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The impact of tDCS on nicotine craving and affective image evaluation

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Abstract

Theoretical background: Transcranial direct current stimulation (tDCS) studies over the left dorsolateral prefrontal cortex (DLPFC) have shown to decrease cue-induced craving, to change affective picture evaluation and to increase working memory performance. In most studies electrodes were used which did not only activate the DLPFC but other brain areas as well. Studies applying tDCS over the left DLPFC with small electrodes to only affect DLPFC could not replicate these results. Hence another area which is affected with tDCS over the left DLPFC using big electrodes needs to cause the effects. Brain imaging studies suggest the ventrolateral prefrontal cortex (VLPFC) to be involved in all three paradigms.

Methods: Anodal tDCS was applied over the left DLPFC/VLPFC using an electrode of 35 cm^2 area. To investigate separately stimulation of left DLPFC and VLPFC, anodal tDCS was applied using an EEG electrode either over the one or the other. Additionally, sham stimulation was done as a control. To examine the effect of tDCS, a craving and affective picture evaluation task and a 3-back task were used. Whereas the craving and affective picture evaluation task measured cue-induced craving, actual craving was investigated by frequent ratings during sessions. To compare craving levels before and after stimulation, a questionnaire was used.

Results: Apart from the result that anodal tDCS over the VLPFC decreases accuracy in the 3-back task, no influence of anodal tDCS was found. Craving evaluation conducted a raise of the craving factor compulsivity in all four tDCS conditions between the beginning and the end of each session. Further craving ratings differed between smoking cues and other pictures as well as valence which was rated differently between all types of pictures (negative, positive, neutral and smoking cues). Arousal was altered between negative and neutral as well as negative and positive pictures.

Conclusion: The results of this study stand in contrast to what was proposed from previous research. Neither left DLPFC nor left VLPFC seem to be the reason for alteration in cue induced craving, picture evaluation and working memory performance in previous studies. For the lacking impact of anodal tDCS using big

electrodes in this study, the differences in tDCS parameters, study conduction and subject traits could be a reason. Further studies to get a clearer picture of tDCS are needed

Introduction

Smoking is a growing health problem in the western society (Tuesta, Fowler & Kenny, 2011). Many people want to stop smoking, but a problem in smoking withdrawal is the high rate of relapse which is strongly induced by craving for nicotine (Jorenby, 1998; Baker, Brandon & Chassin, 2004; Swan, Ward & Jack, 1996).

Emotion dysregulation is associated with diseases like drug addiction (Gross, 1998; Heaterthon & Wagner, 2011). Neuronal substrate for regulation of emotions and nicotine craving is inter alia the lateral prefrontal cortex (Davidson, 2004; Lee, Lim, Wiederholf & Graham, 2005; Wager, Davidson, Hughes, Lindquist & Ochsner, 2008; Wilson, Sayette & Fiez, 2004; Yalachkov et al., 2012)

For both – nicotine addiction and emotion dysregulation – several studies using transcranial direct current stimulation (tDCS) have proposed that this non-invasive method could be used as a future treatment (Boggio et al., 2007; Boggio et al., 2008a; Boggio et al., 2009a; Brunoni et al., 2011a; Ferrucci et al., 2009). But not all studies agree in the effects of tDCS on smoking and emotion (Köhler, 2012). Hence further research is required to investigate the effects of this possible future treatment.

Therefor this study compared different settings of tDCS on their influence on emotion and craving. Additionally the impact on working memory was examined and used as a reference, because several tDCS studies with varying parameters successfully modified working memory performance (Fregni et al., 2005; Keeser et al., 2011; Marshall et al., 2005; Ohn et al., 2008).

Theory

Transcranial direct current stimulation

The principle

For tDCS a pair of battery-driven electrodes is used to build a circuit of controlled current. It is a cheap, non-invasive, flexible and well-tolerated method. Its disadvantages are the lack of a precise focus and the small stimulation intensities (Dmochowski, Datta, Bikson, Su & Parra, 2011).

Up to 2 mA for a stimulation period of 20 min are regarded as safe (Utz, Dimova, Oppenländer & Kerkhoff, 2010). Metal implants after brain surgery, sensible scalp and epilepsy are listed as exclusion criteria (Hesse et al., 2007). Furthermore, Hesse et al. (2007), who tested stroke patients for their studies, excluded patients taking neuroleptic and antiepileptic drugs, antidepressants, L-dopamine and benzodiazepines.

TDCS generates a current that flows between two or more electrodes and thereby changes the polarity in the brain. Depending on the polarity of the treatment, this noninvasive method can activate or deactivate the affected brain region (Andrews, Hoy, Enticott, Daskalakis & Fitzgerald, 2011; Nitsche et al., 2007; Suh, Lee, Cho, Kim & Kim, 2010).

In anodal stimulation, the active electrode is an anode, the referring electrode a cathode. Hence the area around the active electrode depolarizes, as the negative charge flows to the cathode. Thereby the neurons near the anode are depolarized, which activates this region (Marshall et al., 2005).

Cathodal stimulation works vice versa, meaning that neurons are hyperpolarized, which makes it more difficult to build an action potential. Thereby the firing rate is decreased (Marshall et al., 2005; Suh et al., 2010).

A third form of treatment is the so-called sham stimulation for which stimulation only happens in the first few seconds of the treatment. It is used as a control condition because it evolves the same itching sensation like a real stimulation at the beginning

of a treatment. This sensation usually vanishes after a few seconds, but subjects do not notice when the current is switched off a few seconds after the start (Fregni et al., 2005; Nitsche et al., 2008; Utz et al., 2010).

Important parameters in tDCS are current intensity, site of stimulation and duration of the stimulation. The first two elements form the current density, which is defined as the quotient from current strength and electrode size (Liebetanz, Nitsche, Tergau & Paulus, 2002; Ohn et al., 2008; Vines, Nair & Schlaug, 2006). Usually, current densities, of 0.029 to 0.08 mA/cm^2 are used (Nitsche et al, 2008). In order to have any effect, a minimum of 0.017 mA/cm^2 is required (Nitsche et al., 2007).

When the electrode size is changed, the current strength has to be changed, too in order to receive the same current density, which is important to obtain the same effect and to not induce too high densities (Vines et al, 2006). Muscle spasm and skin burn could occur (Im, Jung, Choi, Lee & Jung, 2008).

Parameters on current intensity reaching the target region are skin resistance, skull resistance, the resistance of intracranial structures such as blood vessels, cerebrovascular fluid and the resistance of the brain tissue, which depends on cell type and cell structure (Brunoni, 2011b). Skull defects also change the distribution of the current in the brain (Datta, Elwassif, Battaglia & Bikson, 2008). The higher the induced current density, the deeper are the regions reached by the current (Vines et al, 2006).

The cerebrospinal fluid, which has the highest conductivity, is important. Regions enclosed/perfused by it are more likely to be reached, even when they are not located directly beyond the electrode (Datta et al, 2009a; Dmochowski et al., 2011; Nitsche et al., 2007).

Whether an anodal stimulation increases excitability depends on the orientation of neurons (Ardolino, Bossi, Barbieri & Priori, 2005; Schlaug & Renga, 2008; Utz et al., 2010; Wagner et al., 2007). Neuronal cells which are located deeper in the cortex may be stimulated by cathodal instead of anodal tDCS (Utz et al., 2010).

If the treatment with tDCS only takes a few seconds, no aftereffects can be found. But if a treatment with an intensity of 1 mA takes 20 minutes, a pause of 48 hours has to be made between two treatments because of aftereffects of tDCS. The changed excitability could last for more than one hour (Nitsche et al., 2008).

Safety

The skin might be reddened after the stimulation. An irritation of the scalp could be caused by heat, changes in pH and other chemical burns. Heat could be produced by chemical reactions at the electrode-gel-border, as well as the joule heat of the electrical current and temperature might be also influenced by a higher blood flow caused by tDCS (Datta, Elwassif & Bikson, 2009b; Minhas et al., 2010).

The brain is sensitive to changes of temperature. An increase of the temperature of 1°C can disturb single neurons as well as the neuronal network function. An exposure to 40°C for a longer period of time leads to damages of the tissue. The temperature is regulated by heat conduction to the surrounding tissue, by scalp heat loss, by the blood flow as well as by other thermoregulatory responses like sweating (Datta et al, 2009b). Datta et al. (2009b) showed that the scalp temperature increases during stimulation, but that the temperature of the brain tissue remains unaffected during tDCS. This means that the scalp might be irritated by the stimulation, but the brain is not affected (Datta et al, 2009b).

Adverse effects of tDCS are inter alia itching, tingling, headache or burning of the skin, which are more often reported in studies with high current (Brunoni et al., 2011c).Tingling and itching occurs at the beginning of stimulation beneath the electrodes, but vanishes after a few seconds (Dundas, Thickbroom & Mastaglia, 2007). Additionally redness of skin can appear, but when a current of only 1 mA is used, it normally disappears after some minutes (Palm et al., 2008).

Biochemical background

Studies report about biochemical alterations caused by tDCS. An example is the second messenger myoinositol which increases after anodal tDCS. The underlying mechanism has not been found yet. There are different explanations including its electric properties or the change of biophysical properties of the membranes. These are obtained by a changed membrane phospholipide mechanism. Thereby, myoinositol as a compound of different phospholipids is affected (Rango et al., 2008).

There are also tDCS induced changes of neurotransmitters. The study of Stagg et al. (2009) showed a decrease of GABA after anodal and a decrease of glutamate after cathodal stimulation. When less glutamate is synthesized out of glutamine, this results in a reduced excitatory neuronal transmission, which matches with effects of cathodal tDCS. In contrast, an explanation for the decreased GABA is the smaller amount of glutamic acid carboxylase 67 during increased neuronal firing (Stagg et al., 2009).

The change in the activity during tDCS can be explained by hyperpolarization and depolarization. After-effects of either anodal or cathodal tDCS are caused by other factors (Nitsche et al., 2003b). Nitsche et al. (2003b) showed that nine minutes of tDCS induced after-effects of up to one hour. Even longer effects (five hours) were shown after a stimulation of 10 to 30 minutes (Nitsche & Paulus, 2000).

Pharmacological studies found that the N-methyl-D-aspartate (NMDA) receptor is involved in longer lasting effects of tDCS (Nitsche et al., 2003a). When dextromethorphane, a NMDA-receptor-antagonist was administered, the after-effects of cathodal as well as of anodal tDCS were suppressed. The influence of NMDA receptors might be due to long-term potentiation (LTP) and long-term depression (LTD), modifications of post-synaptic connections which are dependent on the NMDA receptor (Schlaug & Renga, 2008). When these proteins are blocked, plastic alterations become unlikely (Liebetanz et al., 2002).

The Bienenstock-Cooper-Munro rule of synaptic modifications uses dynamic adaption of modification thresholds to explain the stabilization of neuronal activity. If

the level of postsynaptic responses decreases, the result is LTD, if the level is higher, it results in LTP (Siebner et al., 2004).

Nitsche et al. (2004) supported the finding of the NMDA receptors´ influence on after-effects of tDCS. It was proven that D-Cycloserine, a NMDA-agonist, increases the after-effects of anodal tDCS. As the drug alone is not able to change neuronal excitability, its effects may be caused by its binding to a glycine binding side on NMDA receptor, which facilitates opening the channel. This is important for LTP (Ardolino et al., 2005).

In case of anodal tDCS the function of the voltage sensitive NMDA receptors in the after-effects might be caused by its activation. Supported by increased intracellular calcium levels, this raises the synaptic strength and thereby induces longer lasting effects (Liebetanz et al., 2002).

In cathodal tDCS the hyperpolarization is followed by a depression of the synaptic strength. Some pharmacological studies led to the theory that these effects were also caused by the NMDA receptor. But an explanation has not been found yet. (Liebetanz et al., 2002)

Another pharmaceutical substance which suppresses the effects of (only anodal) tDCS is carbamazepine. Its function is to stabilize the membrane potential via voltage-gated sodium channels. This works through binding to blocked sodium channels and thereby slowing down their recovery. The positive charged sodium ions play a role in depolarization (Liebetanz et al., 2002; Schlaug & Renga, 2008).

The observation that carbamazepine only influences the effects of anodal but not of cathodal tDCS could be explained by the fact that it is only active when the membrane potential is reduced (Liebetanz et al., 2002).

In short, these findings try to explain the mechanisms behind the lasting effect of tDCS. Results show that the NMDA receptor, LTPs and LTDs play a crucial role in the remaining of depolarization via anodal and hyperpolarization via cathodal tDCS. Additionally, the depolarization is influenced by sodium ions, as the study with carbamazepine suggests.

Applications

TDCS has shown to increase cognitive functions in healthy subjects like the working memory (Andrews et al., 2011; Fregni et al., 2005), verbal comprehension (Fecteau et al., 2007b; Boggio et al., 2010a) and the declarative memory (Javadi, Cheng & Walsh, 2011). Furthermore, muscle endurance can be increased and muscle fatigue decreased through anodal tDCS, which can be applied in normal as well as in pathological conditions (Cogiamanian, Marceglia, Ardolino, Barbieri & Priori, 2007).

One branch of current research focuses on clinical applications of tDCS. To improve motor function in stroke patients (Hummel & Cohen, 2005; Schlaug & Renga, 2008) and Parkinson´s disease patients (Fregni et al., 2006a), the motor cortex is stimulated. In the therapy of stroke the aim is to decrease the imbalance of the two hemispheres. Two different treatments are used: Anodal stimulation on the lesional motor region or cathodal tDCS on the contralesional motor region (Schlaug & Renga, 2008). In addition to motor function, speech rehabilitation after a stroke could also be supported by tDCS (Dmochowski et al., 2011).

Further possibilities for clinical application might be cases of migraine (Antal et al., 2008), depression (Brunoni et al., 2011a; Boggio et al., 2007; Boggio et al., 2008a), fibromyalgia (Fregni et al., 2006b) and pain (Boggio, Zaghi & Fregni, 2009b), epilepsy (Fregni et al., 2006c) as well as cases of drug addiction (Boggio et al., 2008b; Boggio et al., 2010b).

Limitations

For tDCS studies big sized electrodes are commonly used (mostly 35 cm^2). Studies with small electrodes, especially below 5 cm^2, are scarce. The advantage of smaller electrodes is that they increase focality, as bigger electrodes cover bigger parts of the head (see figure 1). Hence more regions are affected by the current.

Nitsche et al. (2007) have shown that a reduction of the active electrode size above the abductor digiti minimi muscle (ADM) region of the primary motor cortex from 35

cm^2 to 3.5 cm^2 changed the affected area. When a big electrode was used, a muscle evoked potential (MEP) induced by transcranial magnetic stimulation (TMS; Nitsche et al., 2005; Nitsche et al., 2007) was found for both, the ADM and the first dorsal interosseus muscle (FDI). But when a small electrode was applied, the FDI muscle didn't show a MEP response any longer (Nitsche et al., 2007).

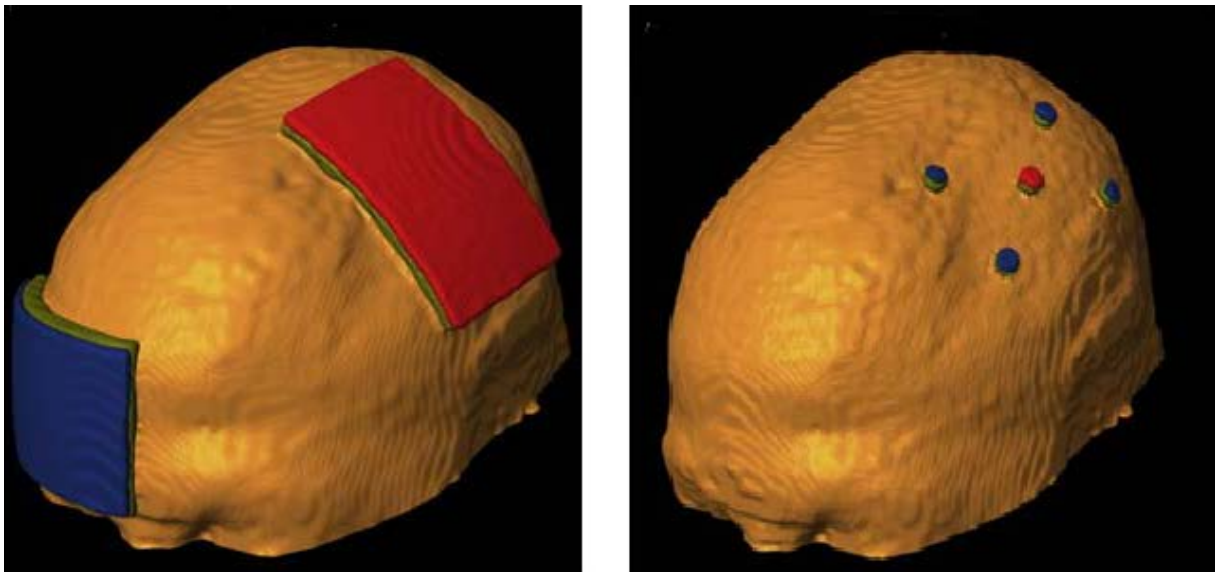

Figure 1: TDCS-setting with 35-cm^2-electrodes (left) as well as with EEG-electrodes (ring setting, right) (picture taken from Datta et al., 2009a)

When changing the electrode size, it is important to also change the current intensity in order to keep the current density constant. This is important for the efficiency (Nitsche et al., 2007).

A lack of accuracy means that not only the target area is reached when stimulating the brain. This problem can be solved in three different ways: These would be, as already mentioned, minimizing the size of the active electrode or increasing the size of the referring electrode, so that its current density is beyond an effective level (Datta et al, 2009a; Nitsche et al., 2007; Nitsche et al., 2008).

Furthermore, the reference electrode can be placed on an extracephalic part of the body. Thereby only the active, but not the reference electrode has an effect on brain activity (Nitsche et al., 2007; Nitsche et al., 2008; Vines et al, 2006). On the one hand, it is not advisable to do so, because it might lead to a stimulation of the brain

stem, which could be dangerous as the autonomous central nervous system could be disturbed (Nitsche et al., 2007; Nitsche et al., 2008). On the other hand, Bikson et al. (2008) showed that currents of less than 1 mA are not likely to be harmful. Current strengths of more than 3 mA, however, were reported to lead to respiratory problems (Bikson et al., 2008).

A change of the reference electrode´s placement is accompanied by an alteration of the current flow around the active electrode. This means that, according to the change in the placement of the reference electrode, the current´s way between the two electrodes is a different one (Brunoni et al, 2011b).

Simulation studies which focused on the improvement of tDCS focality used different electrode settings for their simulations (Datta et al, 2009a; Faria et al., 2009; Suh et al., 2010). Faria et al. (2009) used three different settings for a cathodal stimulation. The first one was one cathode and contralateraly placed one anode. In the second case, there were a cathode and three contralateral anodes and in the third setting, four anodes were placed around the cathode like a ring. The ring setting showed the highest focality (Faria et al., 2009). The electrical peak maxima were directly beneath the active electrode, whereas for 35 cm^2 electrodes the maximum is not necessarily found directly below the active electrode. In this case, a diffuse modulation occurs and several high electric field clusters can be found (Datta et al, 2009a).

Under the big electrode most of the current enters the head over areas where the scalp is thin, because these parts are easier to penetrate. In the head current flow is best conducted by cerebrospinal fluid and thereby depends on its distribution (Datta et al, 2009a).

A comparison of ring settings with other electrode configurations shows that in the ring setting a great amount of the current does not reach the inner part of the head. This is because the current is shunted by the scalp and directly flows to the reference electrodes (Datta et al, 2009a; Miranda, Lomarev & Hallett, 2006; Wagner et al., 2007).

A finite element model established by Faria et al (2009) showed that placing the small reference electrode(s) contralaterally results in 0.073 mA/cm^2 on the surface of the brain when the injected current was 0.5 mA. Using a ring setting, 0.8 mA were needed to reach the same current density on the brain. The small electrodes used in this study were EEG-electrodes.

