density)

ACC = anterior cingulated cortex

Ag/AgCl = argentum/argentum chloride (silver/silver chloride)

AMPA = α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

ANOVA = analysis of variance

BDNF = brain -derived neurotrophic factor

CIC = cue-induced craving

CBS = brainstem system

COPD = chronic obstructive pulmonary disease

DLPFC = dorso-lateral prefrontal cortex

EEG = electroencephalogram

FDI = first dorsal interosseus muscle

FTND = Fargerström Test for Nicotine dependence

FFT = Fast Fourier Transformation

GABA = gamma-Aminobutyric acid

Hz = Hertz

ICD-10 = ICD-10: International statistical classification of diseases and related health problems, 10th revision

ITI = inter train interval

LTP = long-term potentiation

LTD = long-term depression

mA = milliampere

min = minute

MEG = magnetoencephalography

MEP = motor evoked potential

ms = millisecond

MR = magnetic resonance

MRI = magnetic resonance imaging

MT = motor threshold

NAcc = nucleus accumbens

nAChRs = nicotine acetylcholine receptors

OFC = orbito-frontal cortex

NMDA = *N*-Methyl-D-aspartic acid

PFC = prefrontal cortex

PSD = power spectral density

SCID = structural clinical interview

sec = second

T = Tesla

tDCS = transcranial direct current stimulation

TMS = transcranial magnetic stimulation

VTA = ventral tegmental area

1 INTRODUCTION AND TECHNICAL DETAILS

1.1 General Introduction

The purpose of this Diploma Thesis is to treat of the comparison between two different state-of-the-art neurostimulation techniques, viz. transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) by means of physiological (EEG) and behavioral (CIC-task) data. In this work the focus lies-besides investigating effects of both of the techniques in general- on the lasting effects for up to one hour after the end of stimulation of both of the techniques in nicotine-addicted brains.

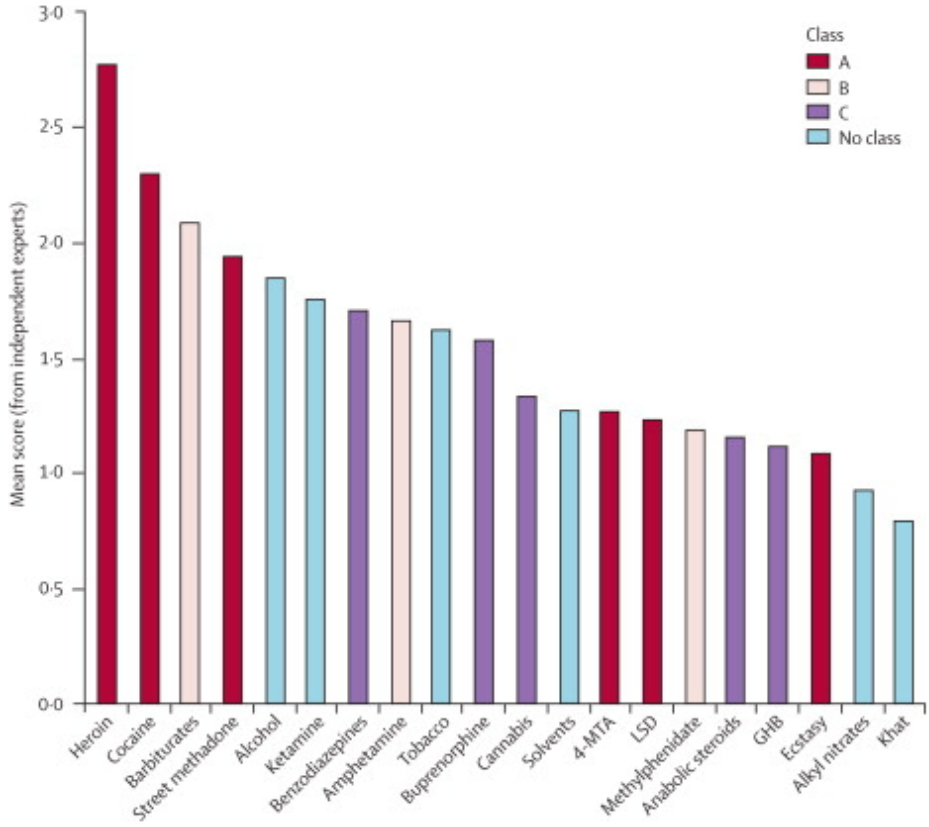
To start this little sequence, it should be mentioned that the stimulation of the nervous system looks back on a long history in human culture. Evidence suggests that already circa 9000 BC bracelets and necklaces of magnetite and amber were used to prevent different kinds of pain, in this case: headache and arthritis (Schechter, 1971a). These techniques were followed by pain treatments with electric minerals and fish, until the first machines, purposed to influence the nervous system, were invented in the 17th century and developed further until today (Simpson, 2003).

Likewise, the consumption of tobacco products looks back on a long history in human culture. Although it was introduced to the western world at the edge of the 15th century, it has been consumed by Native Americans for far longer during sacrificial ceremonies. Already in the 16th and 17th century, there had been attempts to prohibit tobacco consumption in Mexico, Germany, Austria, Russia, China, Japan and Turkey, which could not be established (Spode, 2010).

Until today, tobacco is a tolerated drug of abuse and tobacco smoking is a major risk factor for various diseases as: cancer, heart attacks, strokes, chronic obstructive pulmonary disease (COPD), emphysema (Dreyer et al. (1997)). David Nutt (2007) listed tobacco on place 9 of the most harmful drugs, emphasizing the parameters physical harm, dependence and social harms (see **Figure 1**). After including more criteria to draw an even more differentiated picture of harmfulness (see Nutt et al., 2010), tobacco

ranked on place six in overall harmfulness. In a recent study by Taylor et al. (2012) nicotine had been classified as the sixth harmful drug to the consumer himself and ranked on place seven in terms of addictiveness. Taken together tobacco smoking is highly addictive and leads to premature death.

Figure 1 Mean harm scores for 20 substances



This figure taken from David Nutt (2007) shows the 20 most popular drugs of abuse ranked by harmfulness in terms of the factors: physical harm, dependence and social harms.

Thus, investigating potential treatments for tobacco addicted individuals is a major public health topic and worth to be investigated in (more than this) one study.

1.2 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation method that was introduced to the neuroscientific research community by Anthony Barker and colleagues in 1985. They were the first ones to conduct successful experiments to stimulate the human motor cortex via a magnetic field induced to the brain, resulting in muscle contractions in participants' hands. Since then TMS has emerged as an applicable tool in human brain research, because of its advantage to enable experimenters altering the brain activity reversibly by inducing random noise into a circumscribed brain area, which might lead to behavioral changes (Miniussi et al. 2008, 2010), i.e. enhanced performance, if an optimal noise level is reached or otherwise a decreased performance in specific tasks.

The effects of TMS are based on a principle of electromagnetic induction first discovered by Michael Faraday. He noticed that an electrical current passing through a wire induces a magnetic field at the periphery of this wire. This magnetic field is then able to induce an electric current in a second wire. In the case of magnetic stimulation the primary magnetic field is generated by the TMS-coil, forming voltages in the brain by changing the magnetic flux density inside of the brain tissue (Jacinta O'Shea and Vincent Walsh, 2007). This might then lead to depolarization in superficial cortical neurons (see e.g. Feil et al 2010; Rachid & Bertschy, 2006; Barker et al., 1985).

The most focal TMS application method is via a figure-of-eight-shaped coil, because two different wires with converse current fluctuations are used that generate a maximum output at the interface of both of them. Apart from this, circular coils and double cone coils have also been used in various studies (Rossi et al., 2009). The output magnetic field has a strength between 1.5-2 Tesla (T) (Rossi et al., 2009).

The magnetic stimulation is supposed to be directed parallel to the scalp and the induced currents are dependent on the brains' tissue inhomogeneity. The shorter and/or sharper

bended the axons are, the lower will the stimulation threshold for a certain area be. Additionally, the larger the diameter of an axon is, the smaller the stimulation threshold is supposed to be (Experimental evidence: Amassian et al., 1992; Maccabee et al., 1993 and theoretical calculations: Nagarajan et al., 1993, cited by Rossi et al. 2009). In contrast to transcranial direct current stimulation (tDCS) electric currents do not pass the scalp, skull and meninges physically, but effect the voltage-gated ion channels of the axons of superficial cortical neurons directly (Rossi et al. 2009).

In general, TMS can be divided into a single pulse (and paired pulse) form, which might be used to evoke motor-cortical responses and the repetitive application variant, i.e. a stimulation in trains repeated in a certain time at a frequency commonly ranging between 1-20 Hz (Thut and Pascual-Leone, 2009). rTMS is subdivided into low frequency rTMS (≤ 1 Hz) and high frequency rTMS (> 1Hz). Low frequency rTMS is more likely to elicit what Walsh and Cowey (1998) termed 'virtual brain lesion', whereas high frequency rTMS is more likely to result in an activating way.

To summarize the effects of TMS, one can say that TMS leads to a depolarization in cortical neurons, which can either result in corticospinal inhibition or facilitation, depending on the frequency applied and the circular brain organization. The effects of high-frequency rTMS resemble those of long-term potentiation (LTP), whereas the effects of low-frequency rTMS are similar to long-term depression (LTD) (Huang et al., 2005; Houdayer et al., 2008, cited by Gerstner 2011).

1.2.1 TMS Side Effects

According to Rossi et al. (2009) TMS, if applied within the safety guidelines, has just minimal side effects. **Table 1** below is adopted from just those guidelines.

Table 1 TMS side effects

Side effect	Single-pulse TMS	Paired-pulse TMS	Low frequency rTMS	High frequency rTMS	Theta burst
Seizure induction	Rare	Not reported	Rare[1]	Possible[2]	Possible[3]
Transient acute hypomania induction	No	No	Rare	Possible[4]	Not reported
Syncope	Possible	Possible			
Transient headache, local pain, neck pain, toothache, paresthesia	Possible	Likely possible, Not reported	Frequent	Frequent	Possible
Transient hearing changes	Possible	Likely possible, Not reported	Possible	Possible	Not reported
Transient cognitive/neuropsychological changes	Not reported	Not reported	Overall negligible	Overall negligible	Transient impairment of working memory
Burns from scalp electrodes	No	No	Not reported	Occasionally reported	Not reported, but likely possible
Induced currents in electrical circuits	Theoretically possible, but described malfunction only if TMS is delivered in close proximity with the electric device (pace-makers, brain stimulators, pumps, intracardiac lines, cochlear implants)				
Structural brain changes	Not reported	Not reported	Inconsistent	Inconsistent	Not reported
Histotoxicity	No	No	Inconsistent	Inconsistent	Not reported
Other biological transient effects	Not reported	Not reported	Not reported	Transient hormone (TSH), and blood lactate levels changes	Not reported

This table adopted from Rossi et al. (2009) (and slightly modified) gives an overview of TMS side effects for which consensus has been reached.

[1] usually protective effect
[2] 1.4% crude risk estimate in epileptic patients; less than 1% in normals
[3] one seizure in a normal subject during cTBS
[4] following left prefrontal stimulation

In sum the most common side effects are transient headache, local pain, neck pain, toothache and paresthesia. Seizures, transient hearing, hormone and blood lactate level changes are also possible side effects.

1.3 Transcranial Direct Current Stimulation

As TMS, transcranial direct current stimulation (tDCS) is a non-invasive (that means that the tissue has not to be penetrated by an object) neurostimulation technique, which is considered safe within the recent safety guidelines (Bikson et al. 2009). The application of electrical currents to animals' brain surfaces began in the 1960s (e.g. Purpura & McMurtry, 1965). Despite of the attempt to apply tDCS in clinical studies those days, tDCS could not be established for that purposes, until it recently gained some popularity (Feil & Zangen 2010).

tDCS is a non-invasive stimulation technique, at which a stimulating electrode (mostly anode) is applied to the scalp above the cortical area, supposed to be stimulated, in order to modulate the membrane potential in the underlying cortical neurons. Weak direct electric currents are injected into the brain, passing the brain and leaving it via a referencing electrode (mostly cathode). The charge of the electrodes can also be reversed, so that the cathode is applied to the area of interest and the anode becomes the referencing electrode. Direct current passes the scalp and skull first and then makes its way through the corticospinal liquor, where the current is carried to cortical neurons. In case of anodal stimulation the excitability of cortical neurons is increased, which leads to higher firing rates. In terms of cathodal stimulation, the effect is the other way round, i.e. the excitability of the cortical neurons is decreased. The conventional application setting for tDCS is to use two rectangular sponge electrode pads (7x5 cm^2). Usually, a current intensity between 260 µA and 2 mA is applied at the stimulating electrode's site (Minhas et al. 2010).

1.3.1 tDCS Side Effects

Possible tDCS side effects due to unsafe application, i.e. current densities higher than 142.9 A/m^2 combined with exposure times longer than 10min (compare Liebetanz et al., 2009) might be brain tissue damage and skin burns (compare Minhas et al., 2010). Bikson et al. (2009) consider an exposure of 25.46 A/m^2 for up to 20min anodal or cathodal as safe in terms of skin damage. If applied within the limits, which are considered to be safe, possible side effects might be transient cognitive side effects, skin irritation, tingling or itching sensations, headache, discomfort and phosphenes, associated with the start or end of the stimulation (Poreisz et al., 2007; Bikson et al., 2009; Brounoni et al., 2011).

1.4 Electroencephalography and Frequency Bands

Human-electroencephalography (EEG) was invented by Hans Berger in 1929. EEG is a noninvasive method to measure brain activity by currents that are generated if cortical neurons are firing at the same time and into the same direction. Therefore EEG has a very high temporal but poor spatial resolution. The electrical signals at the surface of the scalp range between 5 and 100 µV (Aurelien et al., 2004), which is the reason why an amplifier is needed to record EEG signals.

Since neurons are firing in different rhythms, measured brain activity can be dissected into different frequency bands. The delta frequency band with frequencies up to 4 Hz is the frequency band with the slowest waves. A frequency range between 4 and 7 Hz is called the theta band, followed by the alpha band which ranges between 7 and 12 Hz. Finally to be mentioned are the fast-wave frequencies beta (13-30 Hz) and gamma (30-100 Hz) and additionally the special mu rhythm at a frequency range between 8 and 13 Hz.

The preponderance of one or more frequencies during a specific period of time can be an indicator for different states of sleep as well as for cognitive processes.

A prominence in alpha rhythm, for instance, is an indicator for the early stage of sleep, whereas delta rhythms are associated with deeper sleep stages.

According to Knyazev (2007), the origin of delta activity is not clear. It is assumed that slow delta waves (i.e. < 1 Hz) are generated directly in the cortex during sleep (Steriade et al., 1993b, cited by Knyazev, 2007). Knyazev reports further in her review that cortical delta generation could be located in the anterior medial frontal cortex (Michel et al., 1992, 1993, cited by Knyazev, 2007) and waking delta in the medial frontal cortex (Alper et al., 1995, 1998, cited by Knyazev, 2007), but also in subcortical regions as the brainstem system (CBS, Lambertz and Langhorst, 1998, cited by Knyazev, 2007), the nucleus accumbens (NAcc, Leung and Yim, 1993, cited by Knyazev, 2007), the ventral pallidum (Lavin and Grace, 1996, cited by Knyazev, 2007), and dopaminergic neurons in the ventral tegmental area (VTA, Grace, 1995, cited by Knyazev, 2007). As will be given a summary further below, the majority of those structures are crucially involved in reward processing.

About the place of generation of theta activity Knyazev (2007) summarized, that those are particularly located in structures that are part of the so-called limbic system (Broca, 1878). In a more recent study that is cited, by Kirk and Mackay (2003), it was found that there are multiple theta generators which facilitate the communication between ‘limbic system’, hypothalamus and brainstem.

Finally, alpha activity is mostly sourced in the occipital cortex. Although alpha waves are supposed to be more likely generated in posterior brain regions, slower alpha components are more likely to show a more anterior placement tendency (after Knyazev, 2007).

1.5 Addiction

1.5.1 Definition

Addiction (substance dependency) is defined as the continuous consumption of a substance despite its adverse consequences on health and social life, notwithstanding the repeated attempt to abandon the consummatory behavior (Hymann & Malenka, 2001, cited by Pinel 2007; Angres & Bettinardi-Angres, 2008).

1.5.2 Neurophysiological Substrates

1.5.2.1 Relevant structures

To date, a widespread consent is obtained about limbic and striatal pathways and the prefrontal cortex being involved in reward processing and thus evolution of addiction. According to a recent review by Feil et al. (2010), the limbic system at the one hand is associated with the incentive sensitization to drugs, whereas the prefrontal cortex is involved in the inhibition control towards addictive stimuli. However, those structures are interconnected.

As Feil et al. (2010) report in their review, there are three different parallel and interconnected fronto-striatal circuits that are involved in executive functioning and inhibitory control: the DLPFC-circuit, the OFC-circuit and the ACC-circuit. The DLPFC-circuit is associated with goal identification and selection. It origins in the DLPFC (dorso-lateral prefrontal cortex), includes the dorso-lateral part of the nucleus caudatus, the globus pallidus and substantia nigra and the thalamus. The OFC (orbito-frontal cortex)-circuit, which is associated with decision-making and regulation of impulsivity, follows a similar way as the DLPFC circuit, except that it is switched at the ventro-medial part of the nucleus caudatus. Finally, the ACC (anterior cingulate cortex)-

circuit consists of the ventral striatum, the globus pallidus, the substantia nigra and the dorso-medial part of the thalamus.

Another crucial structure involved in reward processing is the ventral tegmental area (VTA). Schultz et al. (2000) where the first ones to show in monkey experiments, that the VTA becomes active during the state of reward anticipation.

1.5.2.2 Neurotransmission

The above mentioned structures are affected by the meso-cortical dopamine system, whose neurons are, because of the network plasticity, sensitive to addictive substances, inducing a shift on the structural, cellular, molecular, and genomic levels (Hyman and Malenka, 2001, cited by Kelley et al. 2002). Kelley et al. (2002) also report a possible crucial role in coincident glutamate NMDA/dopamine D1 receptors activation in motivationally driven and learning behavior. Stuber et al. (2010) where able to show, that dopaminergic terminals in the nucleus accumbens themselves co-release glutamate. According to Pinel (2007), learning plays a crucial role in incentive sensitization. This thought is completed by Schmidt and Beninger (2006), whose work underpins that dopaminergically driven incentive learning promotes the shift from neutral stimuli to reward cues and the subsequent incentive salience and approaching behavior. Furthermore, Vargas-Perez et al. (2009) could show, that opiate dependency in rat brains leads to changes in the cyanatomy of the VTA, which could be led back to increased BDNF levels in the VTA. This again leads to changes in AMPA receptors of VTA GABAergic interneurons inducing a shift from inhibitory to excitatory. Those changes induce a shift from GABAergic to dopaminergic reward processing in opiate addicted brains.

1.5.3 Tobacco Addiction

ICD-10

Tobacco addiction is classified in the current version of the ICD-10 (WHO, 2013) under

point **F17 Mental and behavioral disorders due to use of tobacco**, subdivision **.2 Dependence syndrome**:

"A cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.

The dependence syndrome may be present for a specific psychoactive substance (e.g. tobacco, alcohol, or diazepam), for a class of substances (e.g. opioid drugs), or for a wider range of pharmacologically different psychoactive substances."

1.5.4 Neural substrates of Nicotine Addiction

1.5.4.1 Mechanisms of nicotine

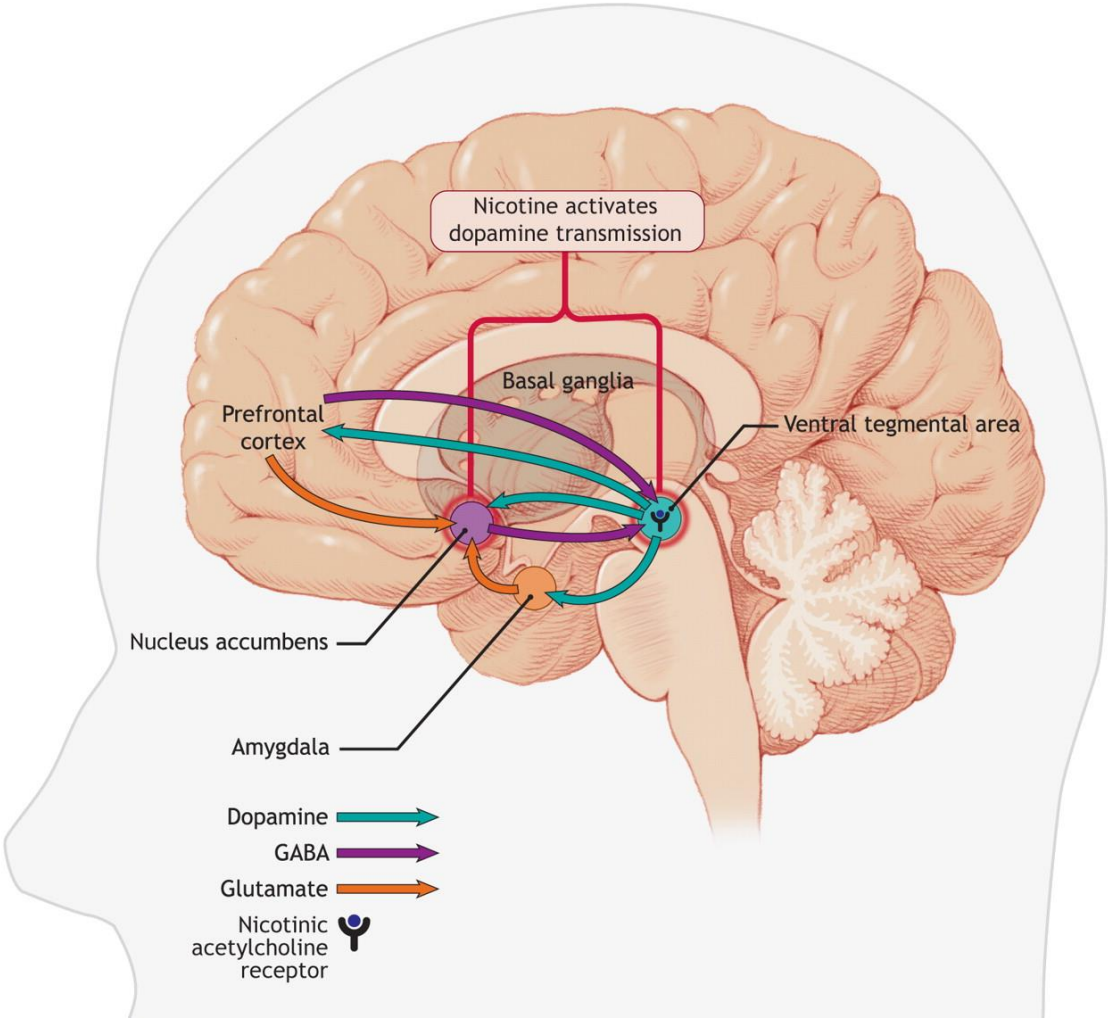
A recent article by Cohen and George (2013), gives a substantial overview of the acute effects of nicotine (see also **Figure 2**). A summary of those is given in the following:

1. Nicotine is docking to **nicotine acetylcholine receptors** (nAChRs) that are distributed throughout the whole nervous system which triggers the release of various neurotransmitters. The specific reinforcing and rewarding effect is mediated by nAChRs.
2. As already mentioned above, the reinforcing effect of drugs of abuse comprising nicotine, is mediated by the **meso-cortico-limbic dopamine system** including the ventral tegmental area (VTA) and projecting to the nucleus accumbens (Nacc), hippocampus, amygdala, and prefrontal cortex (PFC). Nicotine administration leads to an increase of meso-limbic dopamine release.
3. Additionally, nAChRs on **glutamatergic neurons** in the VTA, NAcc, amygdala, hippocampus, and PFC are receiving nicotine and project consequently to dopaminergic neurons in the VTA and nAChRs on **inhibiting GABAeric**

neurons in the VTA, who desensitize faster than nAChRs on dopaminergic neurons, resulting in a facilitation of those.

4. Finally, the endogenous opioid system, the serotonergic system and the endo-cannabinoid system are supposed to play a crucial role in the rewarding and reinforcing effects of nicotine. (For further explanations see Cohen and George, 2013).

Figure 2 Neuronal substrates of nicotine addiction



Picture taken from Le Foll & George (2007)

1.5.4.2 Nicotine withdrawal

Chronic nicotine administration leads to a desensitization in VTA GABA neurons' nAChRs, which suppresses their activity and results in an inhibition of dopamine neurons. Simultaneously, nAChRs on afferent glutamatergic neurons stay unaffected, thus facilitating glutamate release in VTA dopamine neurons, which leads to a facilitated dopamine release in the NAcc. In contrast, during the phase of withdrawal VTA glutamate levels decrease and GABA levels increase.

Generally spoken nicotine withdrawal leads to decreased firing rates in VTA dopamine neurons and decreases dopamine levels in the NAcc, which is associated with heightened brain reward thresholds. On a behavioral level, this state of dopamine deficit leads to a negative affective state and attention deficits, supposedly, because nicotine withdrawal affects neurobiological mechanisms associated with positive reinforcing and recruitment of stress systems (after Cohen and George, 2013).

1.5.5 Nicotine Addiction and Executive Functioning

Feil et al. (2010a) give an extensive overview (see **Table 2&3**) of the cognitive and neuronal correlates, appearing in connection with nicotine addiction and craving. They report a correlation between aberrant function of the PFC, OFC and ACC and nicotine and craving (Domino et al., 2000a, b cited by Feil et al. 2010a).

Table 2 Executive malfunction due to Nicotine Dependence (cognitive tasks)

Study	Participants	Measurements/methodology	Significant findings
Razani et al. (2004)	127 Older healthy smoking adults (47–83 years) divided into non-light, moderate and heavy smokers. Self-reported smoking histories	Neurocognitive tasks	Heavy smoking history was associated with reduced executive/problem solving skills. Heavy smokers performed worse than both groups on tests assessing executive function and problem solving skills.
Dawkins et al. (2007)	145 Chronic smokers	Oculomotor Task of Response Inhibition Continuous Performance Task Spatial Working Memory Test Verbal fluency Test	Acute smoking abstinence is associated with impaired response inhibition. Chronic nicotine smokers presented with impaired inhibitory control, and these impairments were reversed with nicotine administration.
Dawkins et al. (2009)	145 Chronic smokers divided into those who attempted to quit and those who continued to smoke	Cognitive tests from Dawkins et al. (2007) repeated at 7 days, 1 month and 3 months	Abstainers significantly reduced desire to smoke compared to continuing smokers. Both abstainers and ongoing smokers showed improvement in appetitive processes and affects states after abstinence. Impairment in response inhibition did not improve over time.

Adopted from Feil et al. (2010)

Table 3 Executive malfunctions due to Nicotine Dependence (imaging studies)

Study	Participants	Measurements/methodology	Significant findings and frontal brain activations
Structural MRI studies			
Brody et al. (2004)	19 Nicotine-dependent individuals 17 Non-smoking healthy controls	High resolution structural MRI Assessed grey and white tissue densities using VBM	Nicotine dependent individuals: Significantly smaller cortical grey matter volumes and densities in the DLPFC and ventro-lateral PFC, and reduced left dACC grey matter volume and right cerebellar grey matter densities in Correlation between lifetime severity of smoking (pack-year) and reduced prefrontal cortical grey matter density
Gallinat et al. (2006)	22 Smokers 23 Non-smokers	High resolution structural MRI Assessed grey and white tissue densities using VBM	Smokers: Reduced grey matter volume and density in frontal regions, such as the ACC, PFC and OFC, the occipital lobe and the temporal lobe, including the parahippocampal gyrus. Altered grey matter volume or grey matter density in the thalamus, cerebellum and substantia nigra Correlation between lifetime severity of smoking (pack-year) and decreased volume of frontal, temporal lobes and cerebellum
Functional MRI studies			
Stein et al. (1998)	16 Active cigarette smokers	BOLD-fMRI Behavioral rating questionnaire	Active smokes: Acute nicotine administration ->dose-dependent increases in behavioral parameters such as feelings of “rush” and “high” and drug liking ->increased neuronal activity in the frontal lobes, cingulate, Nacc and amygdala
Wilson et al. (2005)	22 Male smokers deprived of nicotine for 8 h	BOLD-fMRI Craving urge scales Smoking and non-smoking cues Smoking expectancy cues	Cigarette-cue exposure ->Significant activation of the ACC Subregions of the PFC, such as the ventromedial, ventro-lateral and DLPFC were activated when cue-induced smoking was modulated by smoking expectancy.