This shows that the current-intensity-to-area-ratio for the estimation of the current density in the targeted brain area is variable. To reach the same current density in the target area, a higher current intensity for smaller electrodes is needed in relation to big electrodes (Miranda et al., 2009). In addition, Utz et al. (2010) found that the further away the reference electrode is from the active electrode, the deeper the areas reached by the current are (Utz et al., 2010).

For big, as well as for smaller electrodes the electric field decreases with a growing distance from the electrode (Nitsche et al., 2007). But as described above, the use of a ring system enables the current to diffuse faster in the brain (Datta et al., 2008; Miranda et al., 2009).

DLPFC, VLPFC & tDCS

The dorsolateral prefrontal cotex (DLPFC) is situated on parts of Brodmann areas 46 and 9 (see figure 2) (Andrews et al., 2011; Nitsche et al., 2007). In the 10-20 international system for electroencephalogram electrode placement, this corresponds to the positions F3 (left) and F4 (right) (Ohn et al., 2008).

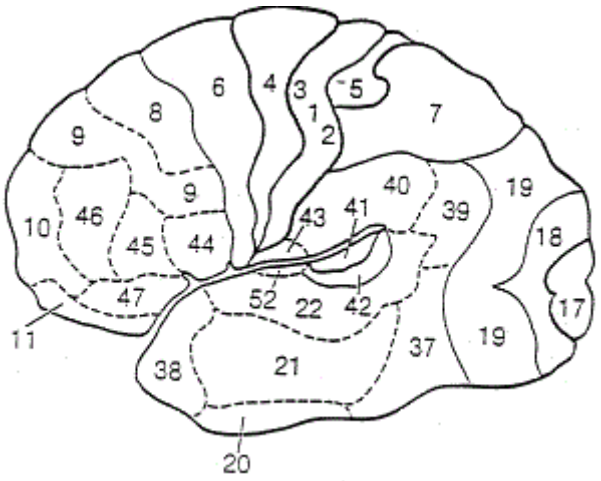

Figure 2: Lateral surface of the brain showing numbered Brodmann`s areas (picture taken from Faw, 2003)

Recent studies using tDCS on the DLPFC resulted in altering the working memory (Andrews et al., 2011; Fregni et al., 2005; Keeser et al., 2011; Ohn et al., 2008), language comprehension (Boggio et al., 2010a; Fecteau et al., 2007a), risk taking (Fecteau et al., 2007a; Fecteau et al., 2007b), lie production (Priori et al., 2008), categorization performance (Ambrus et al., 2011), planning function (Keeser et al., 2011), emotion processing (Pena-Gomez et al., 2011) and craving (Boggio et al., 2008b; Boggio et al., 2010b; Fregni et al., 2008a,b; Goldman et al., 2011).

According to current research results, tDCS on the DLPFC may be used for the therapy of (drug-resistant) major depression (Boggio et al., 2007; Boggio et al., 2008a; Brunoni et al., 2011a; Ferrucci et al., 2009), Parkinson´s disease (Boggio et al., 2006), drug addiction (Boggio et al., 2009a) and pain (Boggio, Zaghi, Lopes & Fregni, 2008c; Boggio et al., 2009b; Fregni et al., 2006b; Mattai et al., 2011).

Until now almost all studies used active electrodes for tDCS on DLPFC which had a rectangular shape and size of 25 to 35 cm^2. Exceptions concerning the size were Cerruti and Schlaug (2009), stimulating with an electrode of the size of 16 cm^2, as well as Javadi, Cheng and Walsh (2011) using 12-cm^2-electrodes. Only Marshal et al. (2004) and Marshall et al. (2005) used smaller round electrodes with a diameter of 8 mm.

While the studies examining the impact of tDCS over the DLPFC using bigger electrodes on working memory performance, Marshal et al. (2005) presented

different results. Anodal and cathodal tDCS was applied bilaterally, with the active electrodes placed on the left and right DLPFC and the reference electrodes over the mastoids. The current intensity of 0.26 mA resulted in a current density of 0.129mA/cm^2. During tDCS a working memory task was given and the performance was compared to sham condition. The results showed a worse performance in cathodal as well as anodal tDCS in relation to sham condition (Marshall et al., 2005).

The working memory is responsible for language comprehension, learning and reasoning (Fregni et al., 2005). It is a multi-component process which makes information temporarily accessible, reorganizes and operates information and provides information for other cognitive operations (Motes & Rypma, 2010). Several studies applied anodal tDCS to the left DLPFC and all of them showed improvement in a working memory task (Andrews et al., 2011; Fregni et al., Keeser et al., 2011; 2005; Ohn et al., 2008; Zaehle, Sandmann, Thorne, Jäncke & Hermann, 2011).

In search of an explanation for the difference between the results of Marshall et al. (2005) and the other studies, several points can be mentioned:

- Marshall et al. (2005) used a bilateral setting whereas all other stimulations were done on left DLPFC, with either the contralateral supraorbital area or the contralateral mastoid as reference sites. Effects might be different when right and left DLPFC are stimulated at the same time, in comparison to unilateral stimulation.
- Marshall et al. (2005) used smaller electrodes, which are supposed to have a higher focality. In contrast to bigger electrodes, no other regions should be affected. So the increase in working memory performance might result from the activity of other regions instead of only from DLPFC.
  Having an increased focality makes it necessary to place the electrodes more accurately in order to be sure to reach the target area. Marshall et al. (2005) placed the electrodes on F3 and F4 according to the 10:20 system. This might not have been accurate enough.
- Marshall et al. (2005) used the Sternberg paradigm whereas other studies always used the n-back task to measure the working memory. In the

Sternberg paradigm, performance differences between the stimulation conditions were observed in reaction time but not in the error rate.
The variables of the n-back task are accuracy, which is the number of correct responses in relation to the number of targets, the error rate, which is defined as the number of wrong hits in relation to the number of foils, as well as the reaction time, which is the time between the presentation of the stimulus and pressing the button. The tDCS studies obtained a change of one or more of these variables.
Keeser et al. (2011) and Ohn et al. (2008) found increased accuracy with anodal tDCS compared to sham condition. Fregni et al. (2005) and Keeser et al. (2011) showed a significant decrease of the error rate.
In none of these three studies did the reaction time change significantly between sham condition and anodal tDCS (Fregni et al., 2005; Keeser et al., 2011; Ohn et al., 2008).

- TDCS was applied intermittently (15 sec on/15 sec off) by Marshall et al. (2005), whereas the other studies used a constant current (Fregni et al., 2005; Keeser et al., 2011; Ohn et al., 2008; Zaehle et al., 2011).
- The current density of 0.129 mA/cm^2 applied by Marshall et al. (2005) was higher than the one by Keeser et al. (2011), who used 0.057 mA/cm^2.

The stimulation duration of 15 min in the study of Marshall et al. (2005) resembles the other studies which opted for a duration of between 10 min (Andrews et al., 2011; Fregni et al., 2005) and 30 min (Ohn et al., 2008), although actual stimulation time is much shorter as Marshal et al. (2005) used intermittent tDCS.

The second study using small electrodes on the DLPFC was done by Marshall et al. (2004). Results show that the subjects´ performance improved in a declarative memory task, when they attended anodal tDCS while they were sleeping in the retention time, which was in-between learning word pairs and doing the task. Only stimulation with tDCS without sleeping during retention time brought no effects. The word pairs had been learned before tDCS was applied and they had to be remembered after stimulation.

There is no study comparable to this one. Javadi, Cheng and Walsh (2011) found effects of anodal tDCS on the left DLPFC on the declarative memory. They observed a higher improvement in a memory task when anodal tDCS was applied during word presentation. The improvement referred to a comparison of no stimulation or stimulation after the word presentation.

When tDCS is applied via 35-cm^2-electrodes on F3 (according to the 10-20-system for EEG placement), the left DLPFC is not the only region which is affected by the current. Due to this low focality, the ventrolateral prefrontal cortex (VLPFC), which like the DLPFC is associated with working memory, could have an impact on the altered working memory performance in the studies described above.

The VLPFC covers partly Brodmann Areas (BA) 44, 45, 47 and 12 (see figure 2) (O´Reilly, 2010).

Some authors suggest a functional separation of DLPFC and VLPFC (O'Reilly, 2010; Agosta et al., 2009). Especially the extent to which working memory can be segregated anatomically to the type of material (e.g., object, verbal, visual, etc.) or underlying processes (e.g., manipulation versus maintenance of information) is controversial discussed (for a review see Agosta et al., 2009). One of these hypotheses suggests that the main function of the DLPFC is spatial encoding, i.e. the localization of an object in space (Agosta et al., 2009; O´Reilly, 2010).The left VLFPC in contrast is suggested to be responsible for processing object information, like the shape and color of an object, in working memory (Agosta et al., 2009; O´Reilly, 2010). Additionally, it was suggested that the verbal working memory is mainly located in the left VLPFC, in the Broca area in BA 44 and 45 (O´Reilly, 2010).

Another hypothesis argues that while the DLPFC organizes information in the working memory and improves the memory for association in-between items in long term memory, the VLPFC selects target-relevant item information and thereby increases representations which are important for features relevant to reach the intended targets (Blumenfeld & Ranganath, 2007). It suppresses irrelevant information on behavior (Spaniol et al., 2009). By separating the working memory functions as described above, a hierarchical organization of working memory is

obtained. The two-stage hypothesis points out that first the VLPFC is activated to guide the active maintenance and to facilitate the retrieval of representations, and then this information can be monitored and manipulated by DLPFC (Wagner, Maril, Bjork & Schacter, 2001).

In summary there are many theories which suggest separated roles for DLPFC and VLPFC, especially in working memory functions which make it plausible that a focused tDCS stimulation of each of these areas induces other effects on working memory performance than when stimulating both areas simultaneously.

Nicotine craving

Introduction

Cigarette smoking can be the reason for many diseases like cancer, cardiovascular diseases and maladies of the lungs (Benowitz, 2010; McKillop et al., 2012; Tuesta, Fowler & Kenny, 2011). Furthermore, smoking is a risk factor for infections of the respiratory tract, adverse postoperative events, osteoporosis, delayed wound healing, diabetes, reproductive disorder, duodenal and gastric ulcers (Benowitz, 2010). Although rather other ingredients of cigarettes than nicotine cause the problems mentioned above, nicotine leads to an addiction and is therefore one of the main reasons why people do not stop smoking (Benowitz, 2010). A problem in smoking withdrawal is the high rate of relapse which is strongly induced by craving for nicotine (Jorenby, 1998; Baker, Brandon & Chassin, 2004; Swan, Ward & Jack, 1996).

Eighty percent of all people who want to stop smoking relapse in the first month. After half a year only three percent are still successful (Dwoskin et al., 2009). Seventy percent of the smokers in the United States want to quit smoking, but only three percent are successful each year (Dani & De Biasi, 2001).

Pharmacotherapies like nicotine replacement therapy, burpropion and varenicline therapy have shown to be successful, but there still remains a risk for relapse. Only 25 per cent of all cases per year are successful (Rose, 2007).

Five millions of deaths occur every year as a consequence of smoking (Hatsukami, Stead & Gupta, 2008). In 2020 smoking will be the largest single health problem worldwide, if the actual trend holds on. In 2020, an estimated 8.4 million people worldwide will die due to smoking every year. In high-income countries, the costs for smoking-related healthcare are predicted to be $160 billion annually, which is between 6 and 15% of the total healthcare costs (Tuesta et al., 2011).

Definition of nicotine craving and withdrawal symptoms

Franken (2003) describes craving as an “appetitive motivational state”, which is induced by conditioned stimuli. These stimuli are associated with the reward effect of behavior or substances. Craving is the desire to reach a new homeostasis when withdrawal symptoms occur (Anton, 1994; Franken, 2003). It is a complex phenomenon including cognitive and affective processes (Wilson, Sayette & Fiez, 2004). Craving exists not only for nicotine, but also for other drugs like opiates, or for behavior such as sex or eating. The different forms of craving share according to Franken (2003) a common neural pathway.

In the ICD-10 (International Statistical Classification of Disease and Related Health Problems, 10th version), tobacco dependence is classified as “Mental and behavioral disorders due to psychoactive substance use”. At least three of the following criteria need to be present at the same time in one month: 1) Strong craving or kind of compulsion to consume tobacco; 2) Decreased ability to control the start, the cessation and the amount of consume; 3) a physical withdrawal syndrome after cessation or reduction of consume, attested by withdrawal symptoms typical for the substance or via intake of this substance or of a similar substance, to decrease withdrawal symptoms or to avoid them; 4) Evidence for tolerance. To obtain the same effects of a psychotropic substance before taken in small doses, an increasing amount has to be used (examples are daily doses of alcoholics and opiate dependent, which could lead to strong impairment or even to death if no evolution of tolerance occurs); 5) Progressive neglect of other enjoyments and interests because of substance consume, long time exposure to obtain the substance, to consume it or to recover from aftermaths; 6) Persistent substance consume despite of evidence of harmful aftermaths, like for example liver impairment after excessive alcohol consume, depressed mood after strong substance consume or degradation of cognitive functions due to drug intake. It should be proven whether the consumer was aware of the type and degree of harmful consequences (Dilling, Mombour & Schmidt, 2011). Accordingly to ICD-10 craving is one of the main criteria of tobacco addiction.

In the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), symptoms for tobacco dependence are described as well, but craving is not mentioned in this context (Saß, Wittchen, Zaudig & Houben, 1998).

Withdrawal symptoms that occur after nicotine deprivation are anxiety, irritability, depressed mood, difficulty in concentrating, frustration, restlessness, insomnia, increased appetite and a decreased heart rate. These symptoms are strongest in the first week after giving up smoking and then decrease to a baseline level between two and four weeks later. The progress of withdrawal symptoms varies according to the individual (Hatsukami et al., 2008).

The effects of nicotine and the development of an addiction

When cigarette smoke is inhaled, the nicotine enters through the lungs into the blood circuit and is transported to the brain, where it binds to nicotinic cholinergic receptors, which leads to cations entering the cell. Through this entrance of sodium or calcium a depolarization takes place and voltage-dependent calcium channels open to have more calcium enter the cells. This induces the release of neurotransmitters like dopamine, glutamate and γ-aminobutyric acid (GABA) (Benowitz, 2010; Lewis, Miller & Lea, 2007).

The most important agonist of nicotinic cholinergic receptors is acetylcholine, but nicotine is also an agonist (Dani & De Biasi, 2001; Davis & Gould, 2008). There are different types of receptors, depending on the subunits they consist of. They differ in their rates of desensitization, recovery from desensitization, regulation, control of the response to an agonist, the speed of activation and the ionic current (Dani & De Biasi, 2001).

Dopamine induces the nicotine reward and also causes addiction. Many nicotinic cholinergic receptors are found in the ventral tegmental area (VTA). The dopamine system most involved in drug rewards is the mesocorticolimbic dopamine system including the dopaminergic cells in the VTA, which project to the prefrontal cortex (PFC), the striatum (Dani & Balfour, 2011; Dome, Lazary, Kalapos & Rihmer, 2010;

Dwoskin et al., 2009; Tuesta et al., 2011) and the hippocampus (Dome et al, 2010; Tuesta et al., 2011). The mesocorticolimbic dopamine system consists of a mesolimbic and a mesocortical circuit which interact, and which both arise of the VTA (Briand, Gritton, Howe, Young & Sarter, 2007). Nucleus accumbens (NAcc), hippocampus and amygdala as elements of the mesolimbic circuit are important in conditioned responses linked to craving and with acute reinforcing effects of a drug, whereas the mesocortical dopamine circuit including the PFC, the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC) are rather associated with the conscious part of drug expectation/craving and compulsive drug administration (Goldstein & Volkow, 2002).

A repeated exposure to nicotine leads to an increase of agonist binding sites and a desensitization of the nicotine cholinergic receptors, which leads to an unresponsiveness of the receptor (Benowitz, 2010; Caggiula et al., 2001; Dani & Balfour, 2011; Dwoskin et al., 2009; Lewis et al., 2007). This plays a role in nicotine tolerance and craving. During typical smoking behavior (during the day) the saturation of the receptors with nicotine is high. If the occupation of the receptors is lower (after a nicotine withdrawal of some hours) and the binding sites are free on the desensitized nicotine cholinergic receptors, they recover to a responsive state which leads to nicotine craving (Benowitz, 2010; Dwoskin et al., 2009). The changes in dopamine receptors followed by an altered dopamine response in addicted subjects lowers the sensitivity of natural reinforcers, which leads to the subject looking for reinforcement by a drug to activate the reward circuits (Volkow, Fowler, Wang, Swanson & Telang, 2007).

.Apart from nicotine, more than 4800 chemical substances have been found in tobacco. Flavorants and procession agents are added to influence the effects of tobacco products and thereby to make them more agreeable. The mechanisms directly affect the nicotinic receptors by increasing the amount of nicotine entering the blood system and by increasing the sensory cues of cigarettes (O´Dell & Khroyan, 2009).

Other compounds apart from nicotine are monoamine oxidase inhibitors, which induce a decreased activity of monoamine oxidase. Therefore, the metabolism of dopamine, which is a monoamine, slows down. Hence dopamine is longer active (Brody, 2006; Dome et al., 2010; Lewis et al., 2007; O´Dell & Khroyan, 2009; Rose, 2006). Additionally, acetaldehyde is said to activate dopaminergic cells and has a reinforcing effect (Dome et al., 2010).

Studies suggest that chemical substances in tobacco are not the only factors that induce craving for a cigarette but that there are also sensory and behavioral aspects which are of importance (Butschky, Bailey, Henningfield &Pickworth, 1995; Rose, Behm, Westman & Johnson, 2000; Tiffany, Cox & Elash, 2000). Drug-related stimuli, which were learnt to be associated with the drug, can induce a dopamine release as well (Franken, 2003).

Butschky et al. (1995) showed that sensory aspects of a cigarette have influence on craving and withdrawal symptoms as well. After 12 hours of abstinence from cigarettes, smokers received normal cigarettes, de-nicotinized cigarettes and cigarettes made of dried lettuce. Smoking of normal cigarettes as well as of de-nicotinized cigarettes, which only differ in the nicotine content, reduced the withdrawal symptoms as well as craving. In contrast, the lettuce-cigarette induced no comparable effects, which proves that sensory aspects of tobacco smoke also play a role in reducing craving (Butschky et al., 1995).

The connection between environmental cues, situations and specific moods with nicotine emerges via classical conditioning. Unconditioned stimuli like the reinforcing effects of nicotine are learned to be associated with smoking functions as conditioned stimuli. This association leads to a conditioned response such as drug-seeking behavior (Davis & Gold, 2008; Weiss, 2005). Conditioned stimuli do not need to be positive. A negative state as for example irritability can be conditioned to induce nicotine craving. Craving can be originally induced by irritability as a nicotine withdrawal symptom. Smoking a cigarette releases this feeling. This leads to the development of an association between irritation and smoking (Benowitz, 2010). Additionally to these negative cues for stimuli, which the association with smoking is

often learned with and which thus can induce craving, are other smokers, a lighter or an ashtray. Furthermore, finishing a meal, being in a bar or drinking alcohol can serve as environmental cues (Hatsukami et al., 2008). In addition to the exposure to these stimuli in daily life, pictures of smoking-related stimuli also induce craving. While being exposed to smoking-related stimuli, the mesocorticolimbic system which also plays a role in learning and memory is activated. The amygdala and the hippocampus are of great importance in this aspect (Davis & Gould, 2008).

Tiffany et al. (2000) presented pictures containing smoking cues to smokers who had not smoked for six hours. The smoking cues induced an increase in craving, in heart rate, in negative affect and in skin conductance levels compared to the exposure to neutral stimuli. Whether smokers had received intravenous nicotine or a placebo during smoking abstinence did not have any effects on the increase of craving after watching smoking cues (Tiffany et al., 2000).