McBride et al. (2006)	20 Regular heavy smokers	BOLD-fMRI (once during abstinent state and once when satiated) Smoking and neutral videotapes Craving scales Smoking expectancy cues	Neural activation in response to smoking cues was largely associated with expectancy, and less so, with abstinence. Smoking cues was related to increased levels of craving and neural activation of the ACC, posterior cingulate cortex, dorso-medial PFC, DLPFC, medial OFC, anterior insula, superior temporal gyrus, visuospatial areas, ventral pallidum and dorso-medial thalamus.
Franklin et al. (2007)	21 Chronic smokers	Arterial spin-labelled perfusion-fMRI Craving self-reports Smoking and non-smoking cues.	Smokers responded to smoking cues with increased blood flow (perfusion) in the amygdala, ventral striatum, thalamus, hippocampus, left insula and OFC. A positive correlation was found between perfusion in both the DLPFC and posterior cingulate and craving self-reports.
Wang et al. (2007)	15 Chronic smokers	Arterial spin-labelled perfusion-fMRI The first scan measured perfusion during smoking satiety, and the second, after overnight abstinence. Craving scales.	Smoking abstinence was associated with increased CBF in the ACC, medial and left OFC. Abstinence-induced cravings were predicted by CBF increases in the right DLPFC, occipital cortex, ACC, ventral striatum/nucleus accumbens, thalamus, amygdala, bilateral hippocampus, left caudate and right insula.
PET studies			
Brody et al. (2002)	20 Heavy smokers 20 Non-smokers	^{18}F-FDG PET scans Smoking and neutral cues Craving scales	Smoking cue exposure in heavy smokers resulted in increased bilateral ACC metabolism, as well as increased left anterior temporal lobe and PFC metabolism. In addition, levels of craving correlated with metabolism in the OFC, DLPFC, the anterior insula and the superior right sensorimotor cortex.

Rose et al. (2007)	15 Chronic smokers	^{18}F-FDG and $H_2{}^{15}O$ PET and MRI PET scan at: Baseline 2 weeks after exposure to only denicotinised cigarettes 2 weeks after resumption of normal smoking habits Fagerström test of Nicotine Dependence Self-report questionnaires (craving and smoking habits) Continuous Performance Task	Cravings levels were reduced in the 2nd session, while regional brain metabolic activity was reduced in the right ACC. Over all sessions, changes in craving negatively correlated with cerebral metabolism in the ventral striatum, PFC and pons.
Brain stimulation studies			
Johann et al. (2003)	11 Tobacco dependent individuals	Single session of high frequency rTMS to the DLPFC VAS (craving levels)	rTMS reduced reported levels of tobacco craving.
Eichhammer et al. (2003)	14 Treatment-seeking heavy smokers	Single session of high frequency rTMS (20 Hz) to the DLPFC VAS (craving levels) Cigarette consumption	High frequency rTMS DLPFC reduced cigarette consumption. Craving levels did not change.
Fregni et al. (2008)	24 Chronic smokers	Single session of anodal 2 mA tDCS stimulation of either left DLPFC, right DLPFC, or sham, for 20min VAS (craving levels) VAS (mood levels)	tDCS of DLPFC temporarily reduced general and cue-induced nicotine craving. No mood changes
Amiaz et al. (2009)	48 Nicotine-dependent individuals	Ten daily sessions of high frequency rTMS (10 Hz) to the DLPFC. VAS (craving levels) Cigarette consumption Smoking and non-smoking cues	High frequency rTMS DLPFC reduced cigarette consumption Cue-induced craving was reduced

Adopted from Feil et al. (2010) (slightly modified)

2 THEORETICAL BACKGROUND

2.1 TMS, Craving, Dopamine System and EEG Delta

According to Fitzgerald et al. (2006b) rTMS "is capable of altering cortical excitability beyond the period of stimulation" (Fitzgerald et al., 2006b cited by Feil & Zangen, 2010b).

The most evident results for lasting effects of rTMS provide stimulation studies of the primary motor cortex (M1), because the effects can be measured directly by motor-evoked potentials (MEPs) in the corresponding muscles. Thus, Peinemann et al. (2004) were able to find a long-lasting increase in corticospinal excitability after 5 Hz rTMS to the M1 region. They showed that lasting effects are dependent on the pulses applied. An application of 1800 stimuli resulted in excitability changes of at least 40min, whereas an application of 900 stimuli changed the excitability for only 5min after rTMS application.

Some authors investigated the (persistence of) influence of rTMS application on delta power as well as on other EEG frequency bands. Jing and Takigawa (2000) applied rTMS at a frequency of 10 Hz and a stimulation intensity of 100% of the motor threshold in trains of 3sec. They did an EEG recording at 1-3min and 3-5min after rTMS application and calculated directed and ordinary coherence. Among others, Jing and Takigawa found an increased intra-hemispheric coherence between cortical areas, but no influence on the dominant frequency. In a follow up study, Okamura et al. (2001) found an increase in peak frequency for the first 2min after stimulation, which then recovered between 2-5min after stimulation, whereas no changes in mean absolute power became obvious in the first 2min after stimulation. Mean absolute power decreased 3-4min after stimulation and increased 4-5min after stimulation. They used the same stimulation protocol as Jing and Takigawa in the previous year.

Graf et al. (2001) did not find an influence on spectral power after rTMS application of 40 2sec lasting trains, at a frequency of 20 Hz with an inter train interval (ITI) of 28sec and an intensity of 90% of the motor threshold (MT) over the left DLPFC, besides a reduction in whole night sleep stage 1 and "and a small enhancement of sleep stage 4 during the first non-REM sleep episode" (Graf et al. (2001)).

Further, Maihöfner et al. (2005) found a decrease in slow magnetoencephalographic (MEG) activity (2-6 Hz) after 10 days of rTMS application over DLPFC in depressive patients.

Griskova et al. (2007) give a first hint on modulation of delta activity after 10 Hz rTMS application above the left DLPFC, viz. an increase in delta activity in widespread parts of the brain. They were the first ones to conduct a sham controlled experiment on EEG lasting effects after rTMS application. They found a 400% increase in delta-power in the DLPFC after stimulation with 10 Hz rTMS and an intensity of 110% ("real") respectively 90% ("sham") of the motor threshold and 2000 pulses (20 pulses per train, 100 trains). This effect did last for at least 10min, but had not been investigated longer. The authors speculate that these delta modulations are due to changes in the dopamine system.

In a review by Thut and Pascual-Leone (2009) it has been summarized (compare **Table 4**), that fast rTMS application leads in most cases to a decrease in alpha-band power and, going along with this, a facilitation in corticospinal excitability, but there is no evidence that those after-effects last longer than an experimental session of approximately one hour.

Table 4 Lasting effects during rest rTMS by frequency

Authors	Subjects	TMS-parameters	EEG-measures	Timing of EEG	Aftereffects	Duration of aftereffects
<5Hz						
Strens et al. (2002)	*N* = 15 healthy	1 Hz/25min M1/90%aMT/1500p	Spectral power coherence (rest and	Before and after TMS	Yes: ~15% focal increase in coherence	Up to 25min recovered after 30min

			task)		(alpha)	
Tamura et al. (2005)	*N* = 12 healthy	1 Hz/10min M1/95%rMT /600p	Movement-related oscillations	Control and after TMS	Yes: ~10% decrease in synchronization (beta)	Not assessed
Brignani et al. (2008)	*N* = 6 healthy	1 Hz/10min M1/110%MT/600p	EEG power (rest)	During TMS	Yes: max 82% focal, cumulative increase in power (alpha)	Not assessed
Pastor et al. (2006)	*N* = 6 healthy	1 Hz/10min Cerebellum/ 60%max/600p	Steady-state potentials	Before and after TMS	Yes: change in prefrontal oscillations (gamma)	At least 7.5min not studied longer
Schutter et al. (2001)	*N* = 12 healthy	1 Hz/20min DLPFC/130% MT/1200p	Spectral power (rest)	After TMS and sham	Yes: increase in prefrontal power (theta)	At least 1 h not studied longer
5Hz						
Oliviero et al. (2003)	*N* = 16 healthy	5 Hz/10 s single train M1/100%aMT/50p	Spectral power coherence (rest and task)	Before and after TMS	Yes: ~25% focal coherence decrease (alpha)	Immediately after TMS recovered after 25min
Fuggetta et al. (2008)	*N* = 11 healthy	5 Hz/20 × 4 s trains: 30 s ITI M1/80–100%MT/400p	EEG power and coherence (rest)	During TMS	Yes: ~30–40% focal incr/decr in alpha and beta power/coherence	Not assessed
>5Hz						
Griskova et al. (2007)	*N* = 18 healthy	10 Hz/100 × 2 s train: 10 s ITI DLPFC/110% MT/2000p	Spectral power (rest)	Before and after TMS	Yes: ~400% increase in delta-power	At least 10min, not studied longer
Okamura et al. (2001)	*N* = 32 healthy	10 Hz/2 × 3 s train: 300 s ITI Frontal/100 %MT/60p	Spectral power (rest)	Before and after TMS	Yes: change in peak frequency and power (~10%, many frequencies)	At least 5min not studied longer
Jing and Takigawa (2000)	*N* = 19 healthy	10 Hz/2 × 3 s train: 5min ITI DLPFC/100%	Coherence (rest)	Before and after TMS	Yes: max 32% focal directed coherence	At least 5min not studied longer

		MT/60p			increase (alpha)	
Schutter et al. (2003)	*N* = 5 healthy	25 Hz/80 × 10 s train: 5 s ITI Cerebellum/ 80%MT/200 0p	Spectral power (rest)	Before and after TMS	Yes: change in prefrontal asymmetry (gamma)	At least 15min not studied longer
Schindler et al. (2008)	*N* = 4 healthy	cThetaBS/33 s right FEF/80%rM T/600p	Spectral analysis (rest)	Before and after TMS	Yes: ~enhanced synchronizat ion in stimulated hemisphere	At least 60min not studied longer
Grossheinric h et al. (2009)	*N* = 12 healthy	cThetaBS/40 s DLPFC,mPFC /80%rMT/6 00p imThetaBS as sham	Spectral analysis (rest)	Before and after TMS	No	n.a.

Taken from Thut and Pasqual-Leone (2009)

Various studies have shown that TMS application influences individual craving levels. Camprodon et al. (2007), as well as Politi et al. (2008) found a transient craving reduction in cocaine addicted subjects after 10 Hz rTMS application over right DLPFC. Other studies found a transient reduction in food craving after 10 Hz stimulation over left PFC (Barth et al., 2011; Uher et al., 2005). Additionally, Van den Eynde et al. (2010) found a reduction in food craving of bulimics after rTMS over left DLPFC. Johann et al. (2003) found a decrease in cigarette craving after rTMS application and as Eichhammer et al. (2003) reported in the same year, rTMS over DLPFC reduced cigarette consumption but not the self-reported craving level. Amiaz et al. (2009) found a lasting reduction of cigarette craving and consumption after 10 Hz rTMS application for 10 days. Furthermore, Li et al. (2013) and Pripfl et al. (2013) found decreased cue-induced craving after 10 Hz rTMS over left DLPFC.

This idea is supported by Cho and Strafella (2009). They found, that fast rTMS of the left DLPFC is associated with dopamine release in the ACC and OFC. The ACC is interconnected with the NAcc, which is playing an important role in dopamine release and reward processing (Wacker et al. 2009).

2.2 tDCS, Craving, Behavioral Inhibition and EEG Theta

Concerning tDCS, Nitsche and Paulus (2001), found a lasting effect on motor-corticospinal excitability, after stimulation. They found an increase of 150% for up to 90min after the end of 13min anodal stimulation.

Also, Nitsche et al. (2003c) found lasting inhibitory effects after 9min of cathodal stimulation of the motor cortex for up to 90minutes, whereas effects only lasted for a couple of minutes after 5 or 7min of stimulation.

The influence of tDCS application on craving has also been shown in some studies. Boggio et al. (2010) found a significant diminishing effect on marihuana craving after right anodal/left cathodal tDCS of DLPFC. In an earlier study by Boggio et al. (2008), it was found that anodal left/cathodal right and anodal right/cathodal left tDCS of the DLPFC leads to a reduction in alcohol craving. Furthermore, Goldman et al. (2010) found a diminishing effect on food craving after anodal right/cathodal left stimulation of the PFC. In terms of smoking, Fregni et al. (2008) found a diminishing influence on cue-provoked craving after anodal tDCS of the left and right DLPFC. Additionally, Boggio et al. (2009) investigated the effects of anodal tDCS of left DLPFC on smoking-cue-induced craving and found decreased craving rates.

There might be a linkage between response inhibition and impulsiveness control and the ability to control craving. Goldman et al. (2011) found an improved capability to control food craving after tDCS of the DLPFC. Beeli et al. (2008) found a decrease in impulsiveness control after cathodal stimulation of the DLPFC.

Jacobson et al. (2011) investigated response inhibition as a component of cognitive control in connection with tDCS of the right inferior frontal gyrus. They found an improvement in response inhibition after 10min of anodal stimulation. In a follow up study (Jacobson et al. 2012) they investigated the connection between changes of oscillatory brain activity and the above mentioned response inhibition, and found a decrease in theta power after anodal tDCS of the right IFC, which was associated with improvement of response inhibition.

2.3 Cue-induced craving

One reason, why people cannot cease sticking to their addiction, is a phenomenon termed cue-induced craving (CIC). This is based on the principle of classical conditioning and means that craving for a specific drug occurs every time the addicted person is exposed to an item, place or situation that is associated with his former drug consumption experience. In case of cigarette craving this might be the vision of an ashtray, waiting at the bus stop or being in a distressed mood (after Pinel, 2007).

The phenomenon of cue-induced tobacco craving has been investigated in various studies (e.g. Sinha & Li, 2007).

3 HYPOTHESES

Derived from the theoretical background given above, following hypotheses concerning the physiological and behavioral feedback to the stimulation, can be derived:

3.1 rTMS

H_{11}: High frequency rTMS application leads to reduced EEG delta power for at least 20min after the end of the stimulation.

H_{12}: Additionally, it leads to decreased craving levels for at least the same period of time.

3.2 tDCS

H_{11}: tDCS application leads to decreased EEG theta power for at least 60min after the end of the stimulation.

H_{12}: Additionally, it leads to decreased craving levels for at least the same period of time.

4 METHODS

4.1 Design

This study is placebo controlled, comparing two samples that were either stimulated with rTMS or tDCS. There were two stimulation conditions within the TMS part of the experiment: “real” and “sham”. For DC stimulation there were also two conditions: “real” (anodal) and sham. Each participant underwent both stimulation conditions on separate days (~7 days gap). The participants were all introduced to stay abstinent from nicotine for at least 6h before the beginning of the experiment and from alcohol and pharmaceuticals one day in advance.

4.2 Participants

For the TMS condition 14 participants were included in the study. Because of strong EEG motion artifacts 3 participants had to be excluded for the final analyses. Finally 11 right-handed smokers (six females; mean age 29.2 years, S.D. = 5.5 years, range 21–38 years) without any self-reported psychiatric or neurological diseases were included in the TMS analyses (see Pripfl et al., 2013 (in press))

For the tDCS condition 14 participants were included in the study (a fifteenth participant decided to quit the study at the beginning of the second session (before stimulation), he reported paresthesia at the scalp, supposedly because of the electrode cap pushing his hair across the grain). Because of technical problems 2 participants had to be excluded for the final analyses. Finally 12 right handed smokers (7 females; mean age 24.75 years, S.D. = 3.25 years, range 20–29 years) without any self-reported psychiatric or neurological diseases were included into the tDCS analyses.

To exclude participants with psychiatric diseases or customary drugs of abuse users, subjects were interviewed using the screening-questionnaire of the structured clinical interview (SCID, Spitzer et al. 1992). Level of nicotine dependence was assessed with

the Fagerström Test for Nicotine Dependence (FTND, Fargerström, 1978; Fargerström & Schneider 1989) and revealed a mean score of 3.64 ± 1.6 within the TMS sample (Pripfl et al., 2013 (in press)) and a mean score of 3.5 ± 1.3817 within the tDCS sample, which indicates a low level of dependence. However, the participants met ICD-10 (WHO, 2013) criteria for tobacco dependence (F17.2) and reported a consumption behavior of smoking at least ten cigarettes per day for at least one year. To exclude subjects with neurologic disorders a TMS-Checklist was administered at the beginning of each session (see **Appendix**).

4.3 TMS

The rTMS stimulation was processed by means of a Magstim Rapid^2 stimulator (The Magstim Company Ltd, U.K., 2011) with a peak electric field between 0.5-3.5 Tesla at 100% output, biphasic output, 400µs pulse width and a ventilated 70mm figure-of-eight shaped coil.

Antecedent to each TMS stimulation, motor threshold (MT) was defined for each participant individually before and after the application of the EEG cap. The M1 target area to define the motor threshold was the representational field of the right first dorsal interosseus muscle (FDI). The motor threshold was defined as the lowest stimulation intensity, producing a motor evoked potential (MEP) response between 0.5-1.0 mV in 3 out of 5 stimuli within a time frame between 15ms and 35ms after single pulse TMS application.

There were two stimulation sessions, one for the “real” and one for “sham” condition. To prevent an order effect, the order of stimulation conditions was counterbalanced. For the “real” condition, the TMS coil was placed above the left DLPFC (compare Cho and Strafella, 2009) for “sham” above the vertex. Stimulation took place at a frequency of 10 Hz with a stimulation time of 5sec per train and a rate of 24 trains. The inter train interval (ITI) was 25sec long. That means the total stimulation time was 12min, total number of pulses was 1200. Stimulation intensity was 90% of the motor threshold.

Additionally, MR structure scans (T1-weighted) were conducted in order to detect different targets (left DLPFC, left M1) via neuronavigation (Brainsight, see below) on a high-field 3T Tim Trio scanner (Siemens Medical, Germany) using a 32-channel head coil (magnetization prepared rapid gradient echo sequence; TR = 2.3s, TE = 4.21ms, 1.1 mm slice thickness, 900ms inversion time, 9° flip angle).

4.4 tDCS

tDCS (neuroConn Ges.m.b.H, Illmenau, Germany) was applied via one EEG-Ag/AgCl-electrode (1.33cm²) for a duration of 15min at 0.4 mA anodal/sham stimulation which results in a current density of 0.3 mA/cm^2, in randomized order. The duration was chosen, because it had been associated with lasting effects of more than one hour in former experiments (Nitsche and Paulus, 2001; Nitsche et al., 2003c) and to match the duration of the TMS application. The stimulating electrode was applied to the skin above the left DLPFC (see TMS condition) cum collodium. The reference electrode was a conventional saline-soaked sponge electrode (35 cm^2) and was placed above the right articulatio temporo-mandibularis next to the right ear. The "reference"-electrode's size was chosen proportionally large, keeping the current density under 0.017 mA/cm^2 (0.014 mA/cm^2), in order to avoid efficient stimulation effects underneath the reference electrode (Nitsche and Paulus 2000; Nitsche et al. 2007, 2008). Impedance was supposed to be lower than 5 Ω and checked with an impedance meter (Ing. Zickler Ges.m.b.H., Pfaffstätten, Austria). To preclude placebo-effects a "sham" condition was conducted. At the beginning of both of the stimulation conditions current intensity was faded in for 15sec until the intensity of 0.4mA had been reached. For the "sham" condition there followed a subsequent stimulation of DC for 30sec and a fade out of 15sec duration. This was to elicit the same skin sensation during "pseudo"-stimulation as during "real"-stimulation. All DC stimulations were double-blinded.

4.5 Brainsight Frameless Stereotaxy

Brainsight is a neuronavigation software for Mac OS X (Brainsight 2, Rogue Research Inc., Canada), which supports frameless stereotactical TMS application. To operate frameless stereotaxy following devices come to use:

1. The Polaris optical position sensor, containing two infrared cameras.
2. Trackers, which are reflectors, whose configuration patterns are visible to the Polaris, attachable to a special pair of glasses (subject tracker), the TMS-coil (coil tracker) and
3. The pointer tool.

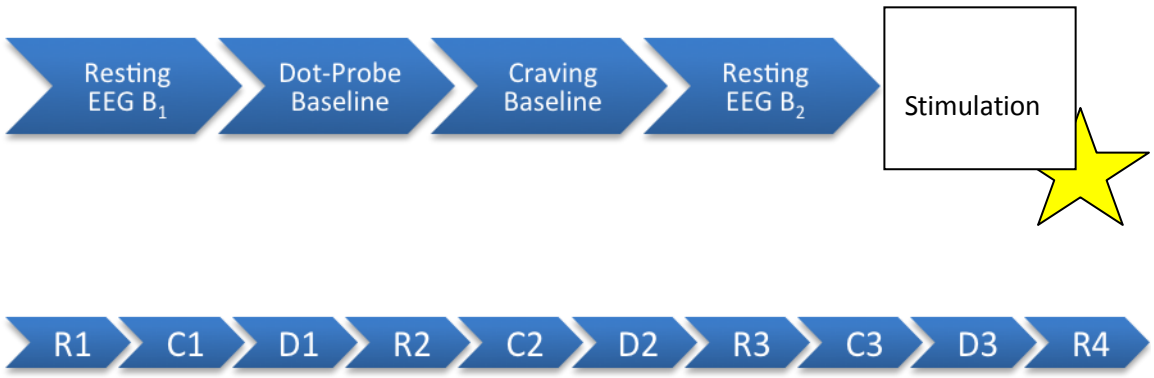
The pointer tool and the subject tracker are essential to locate the subject's head in the room. Once the subjects' loci have been registered, it is possible to track the person's skull and brain by means of a T1-weighted magnetic resonance imaging (MRI) structure scans, displayed by the Brainsight software. This allows placing the TMS coil above a target region in the cortex to improve stimulation focality. The same procedure was applied within the real and sham condition of the tDCS experiment.

4.6 EEG recording

Physiological effects of TMS/tDCS application were assessed using a TMS-suitable EEG cap (Easycap GmbH, Herrsching, Germany) with 65 electrodes, placed according to the '10-20' international system, connected to a NEURO PRAX® DC-amplifier (neuroConn GmbH, Illmenau, Germany). During the resting state recording, participants were introduced to keep their eyes closed but to stay in an alert state, in a sound-attenuated room. Resting EEG recording took place twice before the stimulation, in order to assess the baseline and baseline after craving induction, and four times after the stimulation to assess stimulation-induced after-effects. Resting Baseline 1 and 2 as well as post1 TMS/tDCS resting EEG, were lasting 5min, the following resting recordings

(post2, post3, post4) were lasting 3min. The sampling rate of the EEG-recordings was 500 Hz.

Figure 3 Experimental procedure



This figure shows the experimental procedure. Resting Baseline 1&2 were 5min. R1 marks the first resting EEG after stimulation, which was 5min lasting. The resting EEGs 2-4 were 3min long. C1-3 are the CIC-tasks. D1-3 means the dot probe paradigm (McLeod, Mathews and Tata, 1985; results not discussed in this thesis).

4.7 Cue-Induced Craving (CIC)-Task

Cue-induced craving is supposed to be one of the main reasons, why addicted persons are not able to abandon their addiction (see Baker et al. 2004; Killian et al. 1997; Shiffman et al. 1996; Swan et al. 1996). In this study cue-induced craving was generated to evaluate behavioral effects on craving after TMS/tDCS application. The craving task in this experiment consisted of a pseudorandomized order of pictures shown to the

subjects. The subjects were alternately exposed to a row of 4 craving cues (adopted from the assignment of Ulla Köhler and Renate Neumann, 2012, see **Appendix**), a row of 4 neutral pictures (taken from the International Affective Picture Scale (IAPS), **see Appendix**) or a fixation cross. Each picture was presented for 3sec (12sec per block) and there were six trials for each category. After each single block of exposure, participants had to rate their present level of craving on a 7 points Likert-like scale.

4.8 Questionnaires

Before and after the recording, the pen-and-paper versions of the PANAS (Watson, Clark & Telgen, 1988) and TCQ-SF (Heishman, Singleton & Moolchan, 2003) were processed by the participants, to evaluate possible mood effects and present levels of tobacco craving. The TCQ-SF represents the craving level on four dimensions: emotionality, expectation, compulsiveness and purposefulness. Additionally, a questionnaire to survey adverse effects as proposed by Brounoni et al. (2011) was administered at the end of each session (Headache, Neck pain, Scalp pain, Tingling, Itching, Burning sensation, Skin redness, Sleepiness, Trouble concentrating, Acute mood change, Others (specify)) (see **Appendix**).

5 DATA ANALYSIS

5.1 Power Spectrum Analysis

In order to perform power spectrum analysis EEG data was filtered (high pass filter: 0.5 Hz, low pass filter: 45Hz), artifact-corrected and downsampled (256 Hz) by means of the EEGlab toolbox for Matlab (The MathWorks, Inc.). In order to process Fast Fourier Transformation (FFT) and power spectrum analysis, the last 60sec of artifact-free recordings were acquired for each participant and point in time of recording.

Subsequently, the means of the spectra of the delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (30–40 Hz) band were calculated using the Matlab 7.5.0 software (The MathWorks, Inc).

5.2 Statistical Analysis

5.2.1 TMS-EEG-Data

For the TMS data Pripfl et al. (2013, in press) applied a repeated linear mixed model, featuring the factors stimulation condition (real, sham), time (post1, post2, post3) and electrode site (F3, Fz, F4, C3, Cz, C4, P3, Pz, P4) for the EEG power spectra alpha, delta and gamma and the EEG baseline (pre2) as a covariate.

5.2.2 Behavioral Data TMS

For the analysis of the CIC-task Pripfl et al. (2013, in press) used the same model as for the physiological data, but with the factors stimulation condition (real, sham), picture

category (neutral, craving-cue) and time (post1, post2, post3) and the random factor subject as well as the CIC-task baseline as a covariate.

5.2.3 tDCS-EEG-Data

Analyses of Variance for repeated measures using the program PASW Statistics 19 (IBM SPSS Statistics 19, Somer, NY, USA) was conducted to investigate differences in total EEG power between real and sham condition of tDCS application. In order to remove the baseline, differences between each after stimulation recording and the second baseline were calculated for each repeated-measures variable. Subsequently, a repeated-measures ANOVA was computed, featuring the independent variables: stimulation condition (real, sham), run (diff_post1, diff_post2, diff_post3, diff_post4) and electrode site for frontal (F3, F4, Fz), central (C3, C4, Cz) and parietal (P3, P4, Pz) and the dependent variable: power.

5.2.4 Behavioral Data tDCS

Similarly, the behavioral data was compared applying a repeated-measures ANOVA (PASW Statistics 19; IBM SPSS Statistics 19, Somer, NY, USA) Therefore, the differences of the variables of the three after-stimulation craving tasks to the baseline were calculated. The three factors for the ANOVA were: stimulation condition (real, sham), run (diff_post1, diff_post2, diff_post3) and stimulus type (craving cue, neutral picture, fixation cross).