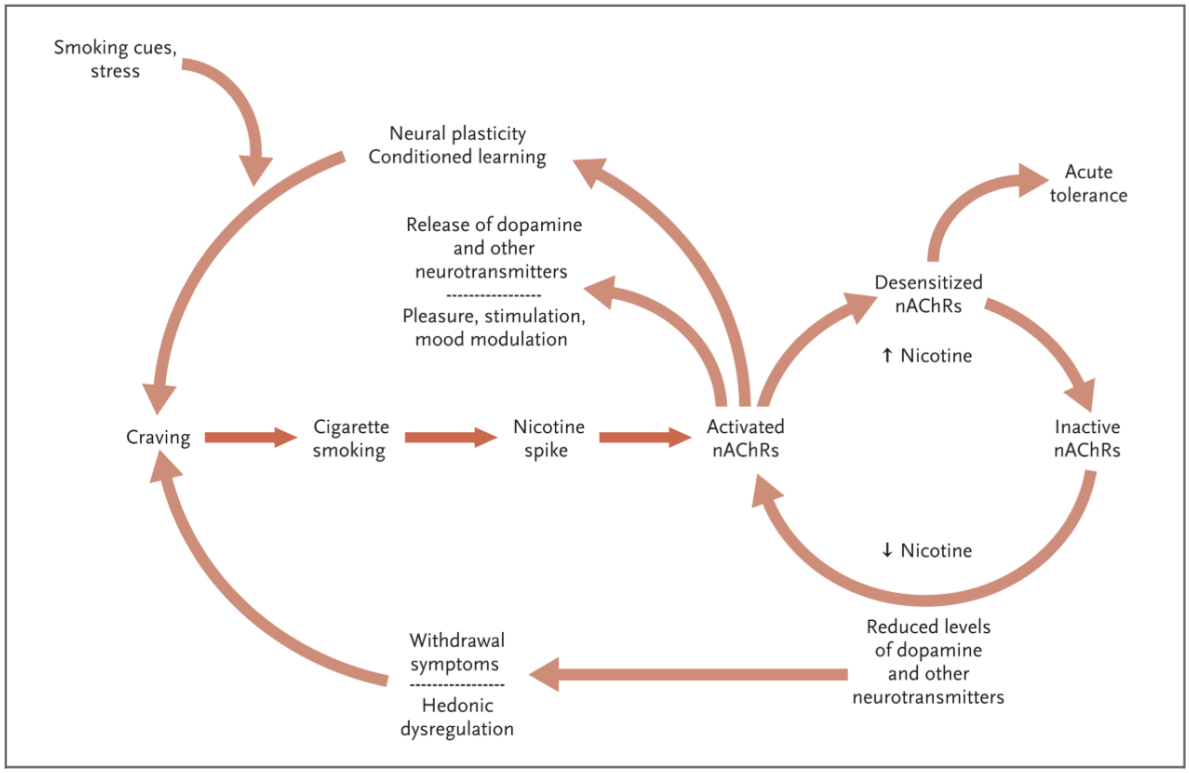

Figure 3: A graphical illustration of craving development. Due to cigarette smoking there is an alteration in the neuronal substrate which induces craving when dopamine levels are too low. Additionally, external inputs like stress and smoking cues which have been learned to be associated with smoking can increase the craving levels. (Picture taken from Benowitz, 2010)

Cultural aspects such as the availability of and the access to tobacco products, the costs and the use of tobacco have an influence on the fact that people start smoking and do not stop. The same holds true for modeling, for example by a peer, and for individual factors like personality (Hatsukami et al., 2008; Ho et al., 2010). Additionally, the tendency to start smoking and the development of dependence are heritable. Responsible genes code for functions involved in the pathway and metabolism of neurotransmitters like dopamine. Examples are variants of the cholinergic receptor genes and monoamine oxidase genes (Gold & Lerman, 2012; Hatsukami et al., 2008; Ho et al., 2010; Uhl, Drgon, Li, Johnson & Liu, 2009).

Brain activity during craving

Brain imaging techniques have shown, that inter alia the insula (Franklin et al., 2007; Kühn & Gallinat, 2011; Wilson et al., 2004; Yalachkov, Kaiser & Naumer, 2012; McBridge, Barrett, Kelly, Aw & Dagher, 2006), the amygdala (Due, Huettel, Hall & Rubin, 2002; Franklin et al., 2007; Wilson et al., 2004), the ACC (Brody, 2006; David et al., 2008; Kühn & Gallinat, 2011; Lee, Lim, Wiederholf & Graham, 2005; McBridge et al., 2006; Wilson et al., 2004; Yalachkov et al., 2010; Zubieta et al., 2005), the VTA (Brody, 2006; Due et al., 2002), the hippocampus (Brody, 2006; Due et al., 2002; Franklin et al., 2007; Zubieta et al., 2005), the striatum (David et al., 2008; Franklin et al., 2007) and the prefrontal cortex (Due et al., 2002; Kühn & Gallinat, 2011; Lee et al., 2005; Wilson et al., 2004; Yalachkov et al., 2012) are involved in smoking-cue induced craving. In the last mentioned especially the dorsolateral prefrontal cortex (DLPFC) (Boggio, et al., 2009a; Fregni et al., 2008a; McClernon, Kozink, Lutz & Rose, 2009; Wilson et al., 2004) and the OFC are associated with craving (Brody, 2006; London, Ernst, Grant, Bonson & Weinstein, 2000; David et al., 2008; Franklin et al., 2007; McBridge, 2006; Wilson et al., 2004). But results are contradictory (Wilson et al., 2004). Brody et al. (2007), for example, did not find an altered activation in the ACC and the DLPFC in cue induced craving compared to neutral cues. But when the subjects tried to resist craving, the ACC was activated.

According to Volkow, Fowler and Wang (2003) the above mentioned regions involved in drug addiction correspond to different circuits associated with functions in addiction. These circuits interact with each other. The NAcc and the ventral pallidum are involved in reward, the OFC is associated with motivation, the amygdala and the hippocampus are responsible for learning and memory and the control is located in the ACC and the PFC (Volkow et al., 2003). An example of the interaction of these circuits is the integration of motivational information from the frontal cortex in the striatum which leads to a behavior in anticipation of a reward (Dwoskin et al., 2009).

The activated regions in drug cue responding mainly belong to the mesocorticolimbic dopamine circuit as described above. But areas associated with the visuospatial-attention circuit including PFC and ACC also show an altered activation after the presentation of visual smoking cues (Due et al., 2002).

Beside the DLPFC and the OFC, the ventrolateral prefrontal cortex (VLPFC) is considered to be involved in craving (Kühn et al., 2011). The prefrontal cortex, especially the DLPFC, the dorsomedial prefrontal cortex (DMPFC) and the VLPFC are involved in craving as these are regions of cognitive control. As described below, these regions are important for emotion regulation and thereby are involved in strategies to alter emotional response. Hence these strategies seem to regulate craving as well. Especially the DLPFC seems to be connected to brain areas responding to nicotine, like the striatum (Kober et al., 2010). This connection could be due to the function of the DLPFC in planning and memory (McBridge et al., 2006).

Kober et al. (2010) showed in a functional magnetic resonance imaging (fMRI) study that subjects who reduced their craving after smoking cue exposure with cognitive strategies had an increased activation of the DMPFC, VLPFC and DLPFC compared to conventional craving, whereas the activation of other regions associated with craving like the ventral striatum, the amygdala, the ACC and the VTA was lower. A correlation between the increase of the DLPFC activation and the decline of the one of the ventral striatum was found.

McClernon, Kozink and Rose (2008) found in a fMRI study that the activation of brain regions depends on several factors like craving before smoker stimuli presentation,

grade of nicotine dependence and sex. Effects were found for the ventral striatum, the ventral anterior cingulate gyrus and the OFC. This leads to the assumption that the amount of cigarettes per day and the time of withdrawal have an impact on smoking cue response. McClernon et al. (2009) compared the reaction of smokers after a 24-hours-abstinence and satiated smokers to smoking stimuli as well as to neutral pictures. In the group of abstinent smokers brain activation differed between smoking stimuli and neutral pictures. However, people who had smoked a cigarette right before the picture presentation had no altered brain activity in relation to neutral stimuli. These findings are in contrast to the findings of McBridge et al. (2006) and Franklin et al. (2007). McBridge et al. (2006) found no significant differences between abstinent smokers and non-abstinent smokers. In this study smokers in the abstinent condition had not been allowed to smoke for twelve hours before. In contrast to McClernon et al. (2009) where subjects smoked at least ten cigarettes per day, the participants in the studies of McBridge et al. (2006) and Franklin et al. (2007) were heavier smokers (at least 15 cigarettes/day). This fact, in addition to the interval of smoking deprivation (24 vs. 12 hours), might have an impact on the response to smoking stimuli.

Smolka et al. (2006) suggest that the severity of smoking and the intensity of craving independently influence the smoking-cue induced activity of the brain. The latter is associated with the activation of areas that belong to the mesocorticolimbic system. Whereas, due to the role of the visuospatial attention system in attention processes, the severity seems to be linked to brain regions associated with this system.

In addition to the impact of abstinence or non-abstinence on the activity of the brain in cue-induced craving, McBridge et al. (2006) showed that areas associated with craving like the DLPFC, the OFC and the ACC are significantly more active in cases where subjects expect to be allowed to smoke directly after the scan than in cases where they would have to wait four hours for the next cigarette. Due to the inconsistent results on the DLPFC activation in smoking cue induced craving, this study, as well as Wilson et al. (2004), proposes, that the DLPFC is only involved in nicotine craving when subjects expect to use the drug soon after the elicitation of craving. If drug consumption is possible, the DLPFC could be necessary to use the

information about motivation, cues, internal state and expectancy in order to integrate it in the planning and regulation of drug seeking or drug-avoiding behavior (McBridge et al., 2006).

The impact of tDCS and repetitive transcranial magnetic stimulation (rTMS) on nicotine craving

Several tDCS as well as TMS studies in association with craving have used the DLPFC as target area. TMS is also a non-invasive method to stimulate cortical neurons. High-frequency rTMS (stimulus rates higher than 1 Hz) leads regularly to facilitatory effects, whereas low-frequency rTMS (stimulus rates of 1 Hz and lower) is commonly associated with the opposite effect. However, vice versa effects have also been observed (Rossi, Hallett, Rossini & Pascual-Leone, 2009).

Fregni et al. (2008a) applied 20 minutes of anodal tDCS (0.06 mA/cm^2) above the DLPFC. Smoking-cue induced craving was decreased after anodal tDCS but not after sham. These results could be explained by an enhanced excitability of the DLPFC, which leads to a better drug-avoiding behavior as the DLPFC is associated with planning functions in drug intake. Furthermore, the tDCS could have an impact on dopamine release (Fregni et al., 2008a). Apart from these short-term effects, an impact of tDCS on smoking behavior for a longer period was found by Boggio et al. (2009a). They showed that anodal tDCS (0.06 mA/cm^2) on the left DLPFC for 20 minutes on five consecutive days significantly decreases smoking-cue induced craving and cigarette consumption (Boggio et al., 2009a).

Amiaz, Levy, Vainiger, Grunhaus & Zangen (2008) showed that ten days of repeated high-frequency TMS treatment significantly decreases the self-reported cigarette consumption and the cotinine levels in the urine, in contrast to sham condition. Additionally, cue-induced craving differed significantly between the first and the tenth session. The results were explained by an increased availability of striatal dopamine due to the connection between the DLPFC and the striatum (Amiaz et al., 2008). This goes in line with the findings of Strafella, Paus, Barrett and Dagher (2001) which

show that high-frequency rTMS on the left DLPFC increases striatal dopamine, as well as with the results of the study of Eichhammer et al. (2003) stating that the amount of smoked cigarettes six hours after high-frequency rTMS treatment decreased. For smoking-cue induced nicotine craving no significant effects were found. In contrast, Rose et al. (2011) report altered smoking-cue induced craving levels after high-frequency rTMS on the superior frontal gyrus.

In contrast to the tDCS study on smoking-cue induced craving by Fregni et al. (2008a), Köhler (2012) found no impact of anodal tDCS on the DLPFC. Fregni et al. (2008a) used electrodes of 35 cm^2, whereas Köhler applied three EEG-electrodes to stimulate the DLPFC with a high focality without directly altering the activation of the Brodmann areas 6, 8, 44 and 45 which could be affected as well when applying tDCS on the DLPFC with big electrodes. Due to the differences in these studies, areas further away from the DLPFC which are reached with a big, but not with a small electrode could be responsible for the alteration in smoking-cue induced nicotine craving after anodal tDCS with a 35 cm^2 electrode.

Another difference between these studies was the fact that the subjects participating in the study of Fregni et al. (2008a) consumed an average of 18.5 cigarettes per day and had a FTND score of 4.46. Hence the subjects in this study were heavier smokers then the ones in the study led by Köhler (2012), where participants smoked an average of 12.05 cigarettes per day and hat a FTND score of 2.45. This fact could have an impact of the reaction to anodal tDCS on the DLPFC as well.

In addition to nicotine craving, craving for food (Fregni et al., 2008b; Goldman et al., 2011; Montenegro et al., 2012; Uher et al., 2005; Van den Eynde et al., 2010) and alcohol (Boggio et al., 2008b; Mishra, Nizamie, Das & Praharaj, 2010) have been shown to decrease via anodal tDCS and high-frequency rTMS respectively over the DLPFC.

Summary

Smoking is a growing health problem in our society (Tuesta et al., 2011). Many smokers want to stop, but there is a high rate of relapse which is strongly induced by craving for nicotine (Jorenby, 1998; Baker et al., 2004; Swan et al., 1996). Craving is an appetitive motivational state, which can be induced by conditioned stimuli like environmental cues, situations and specific moods (Franken, 2003).

Neural substrates associated with cue-induced craving are inter alia the DLPFC (McClernon et al., 2009; Wilson et al., 2004) and the VLPFC (Kühn et al., 2011).

TDCS was suggested to be a future method in nicotine withdrawal as anodal tDCS above the left DLPFC showed to reduce cue-induced craving (Boggio et al., 2009a; Fregni et al., 2008a). Another study applying anodal tDCS over the left DLPFC did not report any effects on cue-induced craving (Köhler, 2012). One reason therefore might be the usage of bigger electrodes in the studies of Boggio et al. (2009a) and Fregni et al. (2008a), which affected also brain regions surrounding the DLPFC.

Emotion and emotion regulation

Introduction

Emotions can support an organism in the decision on how to behave, how to enhance memory for important events, how to facilitate decision making (Gross & Thompson, 2007) and social interaction (Gross, & Thompson, 2007; Heatherton, 2011; Heatherton & Wagner, 2011). On the other hand a dysregulation of emotions can lead to social difficulties as well as psychical and physical illnesses. Therefore, it is important to regulate emotions appropriately (Gross & Thompson, 2007).

Emotional dysregulation is associated with half of all DSM-IV axis I disorders and with all disorders in axis II (Gross, 1998). Examples are binge-eating (Gross, 1998), anxiety (Amstadter, 2008; Gross, 1998) and mood disorders (Andreasen, 1997; Mayberg, 1997; Gross, 1998), schizophrenia (Andreasen, 1997; Gross, 2002) as well as drug abuse such as cigarette smoking (Gross, 1998; Heaterthon & Wagner, 2011). Additionally, the perception of pain includes affective components (Maeoka, Matsuo, Hiyamizu, Morioka & Ando, 2012).

The connection between drug abuse and the emotion regulation can be seen in several aspects. First, cognitive strategies like the ones used for emotion regulation resemble strategies used to stay abstinent from smoking (Gross, 1998). Second, drug consumption can be used to modify emotional experience. Smoking a cigarette, for example, helps to reduce anxiety (Gross, 1998; Gross & Thompson, 2007). Third, negative affect can lead to an increase of craving and thereby increase smoking intensity (Heatherton & Wagner, 2011).

Definition of emotion

According to Gross (1998, 2007) emotions like disgust, fear and happiness are subcategories of affects. Other subcategories of affect are emotion episodes like bringing bad news to a friend, traits like cheerfulness, dispositional states like hating as well as moods like depression and euphoria. Differences between these

categories are the duration in time and space, as well as the fact that emotion and emotion episodes are more focused on a special object or one situation, whereas mood is more diffuse.

Emotions are multi-facetted whole-body phenomena. As a reaction to a situation they can change, but they can also make us stop doing something (Gross, 2007).

Emotion and cognition

Emotions influence cognitive processes like memory, decision making and attention (Pena-Gomez, Vidal-Pin, Clemente, Pascual-Leone & Bartrés-Faz, 2011). But cognitive processes also change affective ones, and are integrated in the brain, using partially the same neuronal substrates (Pessoa, 2008).
Emotion regulation is a part of the self-regulation, including cognitive processes like decision making, memory, attention and the working memory (Blumenfeld & Ranganath, 2006), and it is defined as the change of emotion by connecting affective processes to cognition like memory and learning (Davidson, Putman & Larson, 2000; Gross, 1998). This process can be automatic or controlled, conscious or unconscious and it can have enhancing or decreasing effects on emotions (Gross, 2007).

Gross (2001) defines the inhibition of ongoing emotion as expressive behavior suppression. In contrast to this, reappraisal is the cognitive reevaluation of the emotion itself (Gross, 2001; Ochsner, Bunge, Gross & Gabrieli, 2002). In a study subjects had to do a memory task while being exposed to slides that show injured men. When the subjects were asked to use suppression in order not to show their reaction to the slides, the performance in the task was worse compared to doing task without altering emotions induced by the slides (Gross, 2001). But when using reappraisal to regulate emotion no alteration of the task performance occurred due to the fact that less cognitive resources were required for regulation (Gross, 2001; Ochsner et al., 2002).

There are different opinions on whether or not the generation of emotions can be separated from emotion regulation. According to the observation that all adult

emotions are regulated, emotion regulation is seen as a part of emotion generation and is therefore not separable. On the other hand, they should be at least partially separable (Gross, 2007). Phan, Wager, Taylor and Liberzon (2002) propose that cognitive components are already present in emotional tasks that comprise recognition/encoding or rating of emotional stimuli.

Neural substrates of emotion

Neuronal substrates associated with affective processes are limbic structures like the hypothalamus (Mayberg, 1997; Pessoa, 2008), the hippocampus (Mayberg, 1997; Pessoa, 2008), the amygdala (Gross, 2002; Mayberg, 1997; Murphy, Nimmo-Smith & Lawrence, 2003; Ochsner et al., 2004; Paradiso et al., 1999; Pessoa, 2008; Taylor, Phan, Decker & Liberzon, 2003; Phan, Wager, Taylor & Liberzon, 2004; Wager, Davidson, Hughes, Lindquist & Ochsner, 2008) as well as the brainstem (Mayberg, 1997), and the striatum (Mayberg, 1997; Paradiso et al., 1999). Additionally, cortical areas like insula (Murphy et al., 2003; Ochsner et al., 2004; Pessoa, 2008; Phan et al., 2004; Taylor et al., 2003) and the frontal cortex including the OFC (Davidson, 2004; Gross, 2002; Murphy et al., 2003; Paradiso et al., 1999), the ACC (Murphy et al., 2003; Pessoa, 2008; Phan et al., 2004), the ventromedial prefrontal cortex (VMPFC) (Pessoa, 2008), the DLPFC (Davidson, 2004; Dolcos, LaBar & Cabeza, 2004; Paradiso et al., 1999) and the VLFPC (Dolcos et al., 2004; Ochsner et al., 2004; Quirk & Beer, 2006; Wager et al., 2008) are involved in emotion processing (see figure 4). The limbic structures are involved in the generation of emotions, while the cortical structures rather have a regulatory function.