Further analyses: All additional analyses where also performed by means of PASW Statistics 19 software (IBM SPSS Statistics 19, Somer, NY, USA).

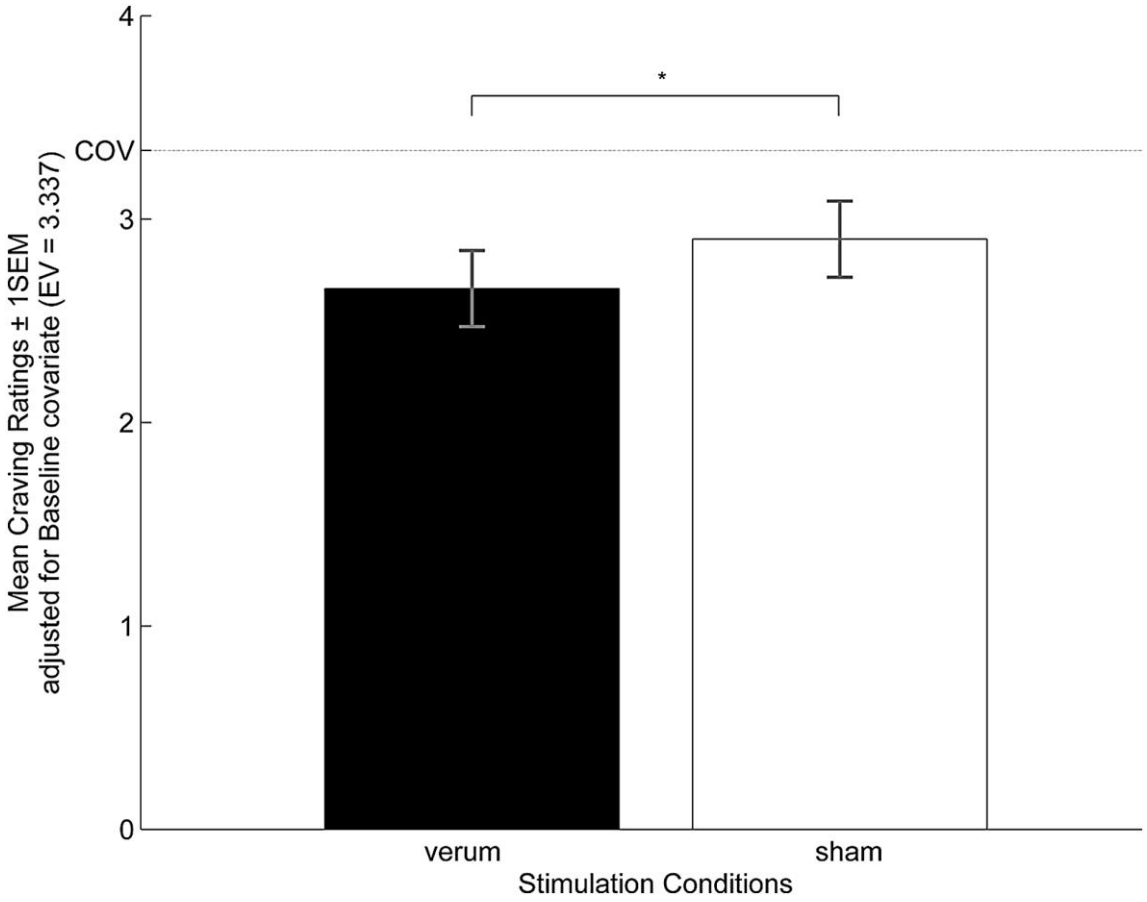
6 RESULTS

6.1 Behavioral Data Cue Induced-Craving (CIC)-Task

6.1.1 TMS

For the TMS condition Pripfl et al. (2013, in press) found significant main effects of the factors picture category (F[1,39] = 5.313, P = .027, (craving cue > neutral picture)) and stimulation condition (F[1,67] = 4.135, P = .046, (real < sham), see **Figure 4**). They report no significant effect for the factor time or any interaction.

Figure 4 Behavioral outcome TMS

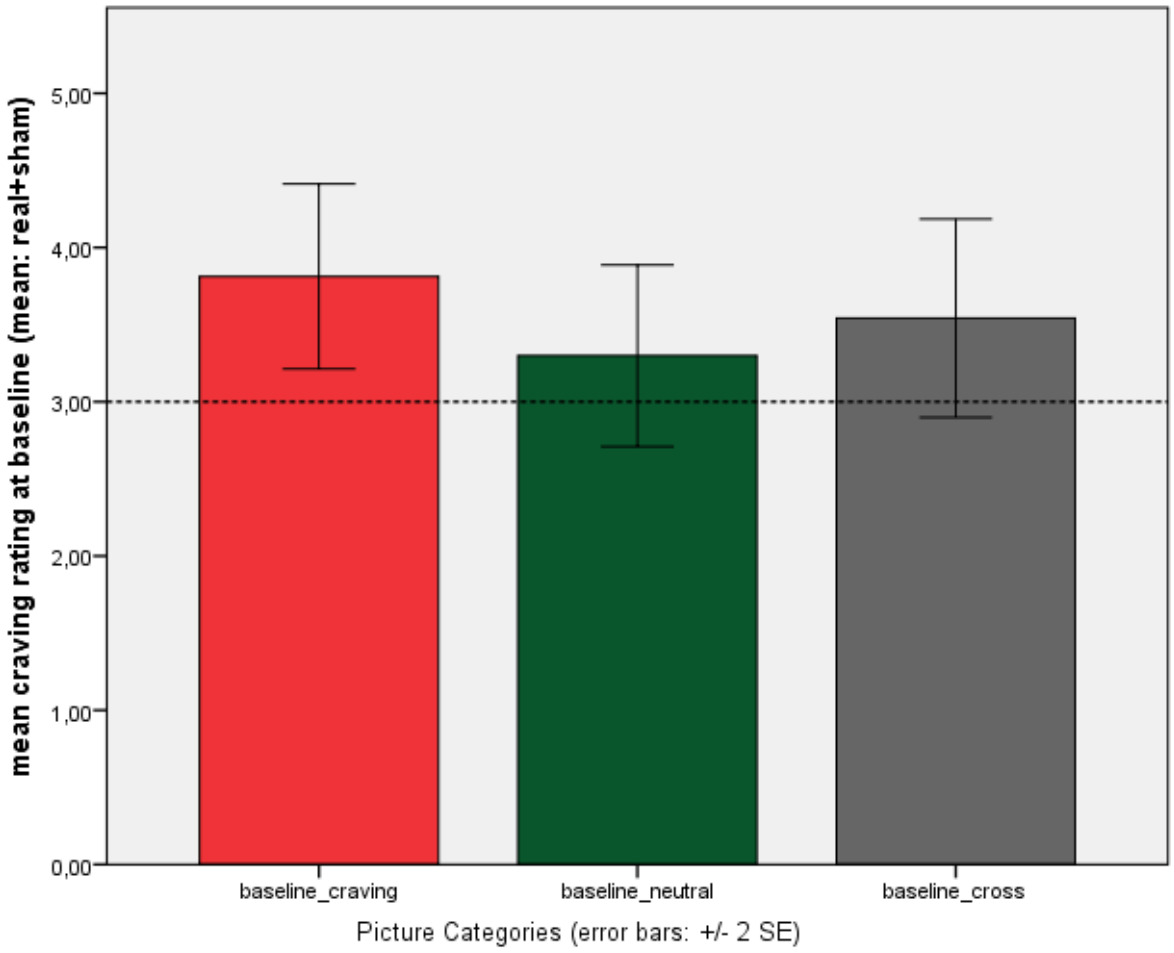


Taken from Pripfl et al. (2013, in press)

6.1.2 tDCS

The repeated measure ANOVA revealed no significant differences for the factors stimulation condition, picture category, run or any interaction. However, paired t-tests revealed a significant difference between picture categories at the baseline (mean: real_baseline+sham_baseline, see **Figure 5**). Differences were between craving_cue > neutral_picture ($t(11) = 4.94$, $P < .001$), craving_cue > fixation_cross ($t(11) = 3.657$, $P = .004$) and fixation_cross > neutral_picture ($t(11) = 2.746$, $P = .019$).

Figure 5 Behavioral outcome tDCS: means at baseline



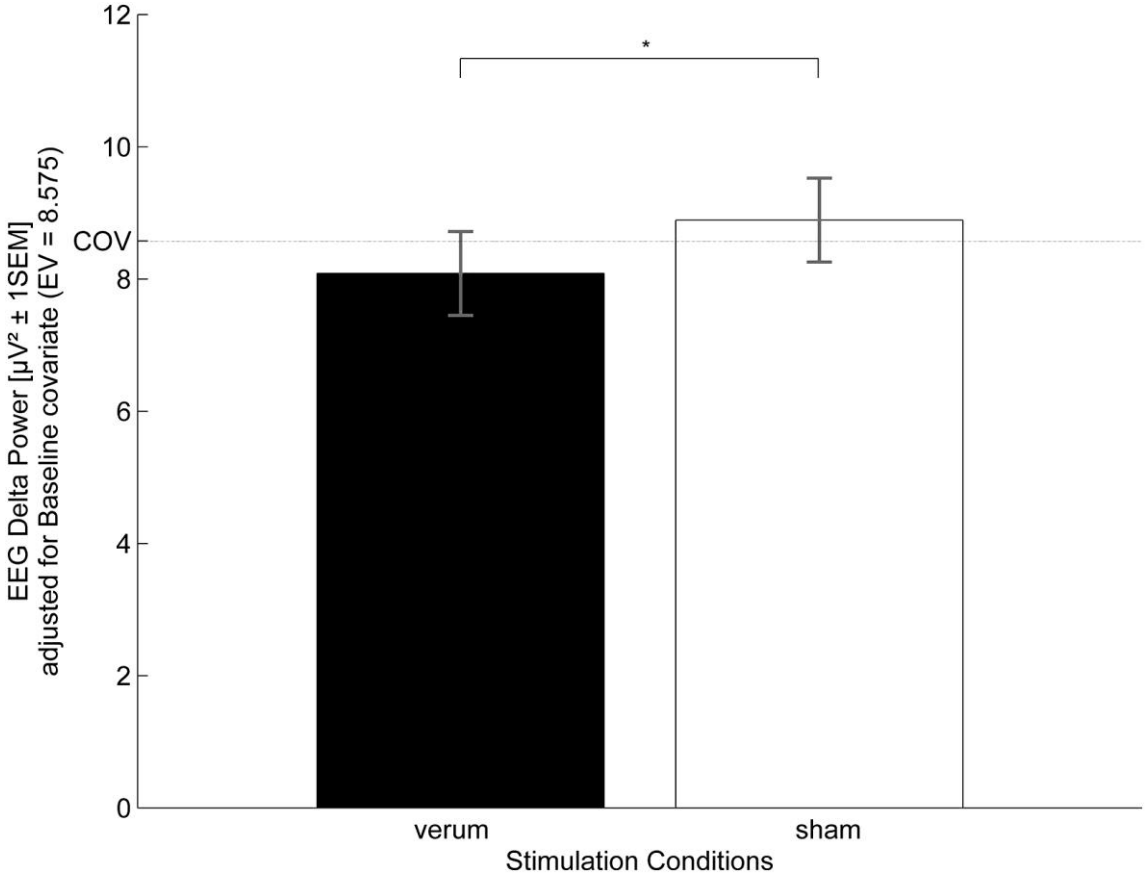
This figure displays the differences in mean for picture category of the CIC-task at the baseline (mean:real+sham).

6.2 Physiological Data

6.2.1 TMS EEG delta mean power

According to Pripfl et al. (2013, in press), the repeated measures ANOVA revealed a main effect for EEG delta (F[1,138] = 3.975, P = .048, see **Figure 6**) as a function of stimulation condition (real < sham), but no effect for the factor run or any interaction. However, there was a significant effect for electrode site (F[8,222] = 2.568, P = .011), with a peak at Fz and a trough at P4.

Figure 6 EEG delta outcome TMS

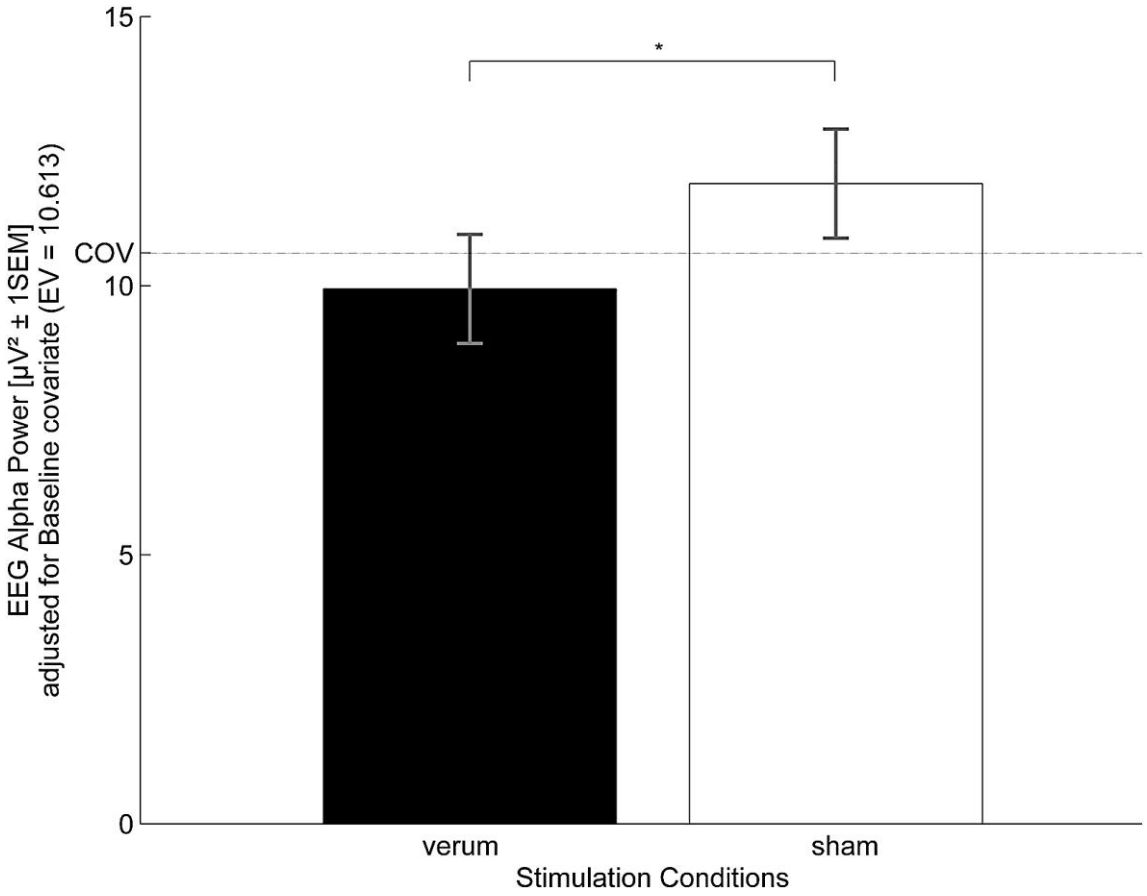


Taken from Pripfl et al. (2013, in press)

6.2.2 TMS EEG alpha mean power

In accordance with Pripfl et al. (2013, in press) the repeated measures ANOVA revealed a main effect in EEG alpha ($F[1,176] = 27.223$, $P < .001$, see **Figure 7**) as a function of stimulation condition (real<sham) as well as a main effect in time ($F[2,360] = 8.599$, $P < .001$) (Bonferroni: post2 < post1). No other effects could be observed for the alpha frequency band.

Figure 7 EEG alpha outcome TMS

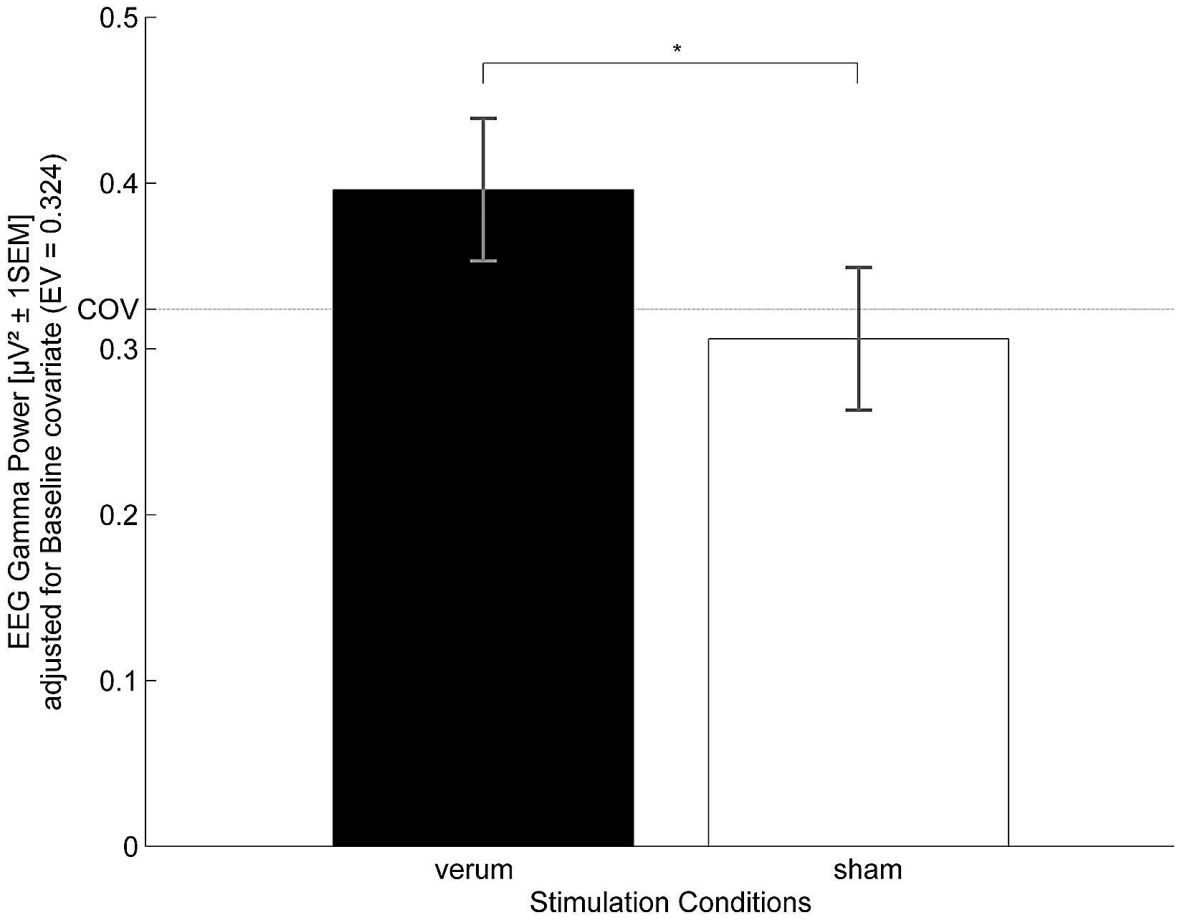


Taken from Pripfl et al. (2013, in press)

6.2.3 TMS EEG gamma mean power

After Pripfl et al. (2013, in press), the repeated measures ANOVA revealed a main effect in EEG delta ($F[1,166] = 19.616$, $P < .001$, see **Figure 8**) as a function of stimulation condition (real > sham), but no effect for the factor run or any interaction. However, there was a significant effect for electrode site ($F[8,259] = 3.824$, $P < 0.001$).

Figure 8 EEG gamma outcome TMS

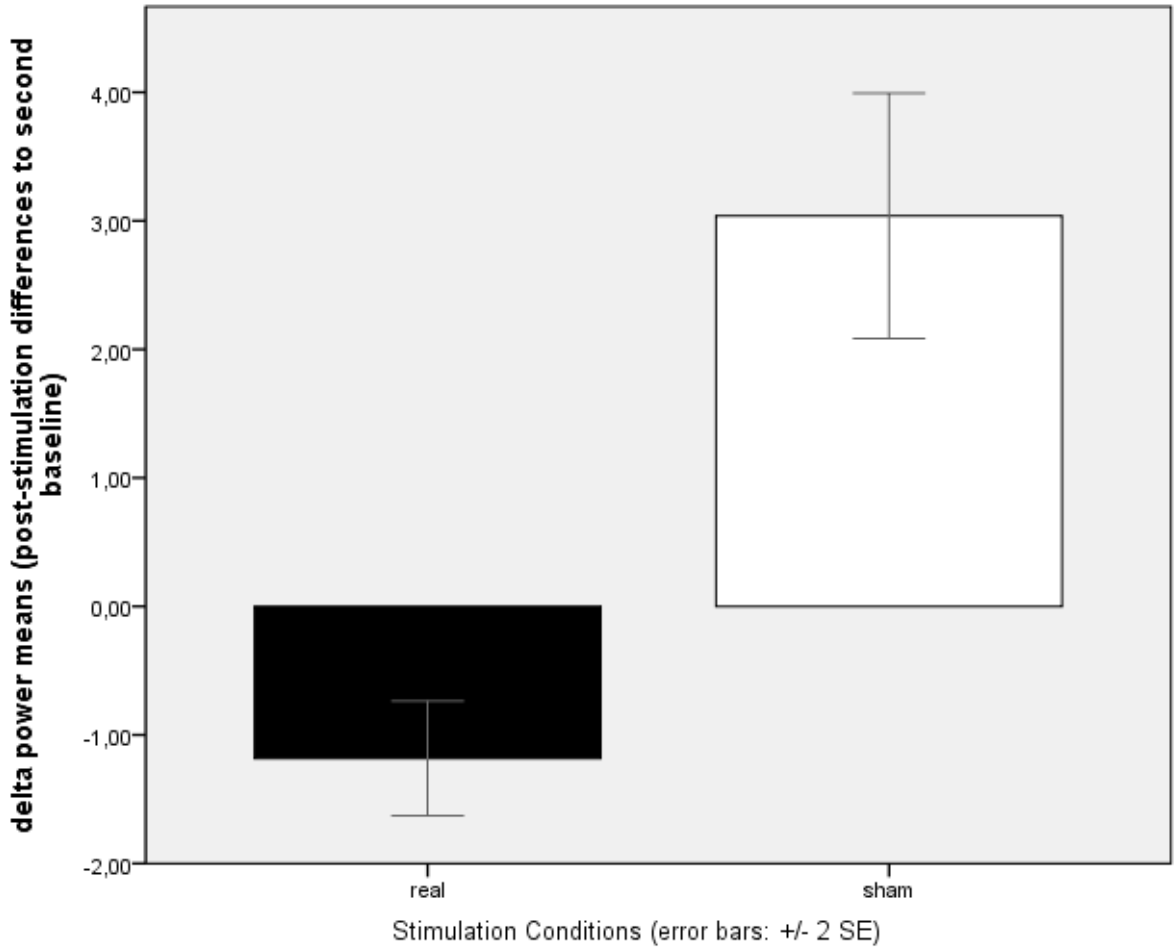


Taken from Pripfl et al. (2013)

6.2.4 tDCS EEG delta mean power

The repeated measures ANOVA revealed a main effect in EEG delta ($F[1,11] = 4.861$, $P = .050$, partial $\eta^2 = .306$, see **Figure 9**) as a function of stimulation condition (real < sham), but no effect for the factors run, electrode site or any interaction.

Figure 9 EEG delta power means tDCS

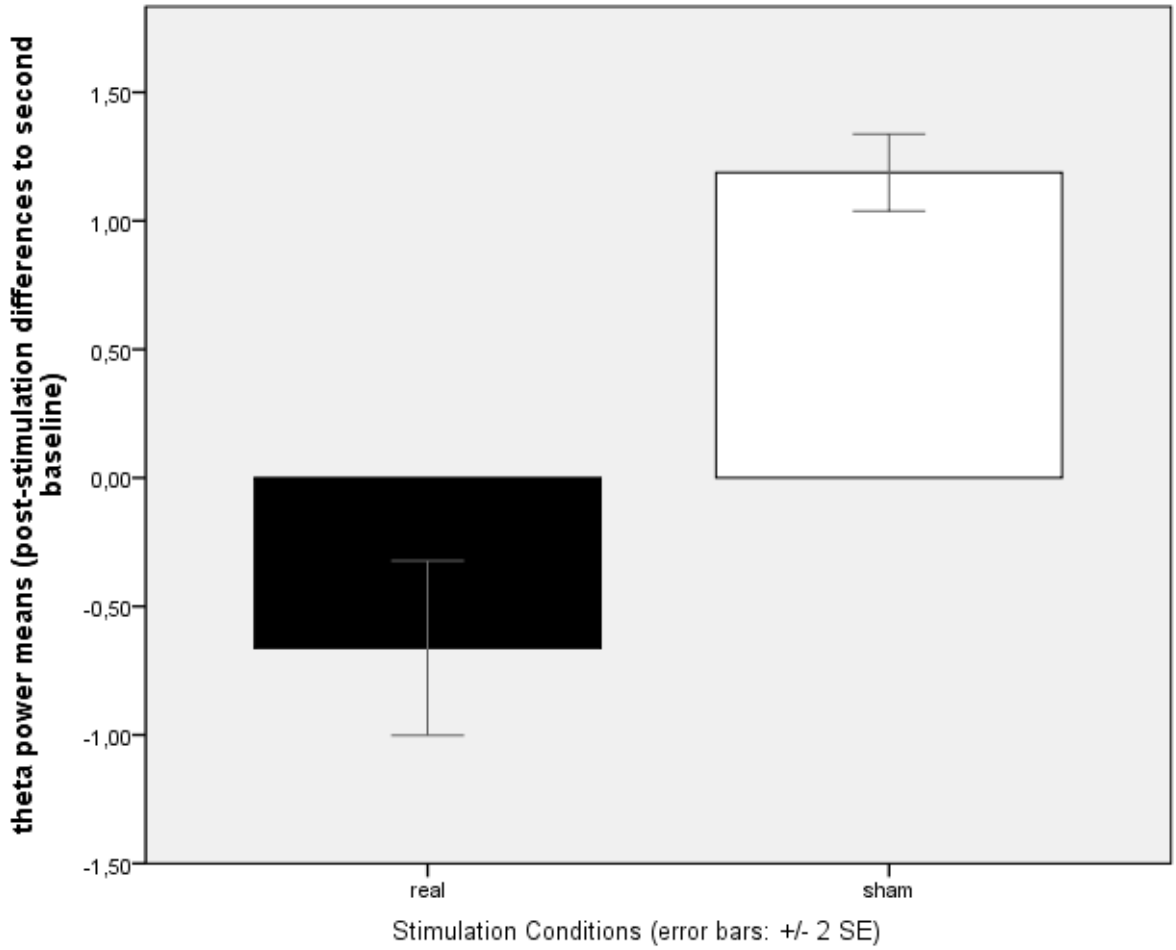


This figure displays the different delta means for real and sham stimulation after subtracting the second baseline from each post-stimulation run and consequently building the mean over all these post-stimulation differences.

6.2.5 tDCS EEG theta mean power

The repeated measures ANOVA revealed a main effect in EEG theta differences ($F[1,11] = 6.038$, $P = 0.032$, partial $\eta^2 = .354$, see **Figure 10**) as a function of stimulation condition (real < sham). However, no other statistical significant effects were observed for the theta frequency band.

Figure 10 EEG theta power means tDCS



This figure displays the different theta means for real and sham stimulation after subtracting the second baseline from each post-stimulation run and consequently building the mean over all these post-stimulation differences.