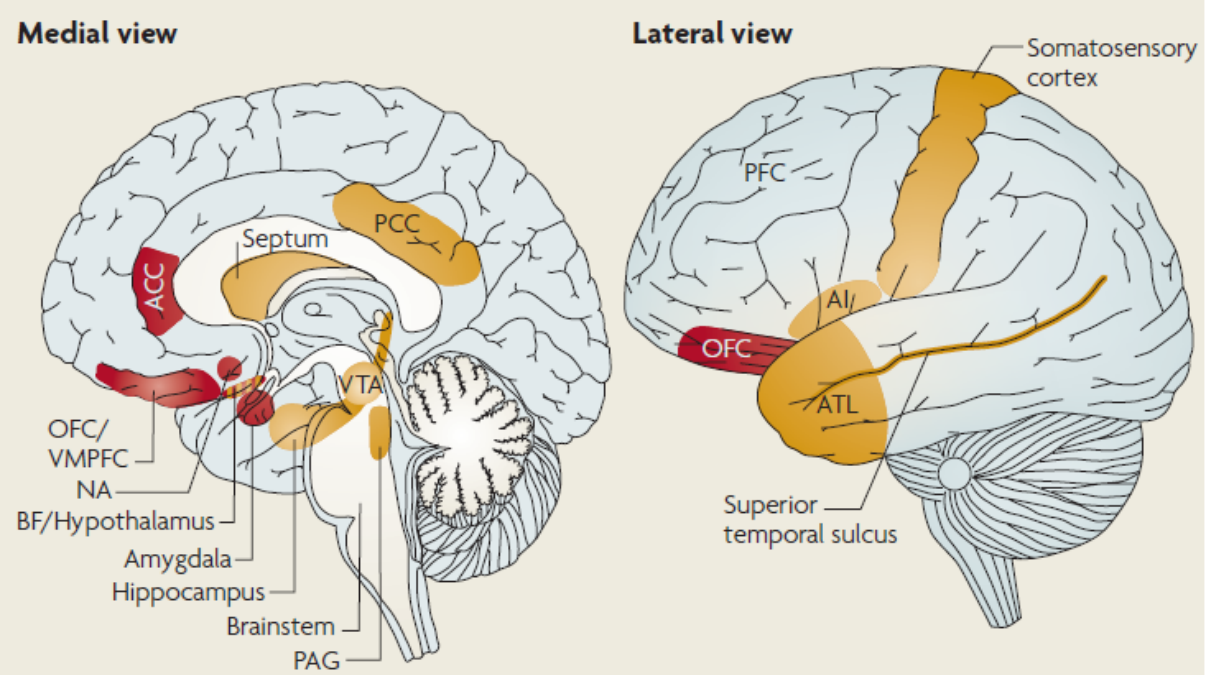

Figure 4: Brain areas involved in emotion processing. Red regions like the ACC, the OFC, the hypothalamus, the amygdala, the VMPFC, the nucleus accumbens (NA) and the the basal forebrain (BF) are more often mentioned in the context of emotion in literature than yellow marked areas like the septum, the ventral tegmental area (VTA), the brainstem, the hippocampus, the periaquaeductal grey (PAG), the posterior cingulate cortex (PCC), the anterior temporal lobe (ATL), the anterior insula (AI), the superior temporal sulcus, somatosensory cortex and the PFC. (Picture taken from Pessoa, 2008)

The functions of the lateral PFC in emotion and emotion regulation are planning, working memory, choice, behavioral self-regulation, selection and initiation of actions as well as novelty processing (Banfield, Wylant, Macrae, Münte & Heatherton, 2004; Ochsner, 2002; Ochsner & Gross, 2008). This region therefore shows a high activation in reappraisal (Cisler & Olatunji, 2012; Ochsner et al., 2002; Ochsner & Gross, 2008; Phillips, Ladouceur & Drevets, 2008).

The lateral PFC is closely interconnected with other regions responsible for emotion like the thalamus, the striatum, the hippocampus, the OFC (Phillips et al., 2008) and the ACC (Bush, Luu & Posner, 2000) as well as with the posterior parietal cortex processing visuo-spatial information (Andreasen, 1997). The interaction between the lateral PFC and the limbic regions during reappraisal has been shown for disgust: the activity of lateral PFC increased, and modulated by this the activity of the amygdala decreased (Gross, 2002; Ochsner et al., 2004).

In addition to studies on lateral PFC activity during affective tasks, findings about altered lateral PFC activity in diseases with emotion dysregulation underline the importance of the DLPFC and the VLPFC in emotion processing (Banfield et al., 2004; Davidson, Fox & Kalin, 2007).

The impact of rTMS and tDCS on affective picture evaluation

Two studies compared the valence ratings of neutral, positive and negative pictures during the appliance of anodal tDCS (0.03 mA/cm^2) on the left DLPFC with ratings in sham conditions (Maeoka et al., 2012; Pena-Gomez et al., 2011). In the anodal tDCS conditions, negative pictures were evaluated less negative than in the sham condition. For neutral and positive pictures no effect was found (Maeoka et al., 2012; Pena-Gomez et al., 2011). According to the PANAS inventory (for detailed description see below), the overall affect was not altered (Pena-Gomez et al., 2011).

In a study by Boggio, Zaghi and Fregni (2009b) subjects receiving anodal tDCS on the left DLPFC (0.06 mA/cm^2) rated pictures that show humans in pain as significantly less unpleasant and less painful. The higher activation of the DLPFC seems to have modulated the emotional compound of pain conception.

Longer lasting effects of anodal tDCS (0.06 mA/cm^2) on the left DLPFC on emotion were described by Boggio et al. (2008a). Patients with major depression received 20 minutes of tDCS per day. After two weeks a decrease of depression was observed. Brunoni et al. (2011a) found similar effects in cases of major depression as well as in cases of bipolar depressive disorder after five consecutive days of anodal tDCS on the left DLPFC (0.06 mA/cm^2) for 20 minutes per day.

In contrast to the above described findings, the pain in fibromyalgia patients in a study by Fregni et al. (2006b) was not altered after five consecutive days of 20 minutes anodal tDCS on the left DLPFC (0.06 mA/cm^2) per day. Instead, anodal tDCS on the motor cortex had an impact.

In another study anodal tDCS on the DLPFC using three EEG-electrodes had no impact on the evaluation of emotional pictures when stimulating the left DLPFC. But when the anode was applied on the right DLPFC, an alteration in the valence ratings of the pictures occurred (Köhler, 2012). In all the studies which reported a down-regulation of emotion by the left DLPFC induced by anodal tDCS, electrodes of 35 cm^2 were used for stimulation (Boggio et al., 2009b; Maeoka et al., 2012; Pena-Gomez et al., 2011). Due to the fact that Köhler (2012) did not achieve the same result, the effects could have been caused by other brain areas which were as well affected by the big electrode centered over F3 (left DLPFC according to the 10-20 international system for EEG placement), such as the VLPFC (Pena-Gomez et al., 2011)

Summary

Emotions help people in decisions, memory and social interactions (Gross & Thompson, 2007). But when emotions are dysregulated, this can be followed by diseases like drug abuse (Gross, 1998; Heaterthon & Wagner, 2011).

Emotion regulation is a part of self-regulation, including cognitive processes like decision making, memory, attention and the working memory (Blumenfeld & Ranganath, 2006).

Neural substrates of emotion are limbic areas which are associated with the generation of emotions, while cortical areas like the DLPFC and the VLPFC are associated with regulatory functions (Dolcos et al., 2004; Gross, 2007).

TDCS studies showed that anodal stimulation over the left DLPFC resulted in altered evaluation of affective pictures. As the active electrode had an area of 35 cm^2 it is not clear whether this effect was caused by the DLPFC or another affected brain region (Maeoka et al., 2012; Pena-Gomez et al., 2011). Another study stimulating the left DLPFC, but using small EEG-electrodes, found no effect of tDCS on affective picture evaluation (Köhler, 2012).

Research questions and hypotheses

This study examined the influence of three different electrode settings of anodal tDCS on the performance of smokers in a 3-back task (working memory performance), on craving ratings (overall craving as well as cue-induced craving was measured) and on affective picture evaluation. The three electrode settings were first anodal tDCS using a 35-cm^2-electrode to stimulate DLPFC and VLPFC at the same time, and second and third anodal tDCS using an EEG-electrode either over the DLPFC or the VLPFC to treat the two regions separately. Additionally a sham condition as control was done.

Working memory

How is working memory performance influenced by anodal tDCS either over the left DLPFC and VLPFC, over the left DLPFC or over the left VLPFC?

The impact of anodal tDCS over the left DLPFC on working memory using 35-cm^2-electrodes is well approved. The performance of the n-back task, which is the most frequent task to measure working memory, was measured in accuracy or reaction time (Andrews et al., 2011; Fregni et al., 2005; Keeser et al., 2011; Ohn et al., 2008). In contrast to these findings, Marshall et al. (2005) reported a decrease of working memory performance, measured with a Sternberg task. Although a difference in working memory measurement could be the reason for these findings, there are other differences like the application of an EEG electrode, the fact that Marshall et al. (2005) used a pair of electrodes to anodal stimulate the DLPFC bilaterally with the cathodal reference located at the mastoids and that he used intermittently current for stimulation.

Previous research has shown that beside the DLPFC, the VLPFC is as well an issue in working memory, especially verbal working memory (O´Reilly, 2010; Spaniol et al., 2009).

When a big stimulation electrode is set over F3 according to the 10-20 EEG placement system, the left VLPFC could be affected as well. Hence the effect of enhanced performance in the verbal working memory task might also be due to the activation of left DLPFC, when anodal tDCS is applied. In the case of Marshall et al. (2005) the VLPFC was not involved in tDCS stimulation. This could mean that it is necessary to affect the VLPFC when working memory performance should be increased.

- H_1: Working memory performance is independently from electrode size higher after anodal tDCS over left DLPFC and VLPFC than without stimulation.
    - 35-cm^2 = VLPFC = DLPFC > Sham

Craving and cue-induced craving

How are craving levels and smoking cue induced craving influenced by anodal tDCS either over the left DLPFC and VLPFC, over the left DLPFC or over the left VLPFC?

In brain imaging studies in context of craving, the prefrontal cortex, especially the DLPFC is frequently mentioned (Boggio, et al., 2009a; Fregni et al., 2008a; McClernon, Kozink, Lutz & Rose, 2009; Wilson et al., 2004). But also the ventrolateral prefrontal cortex (VLPFC) is described to be involved in craving (Kühn et al., 2011).

These two regions are associated with cognitive control. Hence they seem to have a regulating function in craving. This presumption was underlined by an increased activity of DLPFC and VLPFC when cognitive strategies were used to decrease cue induced craving (Kober et al., 2010). Furthermore Boggio et al. (2009a) and Fregni et al. (2008a) reported decreased cue-induced craving after anodal tDCS over F3 using a 35-cm^2-electrode.

Thus up-regulating the activity of DLPFC and VLPFC by anodal tDCS might help nicotine abstinent subjects by the mechanism of having better cognitive control over their craving.

The results of Köhler (2012) which show no effect on craving of anodal tDCS over the left DLPFC when EEG-electrodes were used, stand in contrast to the studies mentioned above. Although the stimulus materials differed from Fregni et al. (2008a) and Boggio et al. (2009a), these findings could lead to the conclusion that the activation of the DLPFC alone is not sufficient to decrease craving. The impact of the VLPFC might be crucial.

- H_2: In contrast to an anodal stimulation over the left DLPFC using an EEG-electrode or in sham condition the level of actual craving is lower after applying anodal tDCS over the left DLPFC and VLPFC using a 35-cm^2-electrode or an EEG-electrode over the VLPFC decrease craving.
    - 35-cm^2 = VLPFC < DLPFC = Sham
- H_3: Smoking cue induced craving is lower after anodal tDCS using a 35-cm^2-electrode over DLPFC and VLPFC or an EEG-electrode over the VLPFC than using an EEG-electrode over the DLPFC or applying no tDCS.
    - 35-cm^2 = VLPFC < DLPFC = Sham

Affective picture evaluation

How is affective picture evaluation influenced by anodal tDCS either over the left DLPFC and VLPFC, over the left DLPFC or over the left VLPFC?

As well as they have importance in working memory and craving, DLPFC (Davidson, 2004; Dolcos, LaBar & Cabeza, 2004; Paradiso et al., 1999) and VLFPC (Dolcos et al., 2004; Ochsner et al., 2004; Quirk & Beer, 2006; Wager et al., 2008) are involved in emotion and emotion regulation.

TDCS studies over F3 using a 35-cm^2-electrode have found that subjects rated negative pictures less negative after anodal tDCS than in a control condition (Boggio et al., 2009b; Maeoka et al., 2012; Pena-Gomez et al., 2011). These findings could be associated with the increased activity of the lateral PFC in reappraisal, were emotions are down-regulated (Cisler & Olatunji, 2012; Ochsner et al., 2002; Ochsner

& Gross, 2008; Phillips, Ladouceur & Drevets, 2008). A connection to tDCS studies over the DLPFC increasing working memory performance could be made due to the fact, that the functions of lateral PFC in emotion regulation apart from planning, choice, behavioral self-regulation and selection is ascribed to its function in working memory (Banfield, Wylant, Macrae, Münte & Heatherton, 2004; Ochsner, 2002; Ochsner & Gross, 2008).

A further study of anodal tDCS over the left DLPFC using EEG-electrodes showed no impact on affective picture evaluation (Köhler, 2012). Similar as in the case of craving this could indicate, that the VLPFC has higher importance in emotion processing then DLPFC, and that the activation of the DLPFC alone is not sufficient for altered evaluation of emotional pictures.

- H_4: Affective picture evaluation differs after anodal tDCS over DLPFC and VLPFC using the 35-cm^2-electrode or an EEG-electrode over the VLPFC compared to an anodal stimulation over the DLPFC using an EEG-electrode or in sham condition.
    - 35-cm^2 = VLPFC ≠ DLPFC = Sham

Empirical part

Materials and methods

Subjects

Subjects were recruited by an online advertisement on http://www.jobwohnen.at/, a student's job announcement website. They were paid 90 euros for their participation.

The announcement searched for 18 to 40 year old right handed smokers (male and female) who – like in the study of Köhler (2012) – have been smoking ten cigarettes per day for at least one year. When they applied, they received a subject's information form including all relevant information's of the project and the tDCS procedure (including risks and exclusion criteria). People who answered after having sent this information and who confirmed to fulfill the criteria were called to fix the dates for the four sessions. Subjects had to sign an informed consent form at the beginning of the first session.

Additional information and further information concerning the fulfilling of criteria was received by the Edinburgh Handedness Inventory (Oldfield, 1971) to confirm the right-handedness of subjects, the German version of Fagerström Test for Nicotine Dependence (FTND) (Heartherton, Kozlowski, Frecker & Fagerström, 1991), and a sociodemographic data sheet.

Due to McClernon et al. (2009) cue induced craving is higher in nicotine abstinence. According to this subjects were asked to not smoke or consume nicotine in any other form six hours before each session. In the study of Fregni et al. (2008a) subjects needed to be abstinent only for 90 minutes. The six hours abstinence was chosen in accordance with Köhler (2012). To ensure subject´s compliance, they were told that before each sessions urine samples would be taken, which in fact was done randomly. But samples have not been analyzed.

Experimental procedure

The study was conducted in the EEG- and tDCS laboratory at the faculty of Psychology (Vienna). The sessions started at June 5th, 2012 and lasted until June, 27th, 2012. Four different tDCS settings were applied to each subject in four sessions, with at least 48 hours between two sessions. The order of tDCS settings over the sessions was randomized.

At the beginning of the first session the German version of Edinburgh Handedness Inventory (Oldfield, 1971), the German version of FTND (Heartherton et al., 1991), and a sociodemographic data sheet had to be filled. Directly at the start of each session, subjects had to sign an informed consent form including subject information as well as the checklist for tDCS participants. Before and after each stimulation they had to complete the German version of PANAS inventory (Watson, Clark & Tellegen, 1988) and the German short form of Tobacco Craving Questionnaire (TCQ) (Heishman, Singleton & Pickworth, 2008).

To place the electrodes, the head of the subject was measured using a measuring tape. Cz (due to the 10-20 EEG electrode placement system) was marked as well as Nz and Oz. Due to these marks an EEG-cap was put on the head to place the electrodes accurately. The EEG-electrodes were attached to the cap over left DLPFC or VLPFC, while the sponge electrodes were stuck under the cap. After application of electrodes, subjects were asked to sit down in a soundproof examination room in front of a 19-Zoll-CRT-Monitor for tDCS stimulation and conduction of tasks. In the first session they did an exercise of three minutes for the n-back task. In the following three sessions only two minutes of n-back task were done to refresh practice.

After having finished practicing, the impedance of electrodes was measured and three minutes of n-back task with scrambled pictures in the background (for more details see below) was done, to have a baseline to compare with further n-back tasks after stimulation.

Before and after this task subjects were asked to rate their actual craving for a cigarette on a nine-array scale represented by a self-assessment manikin (SAM) with

cigarettes like it had been used by Köhler (2012). This scale was an adapted version of SAM from Lang, Bradley and Cuthbert (2008), who used it for arousal and valence ratings. Array 9 indicated the highest craving by showing a big cigarette. The lowest craving was represented by a figure without a cigarette on array 1 (see figure 5). The scale from highest craving to no craving was glued on the keyboard on the keys “1” (strongest craving) to “9” (no craving) with the numbers of the keys not visible. This investigation of craving, as well as the other tasks used, was created using the program E-Prime 2.0 (Psychology Software Tools, Inc., Pittsburgh, PA).

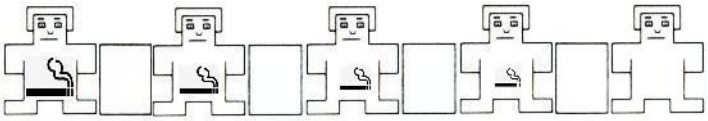

Figure 5: SAM for nicotine craving (picture taken from Köhler, 2012)

TDCS stimulation was applied for 13 minutes. After five minutes of stimulation subjects were asked to rate their craving for a cigarette again.

Additional, first the craving and affective picture evaluation task (duration: 12 minutes) and second the 3-back task (duration: 10 minutes) was presented. The craving and emotional image task always had to be done before the 3-back task, for avoiding the evaluation of pictures being influenced by the highly affecting pictures used in the 3-back task.

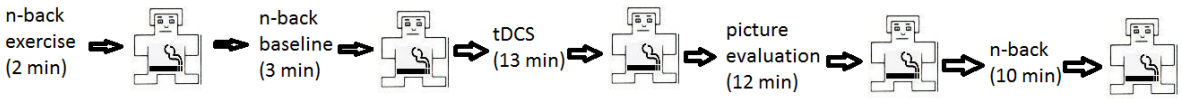

Figure 6: Overview over the conduction of each session

In-between and after the tasks, actual craving level for a cigarette was measured with the SAM scale. After the last craving rating, subjects left the examination room to remove the electrode cap as well as the electrodes and to fill the TCQ and the PANAS inventory once again. At the end of each session a questionnaire concerning adverse side effects of the tDCS procedure had to be filled in.

Transcranial direct current stimulation

Anodal tDCS and sham condition was applied. Therefor the active electrode was placed either over the left VLPFC and/or over the left DLPFC, and the reference electrode over the right DLPFC (F4 according to the 10-20 EEG system). Electrode placements due to the 10-20 EEG system are shown in figure 7. The parameters for the settings were as follows:

- Big electrodes: The active electrode was placed over the left DLPFC and the left VLPFC (F3 and CF5 according to the 10-20 EEG system), whereas a current of 1 mA was applied. As the active electrode had an area of 35 cm², current density was 0.029 mA/cm^2. At the reference electrode, which had an area of 100 cm^2, the density was 0.01 mA/cm^2. According to Nitsche et al. (2007), a current density lower than 0,017 mA/cm^2 showed no effects.

- Small electrode over DLPFC: The EEG electrode (1.33 cm^2) used as active electrode was placed over the left DLPFC (F3 according to the 10-20 EEG system) and the current applied had an intensity of 0.4 mA, which lead to a current density of 0.301 mA/cm^2. Current density at the reference electrode was 0.014 mA/cm^2, as it had a size of 35 cm^2.

- Small electrode over VLPFC: The same electrode was used as for small electrodes over DLPFC, but instead of the DLPFC, the VLPFC was stimulated. According to the findings of Kühn et al. (2011) in respect to brain activation in craving, the location of the electrode was in BA 44, on the MNI coordinates -47,13,7 (FC5 according to the 10-20 EEG system).

- Sham condition: Randomly one of the three settings described above was used for sham condition, whereby each was applied at one third of the subjects, chosen randomly.

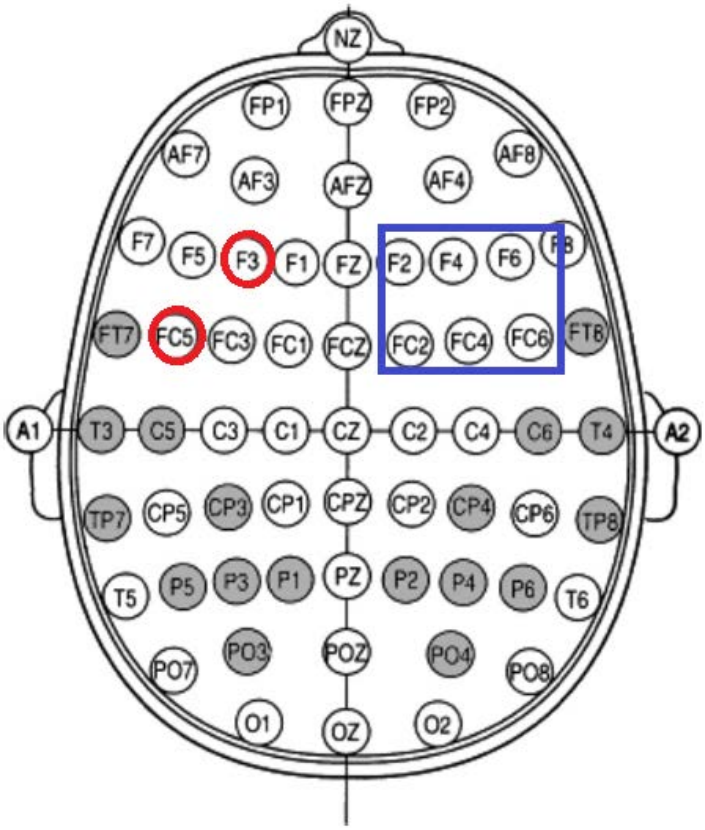

Figure 7: Electrode placement. The red circles show the EEG electrode (anode), which was either placed over the DLPFC (F3) or the VLPFC (FC5). The reference electrode (cathode) was set over the left DLPFC (F4). In the setting with the big electrode the 35-cm^2-electrode was applied likewise on the left side, covering bothF3 and FC5 (is not sketched in this figure). The size of electrodes in this illustration was not taken precisely. (Picture taken and and modified from Cabrera and Dremstrup, 2008).

Questionnaires

Checklist for tDCS participants

A checklist was used to examine whether subjects fitted to the criteria to apply tDCS without health risks. The list consists of 18 questions examining 1) negative reactions to previous tDCS stimulations, 2) previous epileptic seizures, 3) previous cerebrovascular accident, 4) previous operations of the head or the brain, 5) having metal in the body (except of dental implants and fillings), 6) having implanted devices like a cardiac pacemaker, 7) having heavy headache or frequent headache, 8) previous diseases concerning the central nervous system/brain, 9) previous diseases

with brain damage as consequence, 10) taking psycho- or neuroactive medicaments like antidepressants, neuroleptics or lithium, 11) if being a woman: actual pregnancy, 12) previous epileptic seizures of a family member; 13) having a profession were regular driving of motor vehicle is necessary (car, truck, bus, train), 14) having slept enough the previous night, 15) having consumed big amount of alcohol, nicotine or other psychotropic substances in the previous night, 16) being addicted to drugs (except smoking), alcohol or medicaments, 17) having chronic disease of the skin and if yes, is the scalp affected, 18) having metallic objects on the body or in the cloth.

Edinburgh Handedness Inventory

The Edinburgh Handedness Inventory is a questionnaire consisting of ten items to examine the handedness of participants (Oldfield, 1971).

In this study a German version was used (see appendix).

Fagerström Test for Nicotine Dependence

The Fagerström Test for Nicotine Dependence (FTND) was developed to ascertain the level of nicotine dependence more valid and reliable, which was verified by several studies (Heatherton et al., 1991; Pomerleau, Carton, Lutzke, Flessland & Pomerleau, 1994).

A total score of ten points can be reached. Due to the score there is a separation into low dependency (0-2 points), average dependency (3-5 points), strong dependency (6-7 points) and very strong dependency (8-10 points) (Fagerström & Schneider, 1989).
The German version which was given to the subjects can be found in the appendix.

Tobacco Craving Questionnaire

The TCQ is a valid and reliable instrument to measure craving levels. Apart from an overall craving level the items can be separated into four factors: Factor 1: “Emotionality, or smoking in anticipation of relief from withdrawal symptoms or negative mood”, factor 2: “Expectancy, or anticipation of positive outcomes from smoking”, factor 3: “Compulsivity, or an inability to control tobacco use” and factor 4: “purposefulness, or intention and planning to smoke to positive outcomes” (Heishman, Singleton & Moolchan, 2003). In this study the TCQ was used to investigate the change of craving levels caused by tDCS sessions.
Subjects were given the German version of the short form of the TCQ, including twelve items, whereas there were three items for each of the four factors (Heishman et al., 2008). For the German version see appendix.

PANAS Inventory

The Positive and Negative Affect Schedule (PANAS) consists of 20 items, whereas always ten are loading on positive and negative affect. To have a reliable and valid instrument to measure positive and negative affect, Watson et al. (1988) developed this questionnaire.

Questionnaire to acquire adverse effects of tDCS

The questionnaire to acquire negative impact of tDCS after each session was taken from Köhler (2012) who had created it according to Brunoni et al. (2011c).
Subjects had to answer whether headache, neck pain, pain of the scalp, prickling, itching, biting, flushing, sleepiness, concentration on problems or acute mood swinging was not present, slightly present, moderately present or strongly present. The symptoms which were rated as present had to be evaluated whether the stimulation could have been the reason or not. Further subjects had to tell whether the symptom occurred at the beginning, the end or during the whole stimulation. Additionally the task during which they had felt it or if they felt it still while filling the questionnaire had to be mentioned.

Tasks

Craving and affective image evaluation task

The craving and affective picture evaluation task was the same used in the study from Köhler (2012). The task consisted of four different categories each having 15 pictures. The categories were first smoking cues, showing for example people smoking or a cigarette box and further neutral (showing e.g. a book or a hair dryer), negative (showing e.g. a shark or a weapon) and positive (showing e.g. a landscape or animal babies) pictures.

The procedure of the task was as follows (also see figure 8): The order of pictures presented was randomized. The evaluation of each picture started with a fixation cross which was showed for two seconds. Then the picture was presented for four seconds. After each picture subjects were asked to rate how much craving the picture induced, using the same scale as for the evaluation of the actual overall craving level (see figure 6). Additionally they had to rate the valence and the arousal of the pictures. For these two evaluations again nine-point SAM scales were used and the scales were as well as in Köhler (2012) glued on the keys of the keybord to facilitate responding for the subjects. Most positive valence was indicated by a laughing figure, while the most negative was represented by a sad figure. In the arousal scale, lowest arousal was expressed by a calm figure whereas the highest was an exploding one (see Lang et al.,2008).

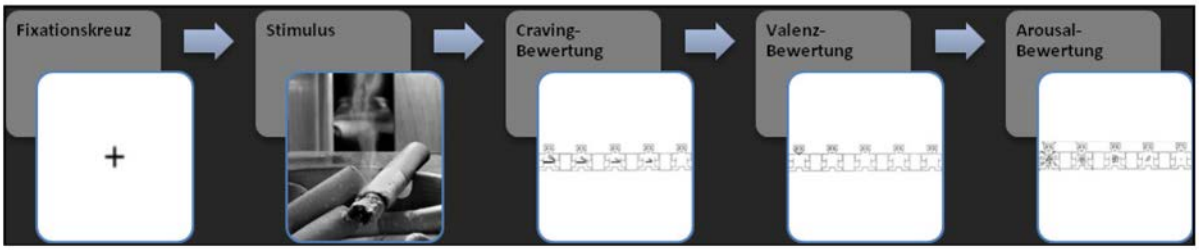

Figure 8: Procedure of the craving and affective picture evaluation task (Picture taken from Köhler, 2012)

3-back task

The verbal n-back task was similar to the one used by Zaehle et al. (2011). But to avoid ceiling effects, a 3-back instead of a 2-back paradigm was set. Additionally instead of four, ten letters were used like in the study of Fregni et al. (2005). These were the letters B, C, D, F, G, H, J, K, L and M. They were presented randomly for 0.5 seconds, with an inter-stimulus interval of 2 seconds. The color of the letters was lime, and the font was Palatino Linotype with point size 90. The letters were presented on a screen with photos as background (see figure 9 as example). In the inter-stimulus interval the background was dark gray with a fixation cross in the center.

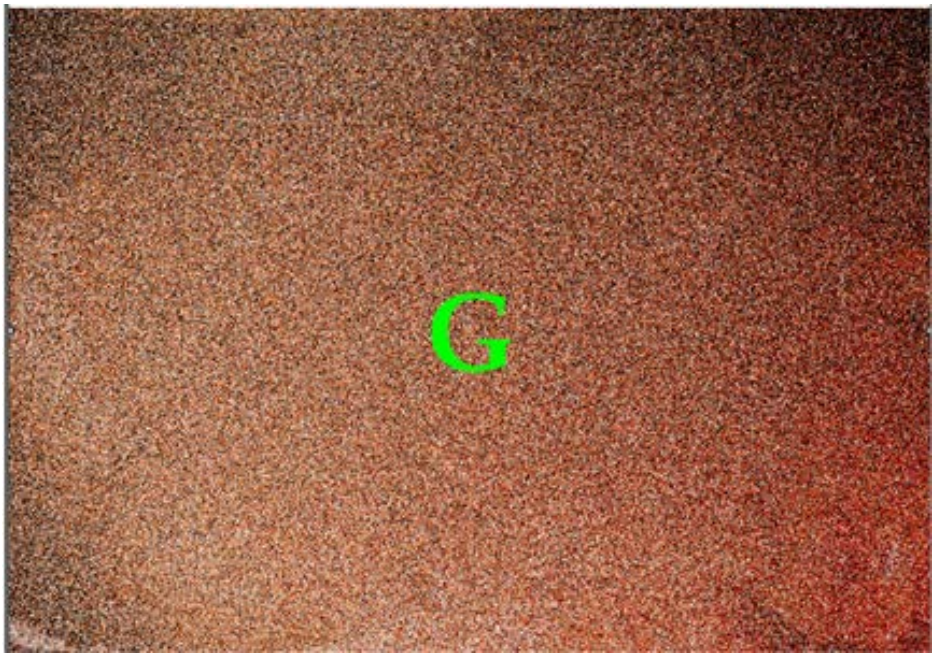

Figure 9: Screenshot of the stimulus presentation in the 3-back task

The subject had to press “2”, when the letter presented three letters before was not the same, as the actual one. This means the letter was a non-target. Targets were defined as letters which were the same as the letter presented three letters before. In this case the subject ought to press “1”.

There existed four conditions of the tasks each presented twice, whereas the order was randomized. Altogether the task took ten minutes. Each block consisted of 20 targets and 10 non-targets.

The four conditions differed in the letters background. One included 28 pictures showing animals, nature phenomenon and arms which ought to induce fear. They were received from the “International Affective Picture System (IAPS) 2007 pictures (Lang et al., 2008) and had an average rating for arousal of 6.1 as well as 3.9 for valence. In the arousal scale “1” is the lowest arousal and “9” the highest arousal. In valence rating “1” is seen as negative and “9” as positive.

The second version consisted of 31 pictures showing wounds, wounded people and dead bodies. These humiliating pictures had a stronger arousal and were more negative than the pictures inducing fear. The pictures were as well received from IAPS 2007 pictures and they had an average rating for arousal of 6.5 as well as 1.8 for valence (Lang et al., 2008).

The third version included neutral pictures. They were as well received form IAPS 2007 and had an average rating for arousal of 2.1 as well as 5.1 for valence (Lang et al., 2008).

The fourth part included scrambled pictures. The photos used for the humiliating and the fear version were edited with a photo editing software (GNU image manipulation program) to make them scrambled. As the same pictures like in the other conditions were used, the same visual input concerning colors, but without recognition of pictures was affirmed by this procedure.

The baseline measurements for the 3-back task at the beginning of each session were done using condition four (scrambled pictures).

Subject’s performance was measured for accuracy (the number of right answers) and reaction time (time between presentation of the letter and button press).

This complex 3-back task including four different conditions was developed for other research purposes. Therefor only condition four, having scrambled pictures as stimulus background, has been considered in the further course of this diploma thesis.

Statistical analysis

The statistical analysis was done using SPSS 19 (IBM SPSS Statistics 19, Somer, NY, USA). For the PANAS inventory a 4 x 2 repeated measurement MANOVA, using within subject factors setting (35-cm^2-electrode, EEG-electrode over DLPFC, EEG-electrode over VLPFC, sham condition) and time (before and after stimulation), was done for positive and negative affect. To analyze data received from TCQ, the same 4 x 2 design was used, but as dependent variable overall craving level was calculated and separately the 4 x 2 repeated measurement MANOVA was repeated for the four factors of TCQ.

The craving level measurements using the SAM scale were calculated in a 4 x 5 repeated measurement ANOVA with within subject factors setting (35-cm^2-electrode, EEG-electrode over DLPFC, EEG-electrode over VLPFC, sham condition) and time (before baseline, after baseline, directly after stimulation, after craving and picture evaluation task and after 3-back task).

Previous research suggests that heavier smokers show altered cue induced craving and a different activity of brain when smoking cues where presented (McClernon et al., 2008). Hence subjects having an FTND score of six or more (strong dependency and very strong dependency) were chosen to do the above described repeated measurement ANOVA with data from TCQ and SAM scale.

For the craving and affective picture evaluation task, a 4 x 4 repeated measurement MANOVA was done, using the four settings and the four kinds of pictures (negative, positive, neutral and smoking cue) as within subjects. Dependent variables were craving, arousal and valence ratings.

To examine working memory performance for each session, average accuracies and reaction times from the 3-back version after stimulation using scrambled pictures were subtracted from the baseline values measured before the stimulation. With these differences a repeated measurement MANOVA was calculated using setting (35-cm^2-electrode, EEG-electrode over DLPFC, EEG-electrode over VLPFC, sham condition) as within subject factor. Dependent variables were target accuracy, non-

target accuracy, target reaction time, non-target reaction time as well as overall accuracy and overall reaction time.

To investigate whether there were different aftereffects between the conditions Cochran´s Q tests, McNemar tests and binominal tests were calculated using data from the tDCS adverse effects questionnaire.

To test requirements of repeated measurement ANOVA for sphericity the Mauchly test for sphericity was used. When sphericity was not given, the Greenhouse-Geisser corrector was used. Post hoc tests for ANOVAs and MANOVAs were calculated using Bonferroni comparisons. Normal distribution was checked by frequency plots and homogeneity of variances was examined using Levene tests. .

In all tests the level of significance was set at $\alpha < 0.05$.

Results

Participants

There were 15 subjects participating in the study. As all fulfilled the criteria and everybody participated in all four session, nobody had to be excluded. All subjects had a Matura (high-school certificate). The highest educational levels were a finished master study (1 person), finished bachelor study (6 persons) and Matura (8 persons).

Subjects had an average age of 27.00 ± 3.84 years and smoked in average 15.17 ± 3.86 cigarettes per day. The average FTND score was 3.80 ± 1.72. Ten persons would like to quit smoking whereas the others did not have this endeavor at the moment.

Working memory

H_1: Working memory performance is independently from electrode size higher after anodal tDCS over left DLPFC and VLPFC than without stimulation.

- *35-cm^2 = VLPFC = DLPFC > Sham*

With the differences between baseline measurements and performance values after the stimulation of the scrambled 3-back version, a repeated measurement MANOVA was calculated using setting (35-cm^2-electrode, EEG-electrode over DLPFC, EEG-electrode over VLPFC, sham condition) as within subject factor. Dependent variables were target accuracy, non-target accuracy, target reaction time, non-target reaction time as well as overall accuracy and overall reaction time.

Table 1: Results of the repeated measurement MANOVA for the 3-back

Dependent variable	**Influence of setting**
Accuracy non-target	**$F(3,42) = 2.986$; $p = 0.042$; $\eta_p^2 = 0.176$**
Reaction time non-target	$F(3,42) = 0.749$; $p = 0.529$; $\eta_p^2 = 0.051$
Accuracy target	$F(3,42) = 0.649$; $p = 0.588$; $\eta_p^2 = 0.044$
Reaction time target	$F(3,42) = 0.113$; $p = 0.952$; $\eta_p^2 = 0.008$
Overall accuracy	$F(3,42) = 1.802$; $p = 0.162$; $\eta_p^2 = 0.144$
Overall reaction time	$F(3,42) = 1.802$; $p = 0.847$; $\eta_p^2 = 0.019$

There were no effects on reaction time non-target, accuracy target, reaction time target, allover accuracy and allover reaction time. Significant effects of setting were found for accuracy non-target (see table 1).

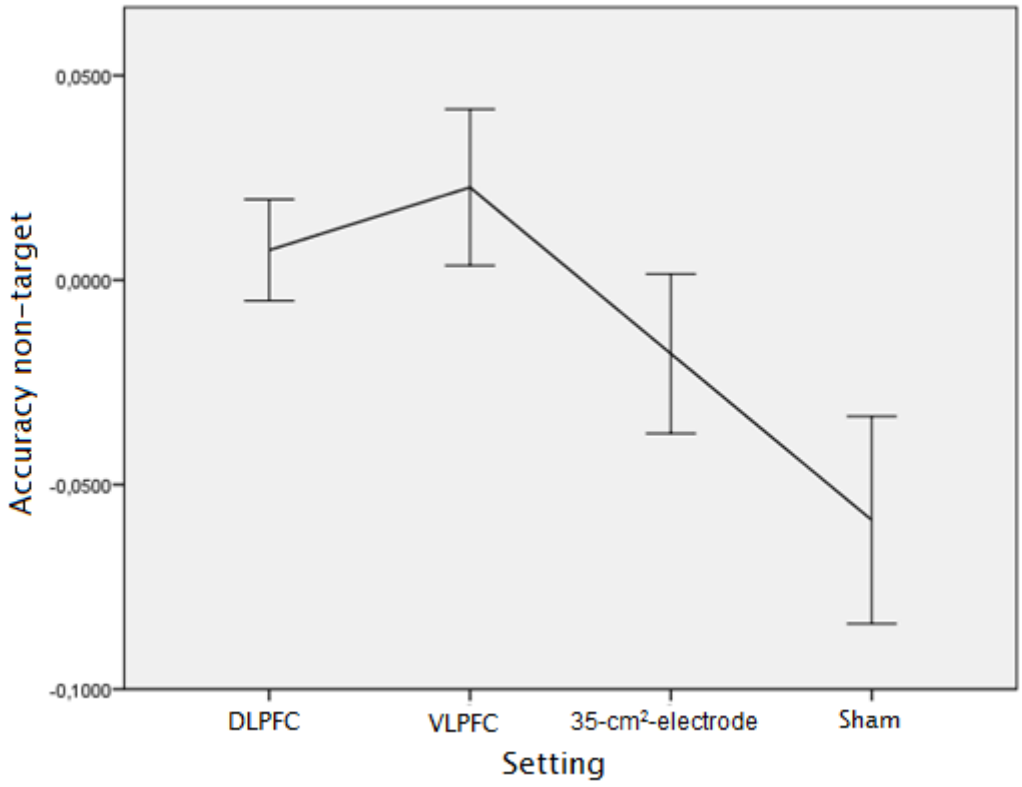

Figure 10: Mean changes and standard error of non-target accuracy (difference values before minus after stimulation, i.e. negative values indicate better performance compared to baseline)

Direct contrasts showed that non-target accuracy was significant better after sham condition than after anodal tDCS over the VLPFC compared to baseline measurements before stimulation. In figure 10 mean differences (and standard errors) between the non-target accuracy of baselines before the four stimulations and after the four tDCS applications is shown.