6.3 Questionnaires

6.3.1 PANAS tDCS

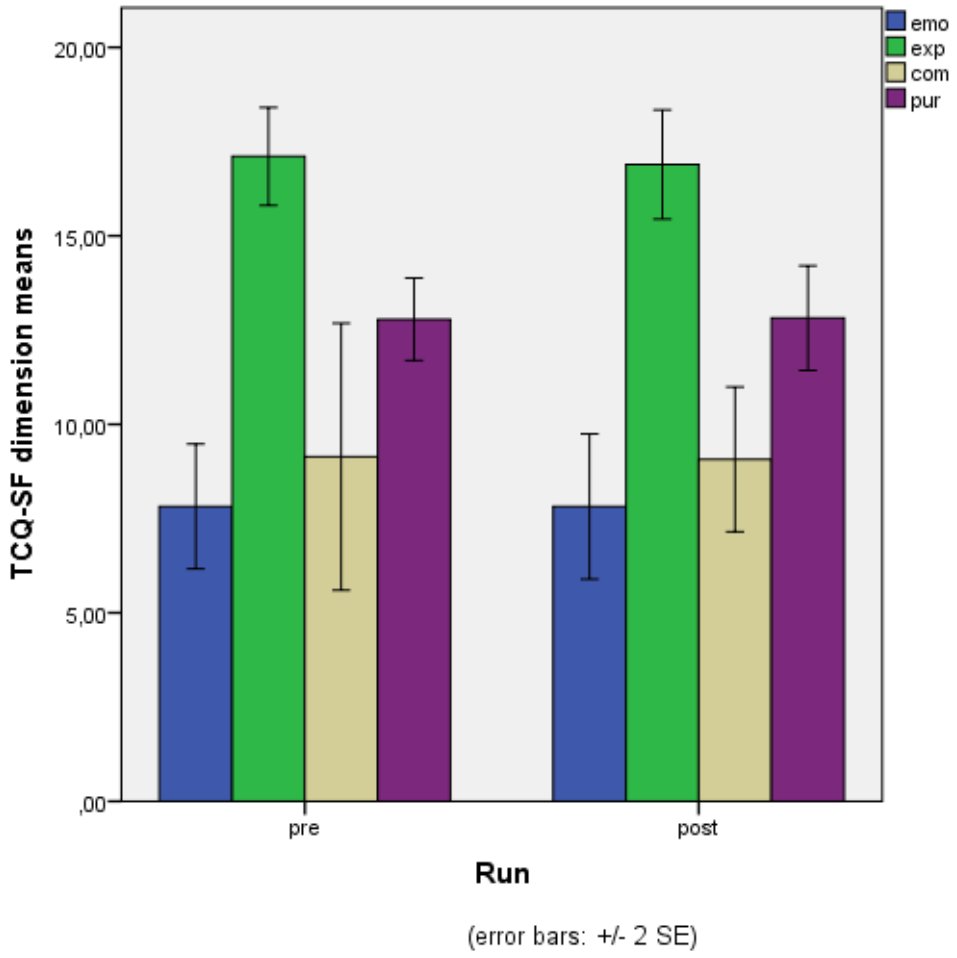
Differences between stimulation condition (real, sham) and run (pre, post) were calculated by means of a repeated measures ANOVA and separately for positive and

negative affect. Positive affect scored lower after experiment ($F[1,12]= 25.672$), $P < .001$) within the tDCS conditions. Negative affect scored lower within real sessions ($F[1,12] = 25.672$), $P = .006$) after tDCS application.

6.3.2 TCQ-SF tDCS

The repeated measures ANOVA (factors: stimulation condition (real, sham), run (pre, post), dimension (emotionality, expectancy, compulsivity, and purposefulness)) revealed a significant main effect for the factor dimension ($F(1.952,21.47) = 16.386$, $P < .001$, see **Figure 11**). No other significant difference could be observed. Since Mauchly's test indicated here that the assumption of sphericity had been violated (χ^2 (5) = 12.435, P = .030), degrees of freedom were corrected using the Greenhouse-Geisser estimates of sphericity ($\varepsilon = .651$). Bonferroni adjusted pairwise post-hoc comparisons revealed significant differences between the categories: emotionality and expectancy ($P < .001$) & purposefulness ($P = 0.019$), expectancy and emotionality ($P < .001$) & compulsivity ($P=.004$) & purposefulness ($P = 0.003$), compulsivity and expectancy ($P=0.004$) & purposefulness ($P = .047$) and purposefulness and emotionality ($P=.019$) & expectancy ($P = .003$) & compulsivity ($P = .047$). Expectancy scored the highest (mean = 17.00, SD = 3.264), followed by purposefulness (mean = 12.792, SD=3.131), compulsivity (mean = 9.271, SD = 6.715) and emotionality (mean = 7.458, SD = 4.506).

Figure 11 Means TCQ-SF tDCS



This figure displays the different means for the TCQ-SF dimensions pre and post the experiment.

6.3.3 PANAS TMS

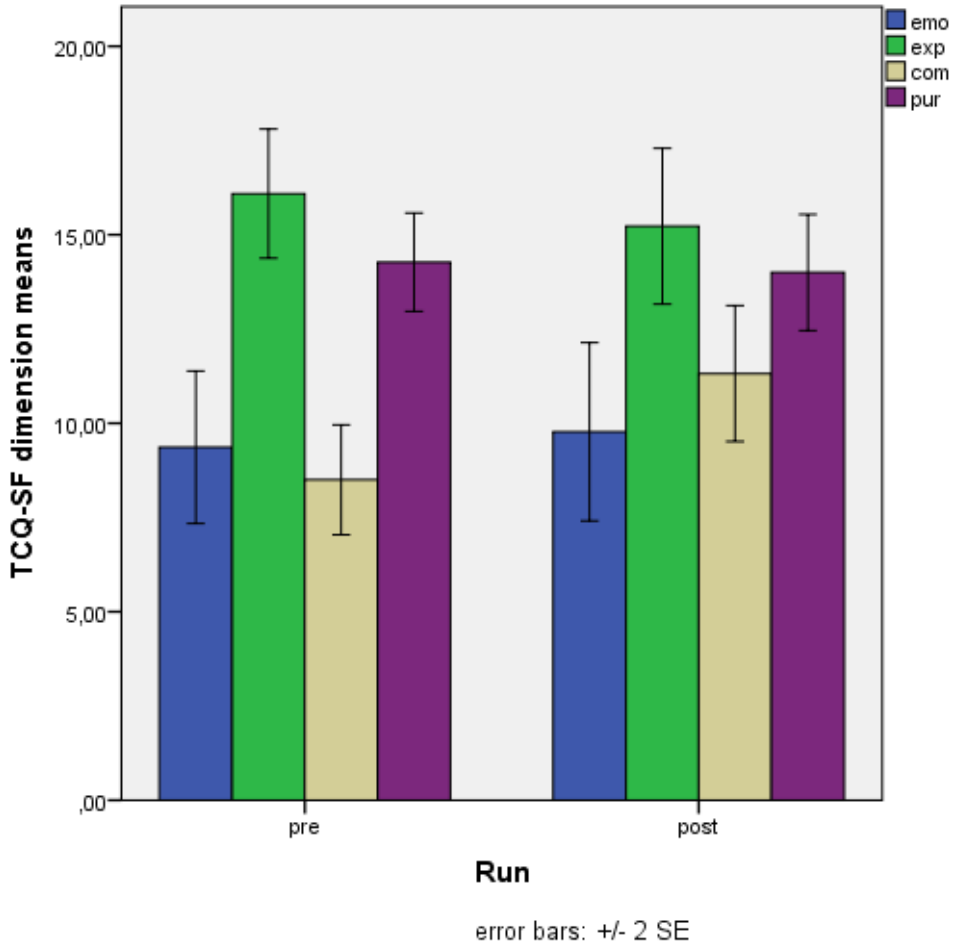
Differences between stimulation condition (real, sham) and run (pre, post) were calculated by means of a repeated measures ANOVA and separately for positive and negative affect. No mood effects could be observed.

6.3.4 TCQ-SF TMS

The repeated measures ANOVA (factors: stimulation condition (real, sham), run (pre, post), dimension (emotionality, expectancy, compulsivity, and purposefulness)) revealed a significant main effect for the factor quality ($F(3,30) = 18.071$, $P < .001$) and the interaction between quality*point in time ($F(1.907,19.075) = 7.28$, $P = .005$) (see **Figure 12**). Since Mauchly's test indicated for the interaction quality*point in time that the assumption of sphericity had been violated ($\chi^2(5) = 14.064$, $P = .016$), degrees of freedom were corrected using the Greenhouse-Geisser estimates of sphericity ($\varepsilon = .636$). Bonferroni adjusted pairwise post-hoc comparisons revealed significant differences between the categories: emotionality and expectancy ($P = .007$) & purposefulness ($P = .008$), expectancy and emotionality ($P = .007$) & compulsivity ($P = .004$), compulsivity and expectancy ($P = .004$) & purposefulness ($P = .002$) and purposefulness and emotionality ($P = .008$) & compulsivity ($P = .002$).

Expectancy scored the highest (meanpre = 16.091, SDpre = 4.023; meanpost = 15.227, SDpos t= 4.849), followed by purposefulness (meanpre = 14.272, SDpre = 3.058; meanpost = 14.0000, SDpost = 3.612) and the interaction of compulsivity over time (meanpre = 8.5, SDpre= 3.419; meanpost = 11,318, SDpost = 4.224). Compulsivity scored lower than emotionality (meanpre = 9.364, SDpre = 4.736; meanpost = 9.773, SDpost = 5.546) before the experiment, whereas it scored higher afterwards.

Figure 12 Means TCQ-SF TMS



This figure displays the different means for the TCQ-SF dimensions pre and post the experiment.

6.4 Adverse effects

Adverse effects where low for both stimulation sessions (real, sham). Adverse effects for tDCS can be found in **Table 5** below

Table 5 Adverse effects tDCS

tDCS	real	sham
Neck pain	2	1
Scalp pain	2	2
Tingling	2	0
Itching	3	0
Skin redness	3	3
Sleepiness	7	7

This table displays the absolute number of subjects reporting diverse adverse effects due to tDCS-application.

For the TMS condition adverse effects were not on hand.

7 CONCLUSIO

As expected, TMS led to a decrease in delta power as well as a significant craving reduction. This effect of the 'real' stimulation could be found over three points in time after stimulation, which means for a duration of circa 40min. This indicates a change in dopamine levels (see Knyazev, 2007) due to TM stimulation and behavioral changes due to TMS.

Similarly, a decrease in EEG delta could be found in the anodal condition of the tDCS group across all four post stimulation runs (circa 55min), also indicating a change in dopaminergic activity.

Those changes give a hint that both methods affect the meso-cortical dopamine system (see the **"Theoretical Background"** section).

Furthermore, as hypothesized, it came to a significant decrease in theta power after DC stimulation. Jacobson et al. (2012) found a similar effect while stimulating the inferior frontal gyrus, which was found to be associated with improved behavioral inhibition. As Feil et al. (2010) summarized, chronic nicotine dependent individuals have deficits in impulse control. Thus, DC stimulation in smokers could be a method to equilibrate this deficit.

Remarkably, changes in delta (partial $\eta^2 = .306$) and theta (partial $\eta^2 = .354$) power both explain about one third of the variance within the post tDCS sample, which is a quite large deal.

However, no behavioral changes after DC stimulation could be observed. There are two explanations (assumed by the author) for this: possibly the current intensity was too weak and/or the unconventional electrode setting did not lead to the expected changes. Furthermore, stimulation could have had an influence on "real world"-behavior. Since there were no differences in craving levels between real and sham, one might assume

that subjects felt the same cravings after each tDCS-application (real, sham), but possibly they could have controlled their cigarette consumption better transiently after real stimulation, because their ability to control their behavior would have been improved, like Jacobson et al. (2012) imply.

Concerning the rTMS experiment, promising observations in terms of future basic research and smoking treatment could be made. For tDCS the results are inconclusive, since the expected neuronal effect (decreased theta power) could be found but no behavioral changes. Further research is needed.

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9 APPENDIX

9.1 CIC Task

Figure 13 Showcase CIC picture

Taken from Renate Neumann und Ulla Köhler (2012)

Figure 14 Showcase neutral picture

Taken from the IAPS (Lang et al.,1999)

VpnCode: _____ *Testdatum:* _____
Testleiter: _____ *Session:* _____

Fragebogen zur Erfassung von Beeinträchtigungen nach Transkranieller Magnetstimulation

Haben Sie eines der folgenden Syptome oder Nebenwirkungen wahrgenommen?

	Kreuzen sie das entsprechende Kästchen an				Wenn vorhanden, ist Ihrer Meinung nach die Stimulaton dafür verantwortlich?			Wenn vorhanden, wann ist es aufgetreten? (Mehrfachantworten möglich)							
								Während Stimulation:			Nach der Stimulation:				
	nicht vorhanden	leicht vorhanden	Mittel mäßig vorhanden	stark vorhanden	nein, sicher nicht	ja, möglicherweise	ja, ganz sicher	nur zu Beginn für ca. eine halbe Minute	nur kurz vor Ende der Stimulation	während der gesamten Stimulations-dauer	während der ersten Aufgabe	während der zweiten Aufgabe	während der dritten Aufgabe	derzeit	
Kopfschmerzen															
Nackenschmerzen															
Schmerzen auf der Kopfhaut															
Kribbeln															
Jucken															
Brennen															
Hautröting															
Schläfrigkeit															
Konzentration auf Sorgen/Probleme															
Stimmungsschwankungen															

1

VpnCode: _____ *Testdatum:* _____
Testleiter: _____ *Session:* _____

Waren die Aufgaben für Sie verständlich?

☐ Ja ☐ Nein

Wenn nicht, welche Aufgabe war nicht verständlich, und warum nicht?

Ist ihnen bei der Präsentation der Aufgaben irgendetwas aufgefallen, dass ihnen sonderbar vorgekommen ist?

[ ] Ja [ ] Nein

Wenn ja, bei welcher Aufgabe und was?