Craving levels

H_2: In contrast to an anodal stimulation over the left DLPFC using an EEG-electrode or in sham condition the level of craving is lower after applying anodal tDCS over the left DLPFC and VLPFC using a 35-cm^2-electrode or an EEG-electrode over the VLPFC decrease craving.

- *35-cm^2 = VLPFC < DLPFC = Sham*

A 4 x 2 repeated measurement MANOVA using within subject factors setting (35-cm2-electrode, EEG-electrode over DLPFC, EEG-electrode over VLPFC, sham condition) and time (before and after the session) was done. Dependent variable was either the overall craving level measured with the TCQ or its four factors. For craving data acquired with the SAM scale, a 4 x 5 repeated measurement ANOVA with five points in time was done.

Table 2 shows that overall TCQ score did neither differ over the four settings nor over time nor was there an interaction between these factors.

Table 2: Results of the 4 x 2 repeated measurement ANOVA for overall craving measured by TCQ and the four factors of TCQ

Dependent variable	***Setting***	***Time***	***Interaction setting-time***
Overall TCQ	F(3,42) = 0.256 p = 0.857 η_p^2 = 0.018	F(1,14) = 0.406 p = 0.534 η_p^2 = 0.028	F(3,42) = 1.666 p = 0.189 η_p^2 = 0.106
TCQ factor 1	F(3,42) = 0.654 p = 0.585 η_p^2 = 0.045	F(1,14) = 2.223 p = 0.158 η_p^2 = 0.137	F(3,42) = 0.256 p = 0.857 η_p^2 = 0.018
TCQ factor 2	F(3,42) = 0.734 p = 0.838 η_p^2 = 0.050	F(1,14) = 1.083 p = 0.316 η_p^2 = 0.072	F(3,42) = 0.256 p = 0.857 η_p^2 = 0.018
TCQ factor 3	F(3,42) = 0.176 p = 0.912 η_p^2 = 0.012	**F(1,14) = 4.973** **p = 0.043** **η_p^2 = 0.262**	F(3,42) = 0.968 p = 0.417 η_p^2 = 0.065
TCQ factor 4	F(3,42) = 0.373 p = 0.773 η_p^2 = 0.026	F(1,14) = 1.538 p = 0.235 η_p^2 = 0.099	F(3,42) = 0.968 p = 0.417 η_p^2 = 0.065

When the MANOVA was calculated for the four factors of TCQ, factors 1, 2 and 4 were neither altered significantly over settings and time as well as no effect of interaction occurred. In contrary, factor 3 (compulsivity) was significant over time, while setting and the interaction setting – time were not. These results in detail are showed in table 2. Due to figure 11, compulsivity of craving was higher at the end of sessions than at the beginning.

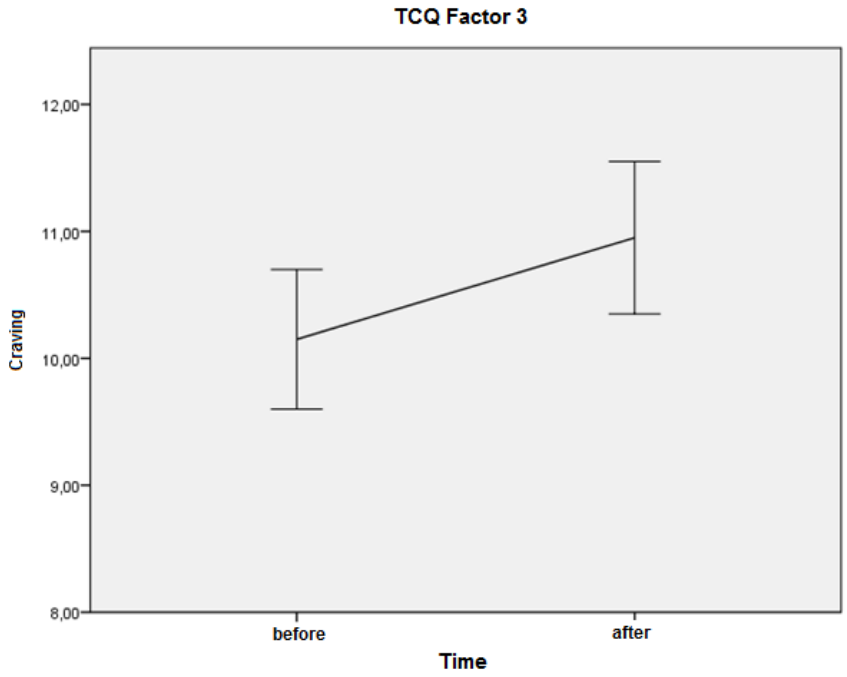

Figure 11: Mean and standard error of TCQ factor three “compulsivity” before and after stimulation

Table 3 shows that actual craving did not alter significantly over settings and time when measured with the SAM scale during the four sessions. An interaction between setting and time was found neither.

Table 3: Results of 4 x 5 repeated measurement ANOVAs for craving measured with the SAM scale. The analysis was done for all subjects and for subjects with an FTND score up from six.

Analysis	***Setting***	***Time***	***Interaction setting - time***
ANOVA for SAM with all subjects	F(3,36) = 0.579 p = 0.633 η_p^2 = 0.046	F(4,48) = 0.949 p = 0.402 η_p^2 = 0.073	F(12,144) = 0.472 p = 0.768 η_p^2 = 0.038
ANOVA for SAM with FTND ≥ 6	F(3,9) = 0.696 p = 0.577 η_p^2 = 0.188	F(6,12) = 1.396 p = 0.293 η_p^2 = 0.318	F(12,36) = 1.370 p = 0.225 η_p^2 = 0.313

When the same ANOVA was done with an FTND score smaller than six as exclusion criterion, neither setting nor time, nor the interaction between these factors was significant (see table 3 for details).

H_3: Smoking cue induced craving is lower after anodal tDCS using a 35-cm^2-electrode over DLPFC and VLPFC or an EEG-electrode over the VLPFC than using an EEG-electrode over the DLPFC or applying no tDCS.

- *35-cm^2 = VLPFC < DLPFC = Sham*

For cue induced craving a 4 x 4 repeated measurement MANOVA was done with within subject factors setting and picture (negative, positive, neutral and smoking-cue), and the dependent variable craving. In the same MANOVA arousal and valence for the affective picture evaluation had been calculated.

The setting had no influence on cue induced craving. But there was a difference between the pictures. Besides, no interaction was found (for details see table 4 together with data to affective picture evaluation).

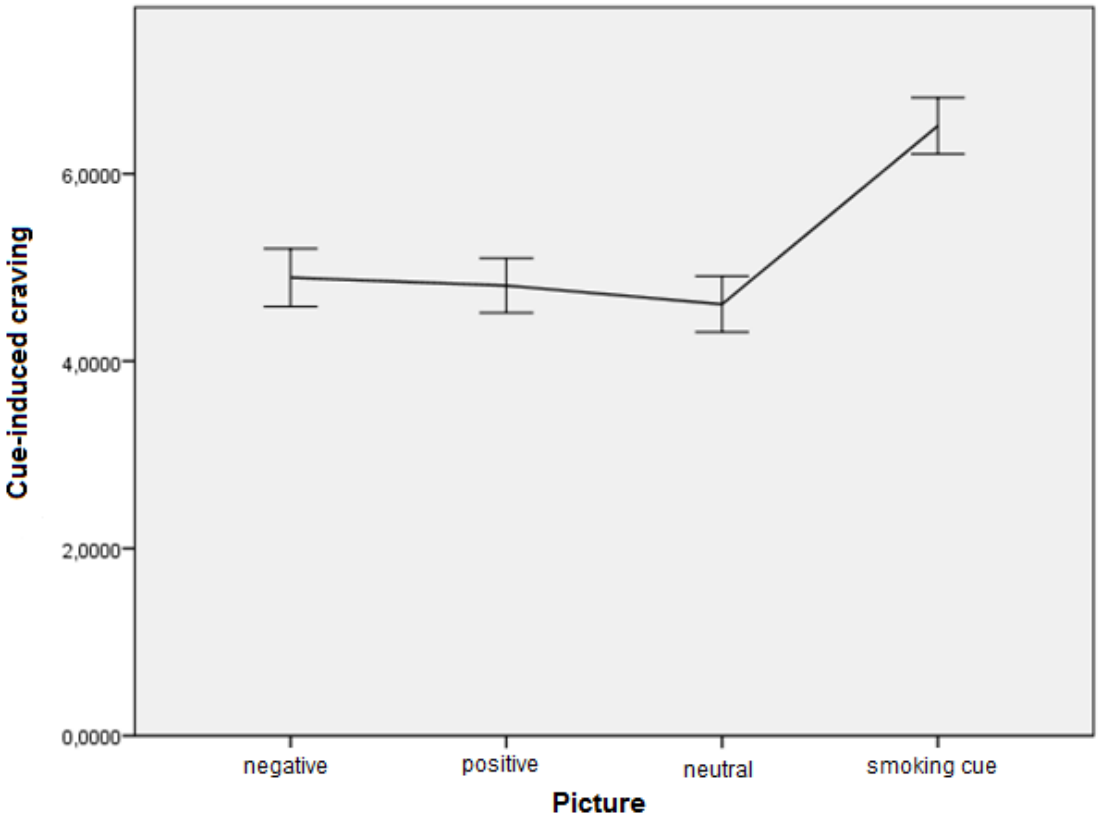

Figure 12: Mean and standard error of cue-induced craving over different types of pictures

The graph in figure 12 shows that craving induced by pictures was the highest for smoking cues. These findings are supported by paired comparisons where the smoking cue induced craving was significantly different ($p < 0.05$) from the other pictures categories.

Affective picture evaluation

H_4: Affective picture evaluation differs after anodal tDCS over DLPFC and VLPFC using the 35-cm^2-electrode or an EEG-electrode over the VLPFC compared to an anodal stimulation over the DLPFC using an EEG-electrode or in sham condition.

- *35-cm^2 = VLPFC ≠ DLPFC = Sham*

The data to examine the affective picture evaluation was taken from the same 4 x 4 repeated measurement MANOVA as it was used for cue induced craving. The difference was that for affective picture evaluation the dependent variables arousal and valence were regarded.

Table 4: Result of the 4 x 4 repeated measurement MANOVA for craving, arousal and valence

Dependent variable	***Setting***	***Picture***	***Interaction setting - picture***
Craving	F(3,42) = 0.296 p = 0.828 η_p^2 = 0.021	**F(3,42) = 0.038** **p = 0.001** **η_p^2 = 0.392**	F(8,126) = 0.411 p = 0.813 η_p^2 = 0.029
Arousal	F(3,42) = 0.547 p = 0.653 η_p^2 = 0.038	**F(3,42) = 14.283** **p < 0.001** **η_p^2 = 0.505**	F(8,126) = 1.727 p = 0.152 η_p^2 = 0.110
Valence	F(3,42) = 0.248 p = 0.862 η_p^2 = 0.017	**F(3,42) = 47.270** **p < 0.001** **η_p^2 = 0.772**	F(8,126) = 0.998 p = 0.446 η_p^2 = 0.067

Due to table 4 on both, arousal and valence ratings, the setting had no influence. Furthermore the effect of interaction between setting and picture was neither significant. But there was a difference between the pictures for arousal and valence.

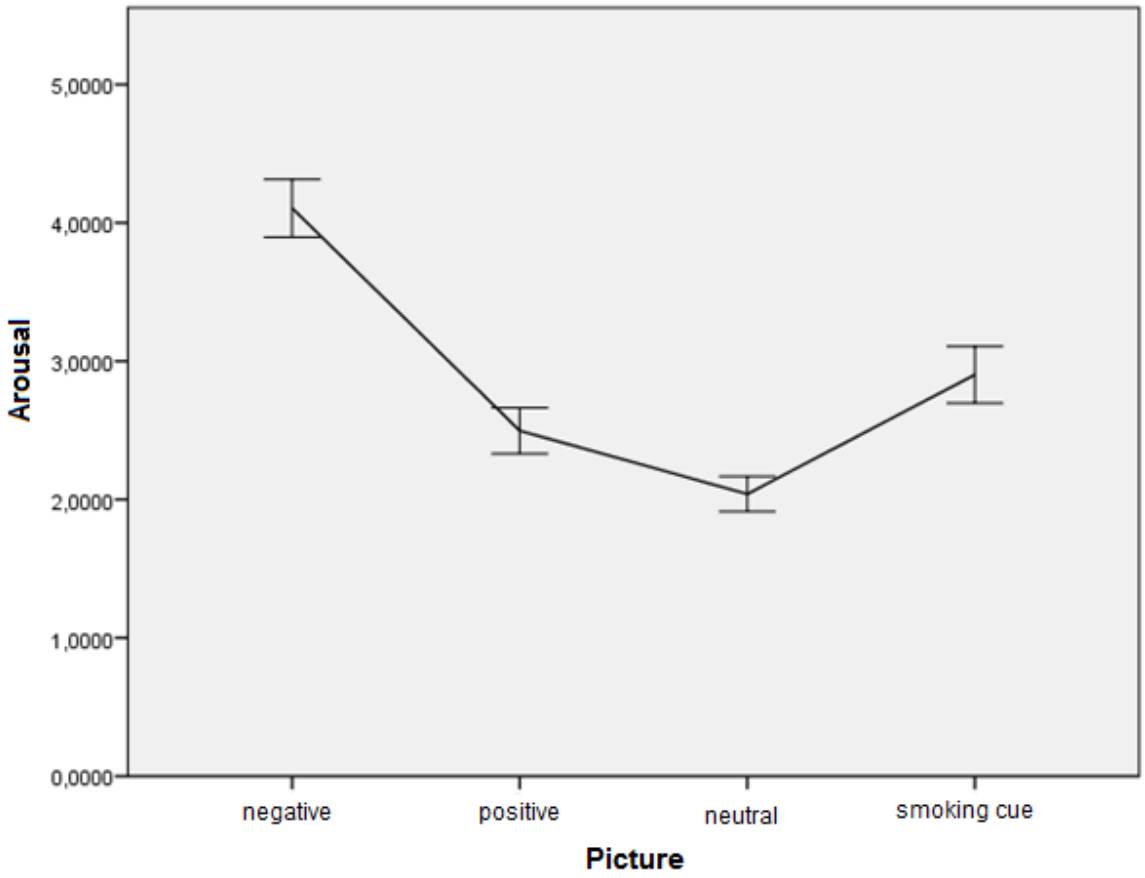

Figure 13: Mean and standard error of arousal over the four different types of pictures

A comparison of arousal levels lead to the insight that arousal for negative pictures was rated higher than for positive ones ($p = 0.03$) as well as negative pictures induced higher arousal than neutral pictures ($p < 0.01$). On the graph in figure 13 can be seen, that the arousal was rated higher for negative pictures than for the three other types of pictures.

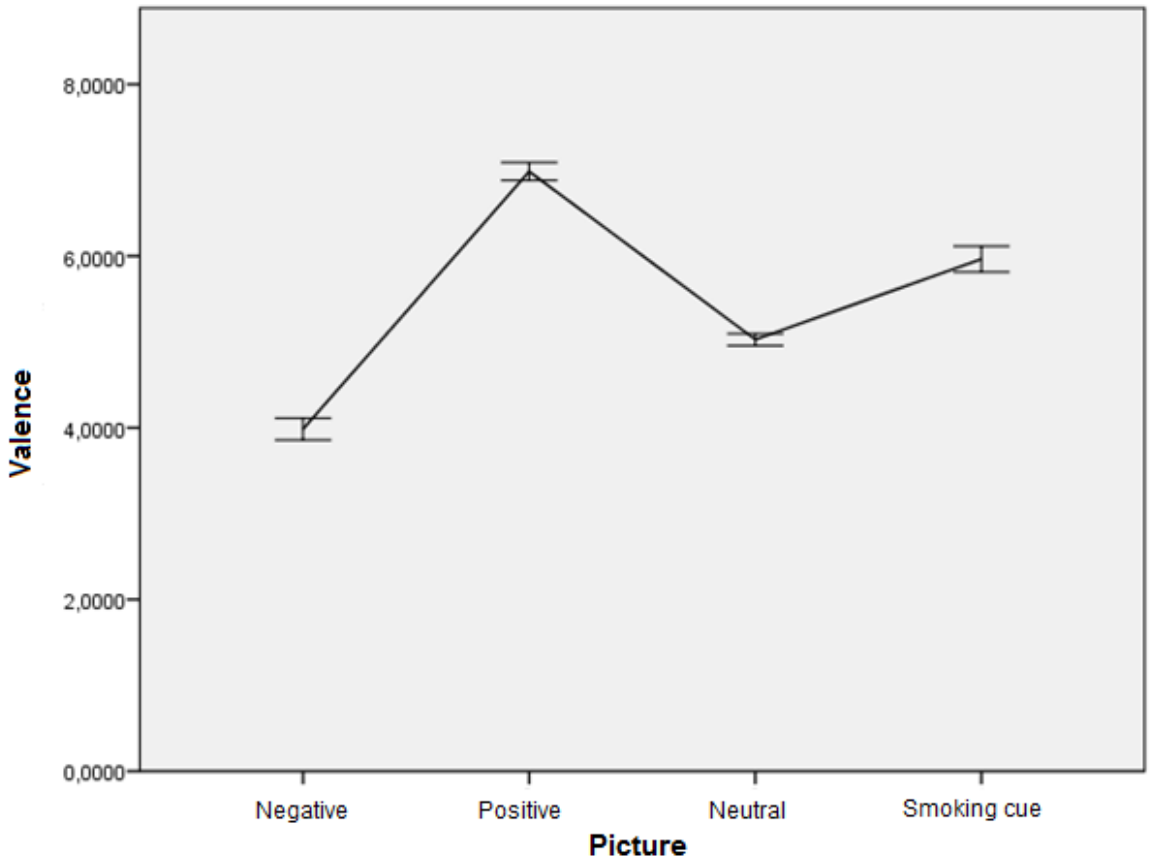

Figure 14: Mean and standard error of valence over different types of pictures

As figure 14 shows, negative pictures had the lowest valence, followed by neutral ones. Smoking cues had a higher valence than the two before mentioned. The highest valence, meaning the most positive ratings, received positive pictures. Due to paired comparisons the differences in valence rating were significant ($p < 0.05$) for all pictures.

PANAS inventory

PANAS was used to consider positive and negative mood changes during stimulation. Therefore a 4 x 2 repeated measurement MANOVA, using within subject factors setting (35-cm^2-electrode, EEG-electrode over DLPFC, EEG-electrode over VLPFC, sham condition) and time (before and after stimulation) was done for positive and negative affect as dependent variables.

Table 5: Outcomes of 4 x 2 repeated measurement MANOVA conducted for PANAS Inventory

Affect	Setting	Time	Interaction setting - time
Negative affect	F(3,42) = 2.522 p = 0.096 η_p^2 = 0.153	F(1,14) = 1.968 p = 0.182 η_p^2 = 0.123	F(3,42) = 0.975 p = 0.379 η_p^2 = 0.065
Positive affect	F(3,42) = 0.745 p = 0.532 η_p^2 = 0.050	**F(1,14) = 30.869** **p < 0.001** **η_p^2 = 0.688**	F(3,42) = 0.387 p = 0.763 η_p^2 = 0.027

As table 5 shows, negative affect did neither change over settings nor over time. Furthermore no interactions were found.

In contrast positive affect changed over time, whereas neither setting nor the interaction between the two factors had an impact. As figure 15 shows, the positive affect decreased during stimulation.

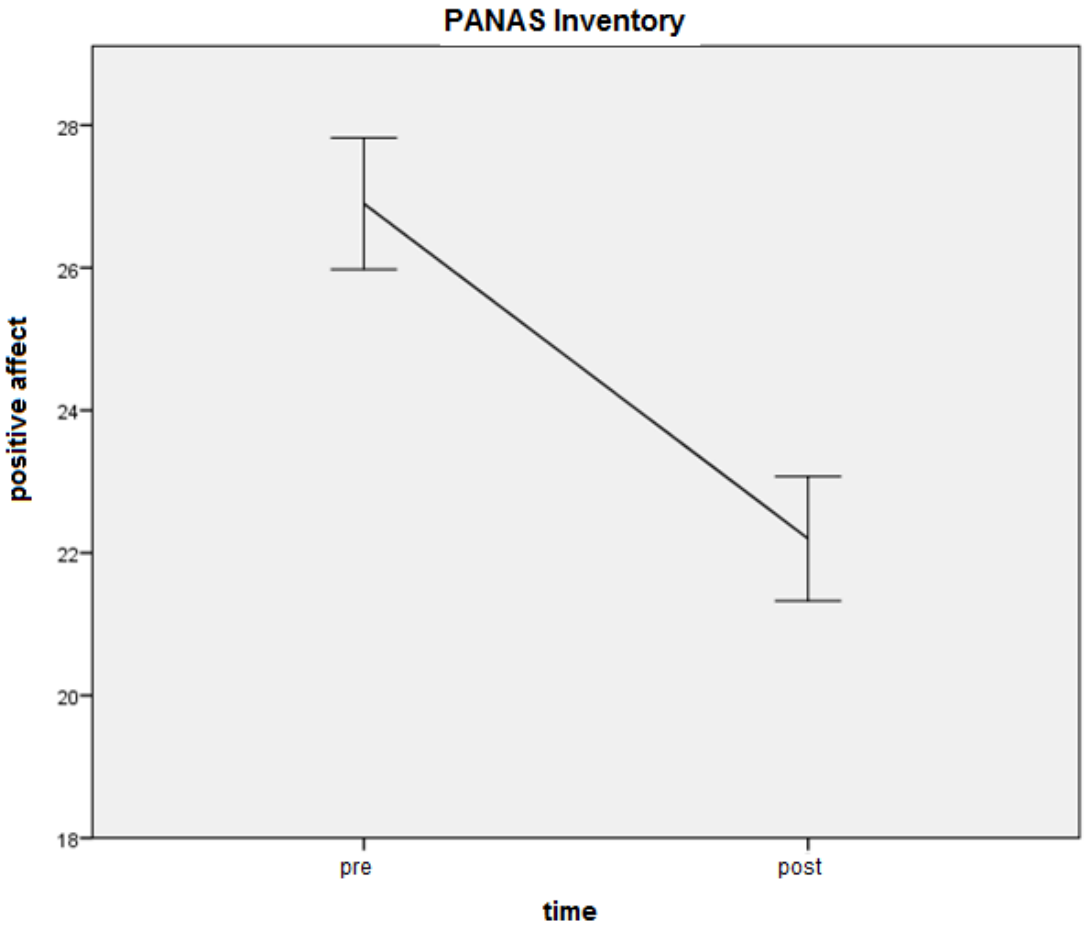

Figure 15: Mean and standard error of positive affect at the beginning and the end of session

Questionnaire to acquire adverse effects of tDCS

To examine differences in negative effects between settings which might have occurred due to tDCS, a Cochran´s Q test was done. When Cochran´s Q was significant, what means that at least two settings differ significantly from each other, binominal tests were done to directly compare the settings.

Table 6: Comparisons of the amount of adverse effects over the settings

Effect	***Level of significance in Cochran´s Q***
Headache	p = 0.392
Neck pain	p = 0.572
Pain of the scalp	p = 0.468
Prickling	p = 0.053
Itching	**p = 0.049**
Binging	**p = 0.045**
Flushing	p = 0.392
Sleepiness	p = 0.107
Concentration on problems	p = 0.194
Acute mood swinging	p = 0.112

Table 6 shows that itching and binging were the only effects which differed significantly in at least two settings. Due to binominal tests itching occurred more frequent after the setting using the 35-cm^2-electrode than using EEG-electrode over the DLPFC (p = 0.020). Binging was the most frequent after using the 35-cm^2-electrode as well. This was significantly higher than using EEG-electrode over the VLPFC (p = 0.014). In figure 16 the different frequencies of itching and binging are shown.

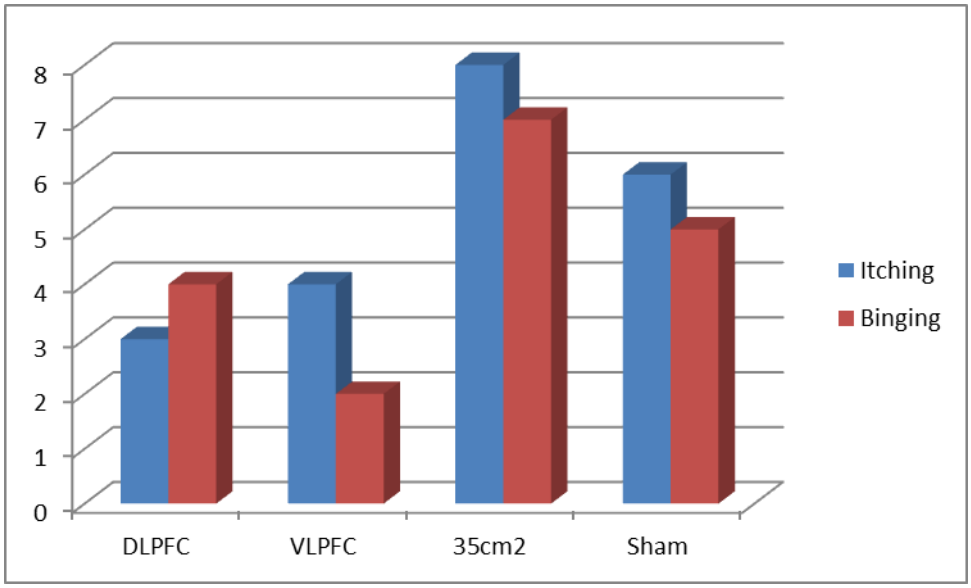

Figure 16: A bar graph showing the absolute frequencies of itching and binging after each of the four settings. Itching differs significantly between EEG electrodes over the DLPFC and the 35-cm^2-electrode, while there is a difference between the setting using EEG electrodes over the VLPFC and the 35-cm^2-electrode.

Discussion

Introduction

None of the hypotheses framed could be confirmed, as the majority of results were not according to predictions generated out of previous research. Yet there is a variety of explanations to defend the outcome.

In the subsequent part the results in working memory performance, of craving levels and cue induced craving as well as of mood and affective picture evaluation will be discussed. Moreover, tDCS as a method will be reflected. Finally the shortcomings of the study will be discussed.

Working memory

Against expectations, the only impact of anodal tDCS on working memory performance found was an improved accuracy in response to non-targets in sham condition than when anodal tDCS was applied to the left VLPFC. Hence the results could be interpreted, that there was a “decreased” performance after anodal tDCS over the left VLPFC compared to sham condition.

Watching the graph in figure 10 shows that subject performance was better after sham condition than in the baseline measurement. In contrast to this, the non-target accuracy after the other settings was almost the same when compared to baseline measurement. This leads to the conclusion, that performance rises after sham stimulation, whereas in the conditions, which for a change had been expected, this alteration seems to be suppressed.

In baseline measurement subjects did three minutes of n-back task. After tDCS session however, the n-back task presented, lasted for ten minutes. A practice session was done at the beginning of each session to avoid practicing effects in the baseline measurements. Still, the performance could have become better over time. Hence the non-target accuracy was highest in the n-back task at the end of each session.

But why there was no such a rise of performance, when anodal tDCS was applied? Due to Marshall et al. (2005) tDCS could interfere dynamics in cortical processing. Hence, in our study the practicing effect could have been disturbed by the stimulation.

However, when comparing these results to the study of Marshall et al. (2005), the differences between these studies have to be considered. The effect of “decreased” accuracy in the working memory task occurred after stimulation of the left VLPFC, not the left DLPFC, as in the study of Marshall et al. (2005). In the current study, anodal stimulation using EEG electrodes on the left DLPFC did not alter working memory performance at all.

Marshall et al. (2005) applied tDCS using two pairs of electrodes to stimulate the left and right DLPFC in parallel. In the current study only one pair of electrodes was used and the reference electrode was over the right DLPFC/VLPFC. Hence the effect on working memory in the study of Marshall et al. (2005) could be due to the activation in the right DLPFC or due to the reference electrodes placed over the left and right mastoids.

A further reason for not being able to replicate the decreased working memory performance in anodal tDCS over DLPFC with EEG electrodes found by Marshall et al. (2005), might be due to the fact that in our study a constant current was applied instead of an intermittent current. Furthermore, placing EEG-electrodes on a cap due to the 10-20 EEG placement system, by measuring the head using a measuring tape, is not an accurate method to effectively place electrodes of approximately 1 cm^2 on the target region. Hence the target region of EEG electrodes placed over F3 in the current study might not exactly have been the same as in the study of Marshall et al. (2005).

A further reflection concerning the comparability of these two studies is the difference in tasks which were used to evaluate working memory performance. Marshall et al. (2005) used a Sternberg task measuring reaction time to rate performance, whereas in this study a 3-back task has been used measuring accuracy and reaction time. Nevertheless, only accuracy altered between settings, while the reaction time did not.

The question rises how much weight can be put on the insight that accuracy of non-target seems to be decreased after anodal tDCS over the VLPFC.

Apart from these findings about the possibilities of interpretation of the outcome in non-target accuracy, there is the question how much the working memory performance is altered, when one from six parameters is significant. Precisely because neither reaction time for non-target, target nor for both together did differ between settings. Moreover, accuracy of target and overall accuracy were also not altered.

Previous studies have used either reaction time or accuracy to report alteration in working memory performance, which means that not both were always measured or only one of these two parameters changed significantly (Fregni et al., 2005; Keeser et al., 2011; Marshall et al., 2005; Ohn et al., 2008). As discussed above, alterations in reaction time could be found in Marshall et al. (2005). In the studies of Zaehle et al. (2011), who used a 2-back task, and Keeser et al. (2011), reaction time was shorter after tDCS. Even though in the study of Keeser et al. (2011) this effect only occurred when a 0-back task was used. For a 2-back task no alteration in reaction time could be observed. The studies measuring working memory performance with a 3-back task found no alterations in reaction time, but increases in accuracy (Fregni et al., 2005; Ohn et al., 2008). Hence in tasks with higher working memory load there might be no influence of tDCS on reaction time.

Following the above discussed previous research, alteration in reaction time might not be expected. The question rises why there was no further influence of tDCS on accuracy beside of the change in non-target accuracy. The EEG-electrodes might not have been placed accurately enough or the target area might have been too small to have an actual effect. Still a revision of the already found results would have been expected by using a big electrode.

In Fregni et al. (2005) the mean of correct responses to targets was 19.8 ± 5.8 in sham condition and 21.7 ± 5.0 during active stimulation. This means for an amount of 30 targets an accuracy of approximately 0.67 and 0.73. Ohn et al. (2011) reported accuracies between 0.65 and 0.71 in sham condition. In both studies the subjects

only had to press the button when a target appeared, which was different in the 3-back paradigm used here. In the study of Zaehle et al. (2011), where subjects also had to press different buttons for target and non-target, no information about the accuracy values was given. Therefore, no direct comparison is possible for non-targets. In our study accuracy for targets was 0.72 ± 0.20 which is almost the same as in Ohn et al. (2011) and Fregni et al. (2005).

Nevertheless, a ceiling effect in the active stimulation conditions might have been occurred, as the accuracy non-target levels for these three conditions were already high prior the stimulation with 0.91 ± 0.08 for DLPFC, 0.91 ± 0.06 for VLPFC and 0.88 ± 0.06 for 35-cm^2-electrode, compared to 0.85 ± 0.13 for sham. These differences in baseline values were as already mentioned the cause for calculating difference measures. A posteriori pre-post comparisons with Bonferroni corrected paired t-tests did neither show any difference for DLPFC, nor for VLPFC, nor 35.-cm^2-electrode, but a significant difference for sham ($p = 0.036$).

Why these differences occurred in baseline measurements could not be explained as the order of settings was randomized over subjects. Perhaps the ability of concentration at the beginning of sessions varied. Subjects had different intervals between sessions. As there were hot days during testing period, more sham stimulation could have been on these warm days. Baseline measurements were conducted at the beginning of each session. Therefor entering the testing room from the heat outside (up to 37°C) could have an impact on task performance, because mental efficiency could be altered due to heat (O´Neal and Bishop, 2010).

In this study the 3-back task was always presented approximately ten minutes after the end of tDCS. Subjects in the study of Ohn et al. (2008) performed the task after the end of tDCS as well. Additionally, aftereffects of tDCS were reported by Nitsche et al. (2008). Hence performing the task some minutes after the end of stimulation should not have an influence on the effects of tDCS. What was different in the current study is that another task was done before the 3-back task. The picture evaluation task always started five minutes after the beginning of stimulation. Therefore, even the last eight minutes of tDCS were done during this task.

Andrews et al. (2011) report, that adjunctive remediation techniques enhance the effect of tDCS. In her study subjects performed an n-back task while they received anodal tDCS over the left DLPFC. One control group did no task during stimulation and another control group received sham stimulation. After stimulation another working memory task was performed, whereas the performance was highest when a n-back task had been done during anodal stimulation.

As there are supporting effects of tasks during stimulation, the reverse effect might occur due to other actions while receiving tDCS.

To investigate further why this study received different outcomes than previous studies, it has to be considered that there have been no studies on the influence of tDCS on working memory performance of smokers. Therefore, there are no comparable results or respectively any hints whether smokers could react differently. Similar brain regions are affected in craving and working memory, whereas the working memory performance of a smoker who is under nicotine deprivation might respond differently to anodal tDCS than other people. Apart from the physiological connection, there are further relations between working memory and smoking. These are due to the fact that alterations in self-regulation and emotion regulation are associated with drug abuse like smoking (Gross, 1998; Heaterthon & Wagner, 2011) and that working memory is a cognitive process in emotion regulation (Blumenfeld & Ranganath, 2006).

Studies on working memory performance of smokers found lower working memory performance of smokers compared to non-smokers. Additionally, smokers in abstinence performed better than smokers who had smoked before doing the task. These findings are explained by the influence of nicotine on working memory by altering neurotransmitter release and in its effect on nicotinic cholinergic receptors. Furthermore, an inverted U-relationship with dopamine is proposed. This means that working memory performance rises with increasing dopamine levels. However, up from a special level of dopamine, the performance decreases (Greenstein & Kassel, 2009).

These findings on working memory performance of smokers and the connection with the dopamine threshold might be a reason for changed reaction of smokers on tDCS concerning working memory. Further Nitsche et al. (2004) reported an influence of N-methyl-D-aspartate receptors (NMDA) on aftereffects of tDCS. D-Cycloserine, a NMDA agonist showed to increase the aftereffects of anodal tDCS. When a NMDA agonist enhances effects of anodal tDCS, the lack of another NMDA agonist like glutamate, which is released after nicotine consumption (Benowitz, 2010; Lewis, Miller & Lea, 2007) and therefore, is deficient in deprived smokers, could influence aftereffects of anodal tDCS as well.

But effects of smoking in connection to tDCS and working memory still have to be investigated before a more detailed interpretation of the outcome could be made in the current study.

To summarize, the effects of tDCS found on working memory performance have to be validated in an additional independent replication study. Comparing the study to previous ones, a variety of explanation for the differences could be found. There were differences in the study settings but also the fact that the subjects in the current study were smokers could have had an impact.

Craving: actual craving, cue-induced craving and TCQ

There was no effect of setting on actual craving nor did the cue-induced craving differ between the four electrode conditions. Only factor 3 of craving measured with the TCQ increased between the beginning and the end of each session. This was against expectations because it was assumed that due to previous studies (Boggio et al., 2009a; Fregni et al., 2008a) craving should be decreased after anodal tDCS. With the raise of compulsivity of craving (TCQ factor 3), which means the inability to control tobacco consume, the opposite occurred, although this was independent of the stimulation condition. This means that there was no effect of any of the three active electrode settings. It is possible, that the frequent exposure to smoking cues and the intensive involvement with the topics smoking and craving in the situation of smoking deprivation have induced a feeling of not being able to control the use of

tobacco. As the score for TCQ factor 3 increased for the three settings equally as for sham condition, the anodal tDCS seems to have no effect on craving evolution.

This supports the findings of Köhler (2012) for the setting when using EEG electrodes over the DLPFC. Thus stimulation of this region alone has no impact on craving. The same occurred while the stimulation using EEG electrodes over the left VLPFC. Therefore, leaving the results of the big electrode in this study aside, the effect on craving of anodal tDCS over F3, as was reported in previous studies (Boggio et al.,2009a; Fregni et al., 2008a), did not depend on activation of either left DLPFC or VLPFC, but maybe on an interaction between these regions or because of other brain areas affected during the use of a big electrode. Including the fact that anodal tDCS over the left DLPFC/VLPFC with a big electrode showed no effect in our study, it could have neither been the interaction between left DLPFC and VLPFC which induced the decrease of craving in previous research. Due to a difference in electrode placement, only brain regions which had not been affected with the big electrode in our study could have caused an effect in the previous studies. But as discussed below, there are further possible explanations.

A further cause for the lack of the setting's influence with the EEG electrode over the left VLPFC could have been the high focality of EEG electrodes connected with the inaccuracy of electrode placement. Due to a review of Kühn et al. (2011) on brain activation during craving, FC5 was chosen for stimulation of VLPFC, because it fitted best with the coordinates published.

Comparing the 35-cm^2-electrode setting with Boggio et al. (2009a) and Fregni et al. (2008a), the appliance of 2 mA current in the previous studies appears in contrast to the here applied 1 mA. The current density of 0.03 mA/cm^2 was possibly too low to have an effect on craving.

Another obvious difference between this study and the research of Fregni et al. (2008a) were the used smoking cues. Fregni et al. (2008a) showed a video including smoking cues to the participants. In contrast, subjects in the current study were frequently exposed to smoking cues over the durance of one task and had to rate their craving level after each picture. The smoking cues used, seemed to induce

craving, as craving levels for these pictures were rated significantly higher than for other types of pictures. Nevertheless, the ratings did not differ between settings.

Furthermore, the question rises to which extent the level of addiction had an impact on the effect of tDCS and craving. Due to McClernon et al. (2008) the level of addiction influences the development of craving. In the current study subjects smoked 15.17 ± 3.86 cigarettes per day. The average FTND score was 3.80 ± 1.72. Compared to Fregni et al. (2008a) the level of addiction was low. Participants of the Fregni et al. (2005) study smoked 18.5 cigarettes per day on average and had an FTND score of 5. The difference in cigarettes smoked per day and FTND scores was not that big compared with the study of Boggio et al. (2009a), were subjects smoked 14.46 ± 4.17 cigarettes per day and had an FTND score of 4.36 ± 1.56. But in this last mentioned study, long-time effects of tDCS were examined. Therefore, participants received tDCS over a five days period. So the short-time effect on craving and cue-induced craving might be dependent on addiction levels.