Social, Cognitive and Affective Neuroscience Unit
tDCS TeilnehmerInnen-Checkliste
Version Oktober 03, 2011

Name: _____ Geburtsdatum: _____

Datum der Untersuchung: _____

Transkranielle Gleichstromstimulation (tDCS) ist eine sichere und nützliche Methode zur Untersuchung der Funktionsweise des menschlichen Gehirns. tDCS kann ohne Risiko für Ihre Gesundheit und Sicherheit eingesetzt werden, sofern Sie bestimmte Kriterien erfüllen. Bitte beantworten Sie wahrheitsgetreu die folgenden Fragen (durch Ankreuzen der entsprechenden Antwort):

(1). Hatten Sie jemals eine negative Reaktion auf eine tDCS-Untersuchung?

[Ja] [Nein]

(2). Hatten Sie jemals einen epileptischen Anfall?

[Ja] [Nein]

(3). Hatten Sie jemals einen Gehirnschlag?

[Ja] [Nein]

(4). Hatten Sie jemals eine Kopf- oder Gehirnoperation?

[Ja] [Nein]

(5). Haben Sie Metallteile in Ihrem Körper (ausgenommen Zahnimplantate oder Plomben), wie etwa Schrapnell, chirurgische Implantate/Clips, oder (auch kleine) Metallteile vom Schweißen oder der Metallbearbeitung?

[Ja] [Nein]

(6). Haben Sie irgendwelche implantierten Geräte, wie etwa Herzschrittmacher, medizinische Pumpen, oder Herzkathether bzw. -drähte?

[Ja] [Nein]

(7). Leiden Sie an schweren Kopfschmerzen, oder haben Sie häufig Kopfschmerzen?

[Ja] [Nein]

(8). Hatten Sie jemals andere, mit dem Zentralnervensystem (Gehirn) in Zusammenhang stehende Probleme oder Störungen?

[Ja] [Nein]

(9). Hatten Sie jemals eine Krankheit, die zu einer Gehirnschädigung führte?

[Ja] [Nein]

(10). Nehmen Sie psychiatrisch verordnete oder sonstige psycho- oder neuroaktive Medikamente (z.B. Antidepressiva, Neuroleptika, Lithium)?

[Ja] [Nein]

(11). Falls Sie eine Frau sind: Sind Sie schwanger?

[Ja] [Nein]

Datum der letzten Periode: _____

Falls länger als 30 Tage: Kann es sein dass Sie schwanger sind?

[Ja] [Nein]

(12). Hatte jemand in Ihrer Familie jemals einen epileptischen Anfall?

[Ja] [Nein]

(13). Sind Sie beruflich regelmäßig mit dem Lenken von Kraftfahrzeugen (Auto, LKW, Bus, Tram, Zug) oder dem Bedienen von sonstigen selbstfahrenden Fahrzeugen beschäftigt?

[Ja] [Nein]

(14). Hatten Sie letzte Nacht unzureichend Schlaf?

[Ja] [Nein]

(15). Haben Sie letzte Nacht große Mengen an Alkohol, Nikotin, oder sonstigen psychotropen Substanzen konsumiert?

[Ja] [Nein]

(16). Sind Sie drogenabhängig, alkoholabhängig, oder medikamentenabhängig?

[Ja] [Nein]

(17). Haben Sie eine chronische Hauterkrankung?

[Ja] [Nein]

Falls ja: betrifft diese Ihre Kopfhaut?

[Ja] [Nein]

(18). Haben Sie metallische Gegenstände in ihrer Kleidung oder am Körper – inkl. Piercings, Ohrringe? Falls ja: bitte legen Sie diese ab.

[Ja] [Nein]

Anmerkungen Testleiter/-in:

Ich wurde darüber aufgeklärt, dass ich für mindestens 3 Stunden nach der Untersuchung kein Kraftfahrzeug lenken darf.

Unterschrift Versuchsperson: _____, am_____

Unterschrift TestleiterIn: _____, am _____

Fagerström Test for Nicotine Dependence (FTND)*

1. Wann nach dem Aufwachen rauchen Sie Ihre erste Zigarette ?		
	Innerhalb von 5 Minuten	3 Punkte
	Innerhalb von 6 bis 30 Minuten	2 Punkte
	Innerhalb von 30 bis 60 Minuten	1 Punkt
	Es dauert länger als 60 Minuten	0 Punkte
2. Finden Sie es schwierig, an Orten, wo das Rauchen verboten ist (z.B. in der Kirche, in der Bibliothek, im Kino, usw.) das Rauchen sein zu lassen ?		
	ja	1 Punkt
	nein	0 Punkte
3. Auf welche Zigarette würden Sie nicht verzichten wollen ?		
	Die erste am Morgen	1 Punkt
	andere	0 Punkte
4. Wie viele Zigaretten rauchen Sie durchschnittlich pro Tag?		
	> 30	3 Punkte
	21 - 30	2 Punkte
	11 - 20	1 Punkt
	0 -10	0 Punkte
5. Rauchen Sie in den ersten Stunden nach dem Erwachen im allgemeinen mehr als am Rest des Tages ?		
	ja	1 Punkt
	nein	0 Punkte
6. Kommt es vor, dass Sie rauchen, wenn Sie krank sind und tagsüber im Bett bleiben müssen?		
	ja	1 Punkt
	nein	0 Punkte

0-2 Punkte: geringe Abhängigkeit, 3-5 Punkte: mittlere Abhängigkeit, 6-7 Punkte: starke Abhängigkeit, 8-10 Punkte: sehr starke Abhängigkeit

***** Fagerström KO, Schneider NG. Measuring nicotine dependence: A review of the Fagerström Tolerance Questionnaire. *J Behav Med*. 1989; 12:159-181.

VpnCode: _____ *Testdatum:* _____
Testleiter: _____ *Session:* _____

PANAS- Inventar

Zeitpunkt der Vorgabe: ☐ vor dem Experiment ☐ nach dem Experiment

Dieser Fragebogen enthält eine Reihe von Wörtern die unterschiedliche Gefühle und Emotionen beschreiben. Lesen Sie bitte jedes Wort und markieren Sie daneben, wie sehr Sie dieses Gefühl derzeitig fühlen.

	gar nicht	**ein bisschen**	**einigermaßen**	**erheblich**	**äußerst**
1. Aktiv					
2. Interessiert					
3. Freudig erregt					
4. Stark					
5. Angeregt					
6. Stolz					
7. Begeistert					
8. Wach					
9. Entschlossen					
10. Aufmerksam					
11. Bekümmert					
12. Verärgert					
13. Schuldig					
14. Erschrocken					
15. Feindselig					
16. Gereizt					
17. Beschämt					
18. Nervös					
19. Durcheinander					
20. Ängstlich					

VpnCode: _____ *Testdatum:* _____
Testleiter: _____ *Session:* _____

Zeitpunkt der Vorgabe: ☐ vor dem Experiment ☐ nach dem Experiment

Kurzform des Tabak Craving Fragebogens (TCQ-SF)

Instruktion:

Im Folgenden sehen Sie eine Reihe von Aussagen, die das Verlangen nach einer Zigarette widerspiegeln. Zeigen Sie, in wieweit Sie der Aussage zustimmen oder diese ablehnen, indem sie ein Kästchen auf der untenstehenden Skala ankreuzen. Durch das Ankreuzen des Kästchens ganz links lehnen Sie die Aussage sehr stark ab; durch das Ankreuzen des Kästchens ganz rechts stimmen Sie der Aussage sehr stark zu. Falls Ihre Meinung zwischen den zwei Extremen liegt, benutzen Sie die dazwischen liegenden Kästchen. Durch das Ankreuzen des mittleren Kästchens stimmen Sie der Aussage weder zu, noch lehnen Sie diese ab.

Bitte füllen Sie den Fragebogen vollständig aus und beurteilen Sie nur Ihr **jetziges, momentanes** Verlangen nach einer Zigarette.

1. Ich würde jetzt gerne eine Zigarette genießen.

Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

2. Wenn ich jetzt gerade eine Zigarette rauchen würde, wäre ich nicht fähig aufzuhören.

Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

3. Wenn ich eine angezündete Zigarette gerade in der Hand halten würde, würde ich Sie wahrscheinlich rauchen.

Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

4. Eine Zigarette würde gerade gut schmecken.

Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

VpnCode: _____ *Testdatum:* _____
Testleiter: _____ *Session:* _____

5. Ich wäre weniger nervös, wenn ich jetzt rauchen könnte.

   Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

6. Es wäre sehr schwer auf eine Möglichkeit zu rauchen zu verzichten.

   Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

7. Ich könnte mich selbst nicht vom Rauchen abhalten, wenn ich Zigaretten hier hätte.

   Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

8. Eine Zigarette jetzt zu rauchen, wäre sehr angenehm.

   Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

9. Wenn ich gerade eine Zigarette rauchen würde, könnte ich klarer denken.

   Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

10. Ich könnte nicht kontrollieren, wie viel ich rauche, wenn ich Zigaretten hier hätte.

VpnCode: _____ *Testdatum:* _____
Testleiter: _____ *Session:* _____

Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

11. Ich könnte nicht leicht einschränken, wie viel ich im Augenblick rauchen würde.

Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

12. Ich könnte kontrollierter agieren, wenn ich gerade rauchen könnte.

Starke Ablehnung ☐ ☐ ☐ ☐ ☐ ☐ ☐ Starke Zustimmung

9.3 CV

Schooling:

- 27.02.10 pre-degree in Psychology
- since 01.10.2012 Southasian studies, University of Vienna
- since 01.10.2008 Psychology, University of Vienna
- 19.06.07 Abitur (Geschwister-Scholl-Gymnasium, Lebach, Germany)

Languages:

- German: *Native speaker*
- French: 7 years (school), *DELF A2*
- Latin: 7 years (school), *advanced proficiency certificate in Latin*
- English: 4 years (school), *IELTS 7.5*
- Swedish: *autodidactical*, several stays in different parts of Sweden
- Modern Tibetan: *Beginner*

Internships:

- February 2009 psychiatric hospital
  (Kliniken am Sonnenberg, Saarbrücken, Germany)
- 01.04.08- 15.09.08 French boarding school for special needs adolescents
  (LeChampdelaCroix, Orbey, Alsace)
- 01.10.08-21.12.08 Swedish psychosocial institution
  (Anne-Ro, Kättsbo, Garpenberg; Dalarna)

Work:

- July 2010-November 2013 Special needs workshop (Komit GmbH)
- Oct. 2012-August 2013 Assisted Living (GIN)

Conferences:

- March 2013 Interdisciplinary College on Cognitive Science
- June 2011 12th European Conference on Traumatic Stress
- May 2011 „Jubiläumskongress", Psychosomatic Centre Waldviertel

9.4 Summary

Abstract. TMS and tDCS are both state-of-the-art neurostimulation methods. However, still few is known about their effects and possible applications. The object of this thesis is to compare the lasting effects of both methods on smokers. All of the subject underwent the same experimental procedure and were either stimulated with TMS or tDCS.

Methods. 28 smokers (final analyses 23 subjects) matching the ICD-10 criteria for smoking dependency underwent either rTMS (12min, 10Hz, 90% of MT) or tDCS (15min, 0.4 mA, anodal) over left DLPFC. Both conditions were placebo-controlled. 4 resting EEGs and 3 CIC-tasks were performed after stimulation.

Results. Significant changes in delta mean power for both stimulation techniques at least 40min lasting for TMS ($F[1,138] = 3.975$, $P = .048$; repeated linear mixed model) and 55min lasting for tDCS ($F[1,11] = 4.861$, $P = .050$, partial $\eta^2 = .306$; repeated-measures ANOVA) could be observed. Additionally, a decrease in theta mean power - also 55min lasting after tDCS ($F[1,11] = 6.038$, $P = .032$, partial $\eta^2 = .354$; repeated-measures ANOVA). Significant craving reduction for ($F[1,67] = 4.135$, $P = .046$, (real < sham)) but no such effect for tDCS could be observed.

Conclusio. Both stimulation conditions had significant lasting effects on EEG frequency bands. However, only TMS application led to a decrease in cue-induced craving. More research is needed.

9.5 Zusammenfassung

Abstrakt. TMS und tDCS sind Neurostimulationsmethoden auf dem neuesten Stand der Technik. Trotzdem ist noch wenig über die Art ihrer Wirkung und potentieller Anwendungsgebiete bekannt. Diese Arbeit hat den Vergleich der anhaltenden Wirkung im unmittelbaren Zeitraum nach der Stimulation von RaucherInnen zum Gegenstand.

Alle Versuchspersonen durchliefen die gleiche experimentelle Prozedur und wurden entweder mit TMS oder tDCS stimuliert.

Methoden. 28 RaucherInnen (endgültige Analysen 23 Versuchspersonen) die den ICD-10-Kriterien für Nikotinabhängigkeit entsprachen, wurden entweder mittels rTMS (12min, 10Hz, 90% des MT) oder tDCS (15min, 0.4 mA, anodisch) über dem linken DLPFC stimuliert. Beide Stimulationsmethoden wurden plazebokontrolliert. Nach der Stimulation wurden jeweils 4 Ruhe-EEG-Aufgezeichnet und 3 CIC-tasks durchgeführt.

Ergebnisse. Eine signifikante Abnahme der durchschnittlichen delta-Leistung ($F[1,138] = 3.975$, $P = 0.048$; repeated linear mixed model) konnte bis mindestens 40min nach Ende der Stimulation beobachtet werden und eine 55-minütige Abnahme für tDCS ($F[1,11] = 4.861$, $P = .050$, partial $\eta^2 = .306$; repeated-measures ANOVA). Außerdem eine 55-minütige Abnahme der theta-Leistung nach tDCS ($F[1,11] = 6.038$, $P = 0.032$, partial $\eta^2 = .354$; repeated-measures ANOVA). Es kam zu einer Verringerung des cravings nach Zigaretten nach rTMS, ($F[1,67] = 4.135$, $P = .046$, (real < sham)), jedoch nicht nach tDCS.

Conclusio. Beide Methoden zeigten einen signifikanten Effekt auf die Gehirnaktivität (Frequenzbänder). Lediglich die Anwendung von rTMS führte zu verringertem cue-induced craving. Weiterführende Studien sind notwendig.