The impact on addiction level is supported by a tendency ($p = 0.225$, $\eta_p^2 = 0.313$, for the interaction setting - time) found in an ANOVA for the actual craving measured five times during the session using the SAM scale. This ANOVA was done with subjects who had an FTND score higher than five. The graph in figure 17, wherefore only the first and the last SAM measurements were used, describes the tendency. Such a FTND score categorized them as highly addicted or very high addicted. As this analysis was done with only four persons, it just supports an idea which needs to be investigated further

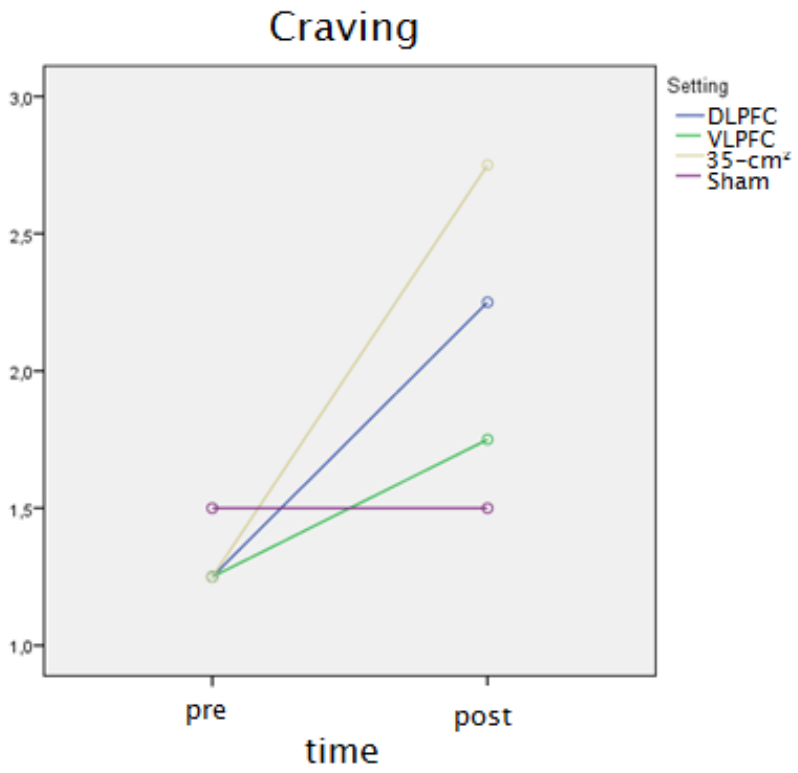

Figure 17: Evaluation of actual craving before and after tDCS for smokers with a FTND score ≥ 6 (pre is the first SAM measurement, while post is the fifth/last SAM)

An additional possible explanation for the lack of results' replication form Fregni et al. (2008a) is the time of nicotine deprivation. Participants in the study of Fregni et al. (2008a) were not allowed to smoke 90 minutes before a tDCS session. In the current study six hours of abstinence were required. According to McClernon et al. (2009), the period of withdrawal has an impact on craving and brain activation owing to craving. In this particular context the session time could also have an impact on the outcomes. Graphs show that craving levels at the start of each session were varying. Ideally craving levels should be the same at the beginning of each session. A reason for this might be that each subject had his/her sessions always at the same time during day, but between subjects the time of sessions varied.

In addition to session time, smoking behavior in association with session time and the time the person got up in the morning need to be considered. Some subjects reported to urgently need a cigarette in the morning. Others did not like to smoke in the morning, but consumed their amount of cigarettes rather in the evening.

Due to participants' statements the day of session had an impact on their actual craving levels as well. To avoid order effects, the order of settings had been randomized over subjects. Because of the different intervals between the sessions it happened that three sham conditions were done one after the other. The study was conducted in June wherefore the days were generally hot (reaching 37°C). Some participants talked of not having any desire to smoke when the weather was that hot. Consequently they indicated to have no or only little craving when coming from the heat outside.

To summarize, there are different possibilities why the expected results have not been received. There were differences in conduction of studies as well as possible influences on craving which had not been considered. On the other hand the results match the findings of Köhler (2012), where no impact of tDCS on DLPFC with small electrodes had been found and with an rTMS conducted by Eichhammer et al. (2003).

The influence of rTMS on the brain bases on other mechanisms than the one of tDCS. Therefore, this could be a reason for the different outcomes between this study and rTMS studies which report decreased craving after high-frequency rTMS over the left DLPFC (Amiaz et al., 2008; Rose et al., 2011). Nevertheless, the results of this study confirm the ones of Eichhammer et al. (2003) where no decrease in smoking cue induced craving could be found, but a smaller amount of cigarettes smoked after rTMS session. Maybe the scales to rate actual craving and cue-induced craving are not sensible enough and the amount of cigarettes smoked in the hours after the session would have been a better method to investigate the impact of tDCS on craving and smoking behavior.

Affect and affective picture evaluation

TDCS had neither an influence on valence nor on arousal ratings of emotional pictures. Between pictures types, valence ratings differed significantly, which means that the separation in negative, positive and neutral pictures was adequate.

The anodal tDCS over the left DLPFC using small electrodes did not influence valence ratings agrees with the findings of Köhler (2012). Additionally, the left VLPFC neither ought to have been the cause for altered valence ratings in the studies of Pena-Gomez et al. (2011) and Maeoka et al. (2012). Apparently it is important that these regions are stimulated together or that there is another part of the brain or even another part of DLPFC or VLPFC which was not reached with the EEG electrodes but which was affected in the previous studies.

But in contrast to previous studies anodal tDCS over DLPFC and VLPFC using 35-cm^2-electrode did not show an effect on valence ratings. As the electrode had been placed over F3 and FC5 (according to the 10-20 EEG system), there might have been a difference in brain areas below the active electrode when comparing this and previous studies. Moreover, other brain areas could have been affected in the studies of Pena-Gomez et al. (2011) and Maeoka et al. (2012) because they placed the cathode over the contralateral supraorbital area, instead of the right DLPFC/VLPFC. Hence the current needed to cross the brain on another way and could thereby affect different brain regions associated with emotional processing. Additionally, their reference electrode only had an area of 35 cm^2 which means that current density below the cathode was high enough to have an effect.

By using the small electrode to separately activate DLPFC and VLPFC, this study intended to show which regions in detail are important for emotion processing, because it was not possible to conclude from the studies of Pena-Gomez et al. (2011) and Maeoka et al. (2012) what was the mechanism in the lateral PFC responsible for the changed valence ratings of emotional pictures. The VLPFC as second target region was chosen, because literature supposes its involvement in emotion processing (Dolcos et al., 2004; Ochsner et al., 2004; Quirk & Beer, 2006; Wager et al., 2008). But brain imaging studies do not correspond. The one report that raised activity in lateral PFC induce decreased activity in amygdala (Gross, 2002; Ochsner et al., 2004), which corresponds with the findings of Pena-Gomez et al. (2011) and Maeoka et al. (2012), who found that subjects rated negative pictures less negatively when the left lateral PFC was activated by using anodal tDCS. On the other hand Wager et al. (2008) proposed a conversed correlation between lateral

PFC and amygdala unlike Gross (2002) and Ochsner et al. (2004) reported. This means that enhanced activity of lateral PFC modulated an increase of amygdala activity. The example shows that mechanisms in the brain concerning emotions are not yet sufficiently investigated.

A further topic which needs to be investigated to interpret data of the current study adequately is the difference in emotional processing between smokers and non-smokers. Smoking dependency is positively correlated with appearance of emotional disorders like panic disorders, depression (Zwolenski, Feldner, Eifert & Brown, 2001) and anxiety disorder (Spada, Nidcevic, Moneta & Wells, 2007). Furthermore, drug dependence is associated with emotion dysregulation (Gross, 1998; Heaterthon & Wagner, 2011). These connections between emotion and nicotine dependence suggest altered emotion regulation of smokers which could also lead to altered response to anodal tDCS in concern of affective picture evaluation. Additionally smoking abstinence of subjects should be considered. Smoking abstinence is associated with a higher negative affect (Spada et al., 2007).

In the current study the PANAS inventory was handed to subjects at the beginning and at the end of the study to investigate changes of affect during session. The negative affect did not change, but the positive affect decreased significantly during the session. This could have been due to the strong emotional pictures presented in the emotional variant of the n-back task. Simon-Thomas and Knight (2005), who used strong emotional pictures to interfere performance in a working memory task, reported the same decrease in emotional affect measured with PANAS.

Concerning the affect evaluated with PANAS inventory, none of the tDCS settings had an influence on emotion. If tDCS affected emotion processing, it could as well alter mood. But on the other hand Pena-Gomez et al. (2011) who found an impact of anodal tDCS on affective picture evaluation could not find an influence on mood measured with the PANAS inventory.

To summarize the findings, there are several reasons why previous studies (Maeoka et al., 2012; Pena-Gomez et al., 2011) could not be replicated. Additionally the strong affective pictures in the working memory task could have had an influence on affect

changes during the sessions. Moreover, it is not clear which influence the target group, namely smokers, had on the outcome.

Adverse effects of tDCS

In the “questionnaire to adverse effects of tDCS” subjects had to rate after the session whether they felt symptoms at this moment or during stimulation which could have occurred because of tDCS.

Apart from itching and binging no differences between settings were found. Both occurred significantly more often in the sessions using the big electrode, compared to either using the EEG electrode over the DLPFC (itching) or over the VLPFC (binging). This fits with literature reporting an itching sensation in the first seconds of stimulation with big electrodes (Fregni et al., 2005; Nitsche et al., 2008; Utz et al., 2010). Binging could occur because of skin irritation by the current (Datta, Elwassif & Bikson, 2009b; Minhas et al., 2010). As the use of EEG electrodes is not common, the only information available is that subjects in Marshall et al. (2005) did not report any aftereffects. Brunoni et al. (2011c) reported that more adverse effects were found in studies with higher current intensities. These findings together with the results in our study suppose, that itching and binging might be mainly related to the current intensity which in our study was lower than in most other tDCS studies due to the smaller area of EEG electrodes used. Perhaps current density which was higher in our study is within specific borders less important for inducing adverse sensations.

Effects and functionality of tDCS

In this study the impact of anodal tDCS on working memory performance, craving and affective picture evaluation was investigated. Except of one result, which needs further replication (see discussion above), any influence of tDCS on neither of the topics could be found. Although the use of EEG electrodes was a new investigation which has not brought results agreeing with other tDCS studies yet, a 35-cm^2-electrode to replicate previous findings was used as well.

As a reference whether tDCS stimulation worked or not, the working memory paradigm was included in this diploma thesis additional to craving and affective picture evaluation. The effect of tDCS on working memory has already been investigated using different electrode sizes, current densities, reference electrode placements and stimulation durations (Fregni et al., 2005; Keeser et al., 2011; Marshall et al., 2005; Ohn et al., 2008). But in our study no effect was found. Even though there could be other reasons for the fail of influence of tDCS, the question raises which parameters or combinations of parameters are essential to induce a behavioral effect.

TDCS has already been proposed to be a future method for the therapy of migraine (Antal et al., 2008), depression (Brunoni et al., 2011a; Boggio et al., 2007; Boggio et al., 2008a), Fibromyalgia (Fregni et al., 2006b) and pain (Boggio, Zaghi & Fregni, 2009b), epilepsy (Fregni et al., 2006c) as well as drug addiction (Boggio et al., 2008b; Boggio et al., 2010b). However, the question remains how valid this method, for example in drug addiction, when there are so many parameters which could influence its effect, is.

There are several studies published promising positive effects of tDCS. But on the other hand it is not known how many studies have been conducted, which found no such effects. Thus, the effect of tDCS needs to be investigated further.

Criticism on the study

Criticisms on this study are that 15 participants are too little to draw valid conclusions. Furthermore, subjects had to do four sessions always passing the same procedure whereby the only difference was tDCS setting. This procedure promised to make the four settings comparable, but on the other hand evaluating the same pictures four times and doing around one hour of working memory task might influence motivation of participants as well as the outcome. Hence this study design was not appropriate. Either a bigger sample should have been used to treat setting as a between subject factor or more studies always comparing only two settings could have been done.

For placement of electrodes an EEG electrode cap with the 10-20 EEG placement system was used. This cap was placed on the head due to specific landmarks, measured by a measuring tape. Especially for the placement of EEG electrodes, which have a high focality, this method is not accurate enough. To reach target regions better, structural MRI data for the placement over special anatomical regions, or fMRI coordinates for the placement over regions activated in a special paradigm should be used.

Further subjects had not the same intersession intervals, which differed between two days and two weeks. Additionally the sessions' point of time should have been chosen considering the time of subjects getting up in the morning and subjects preferences of smoking (morning vs. evening), or as another alternative, subjects should have been tested all at the same time during the day.

In this study affect, emotion regulation and working memory were investigated having smokers as sample. Yet the neuronal underpinnings of these complex relationships i.e. the impact of smoking on working memory and emotion regulation, is far from being disentangled. Hence the results should not be generalized.

Conclusion

The study has investigated the impact on different tDCS settings on working memory, craving and affective picture evaluation. In contrast to previous studies, anodal tDCS over DLPFC/VLPFC using a big electrode had no impact on any of the three paradigms. This might be due to differences in tDCS parameters, study design or the sample itself.

The leaking impact of anodal tDCS over DLPFC and VLPFC separately support the findings of Köhler (2012) that the activation of DLPFC alone has no impact on neither craving nor affective picture evaluation or working memory. These findings also lead to the conclusion that activation of VLPFC might not be the reason for the effects showed with big electrodes over the left DLPFC in previous research.

To investigate whether one of the above discussed reasons caused the lack of influence of anodal tDCS on working memory, affective picture evaluation and craving, previous studies should be replicate, which means to use the same procedure, the same parameters of tDCS, the same sample size, the same features of subjects and the same stimulus materials. In case previous studies were repeated, but results were not replicable, it should be discussed whether tDCS is such a promising method as it is always described.

Additionally, brain imaging methods could be used to investigate the effects of tDCS better. This – in contrast to behavioral data - would be a direct method to examine the impact of tDCS on the brain.

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Appendix

N-back task

Introducing text

Sie werden nacheinander einzelne Buchstaben auf dem Bildschirm sehen.

Wenn der Buchstabe auf dem Bildschirm derselbe ist wie derjenige, der DREI Buchstaben vor dem aktuellen präsentiert wurde, drücken Sie "1".

Wenn der Buchstabe auf dem Bildschirm nicht derselbe ist wie derjenige, der drei Buchstaben vor dem aktuellen präsentiert wurde, drücken Sie "2".

Es ist wichtig, dass Sie bei der Präsentation eines Buchstabens IMMER eine Taste drücken.

Auf der nächsten Seite folgen einige Beispiele. Bitte drücken Sie die LEERTASTE, um fortzusetzen.

Es erscheint ein P. Richtige Antwort: 2.

Es erscheint ein U. Richtige Antwort: 2.

Es erscheint ein X. Richtige Antwort: 2.

Es erscheint ein P. Richtige Antwort: 1.

Es erscheint ein A. Richtige Antwort: 2.

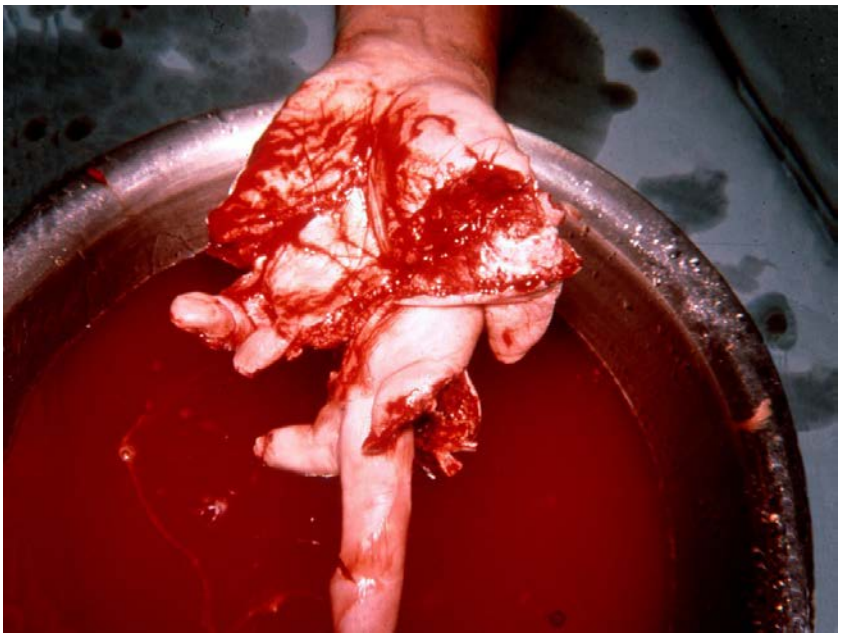
Es erscheint ein X. Richtige Antwort: 1.

Es erscheint ein K. Richtige Antwort: 2.

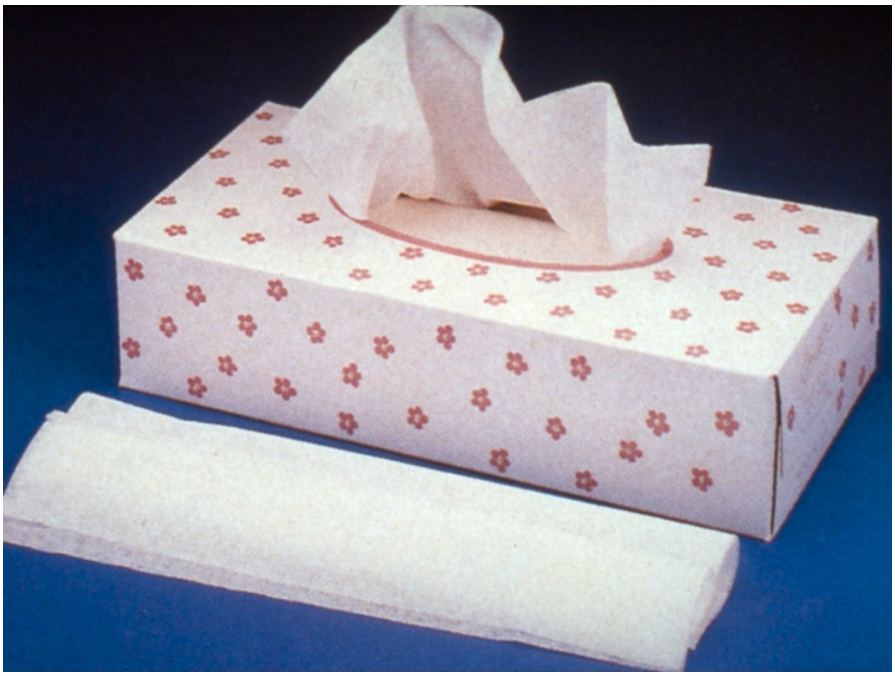
Es erscheint ein X. Richtige Antwort: 2.

Stimulus materials

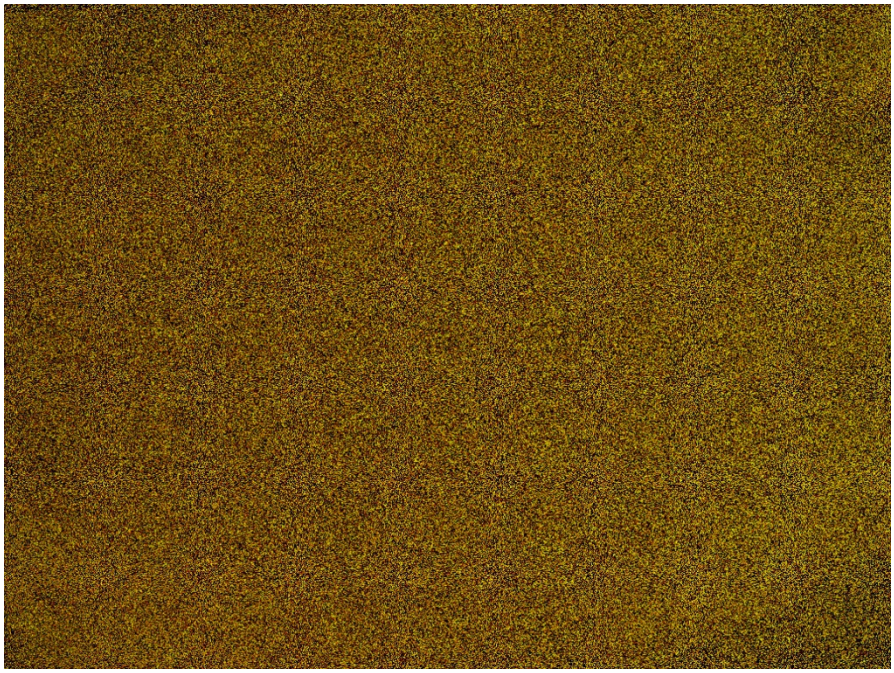
Example for fear inducing pictures



Example for humiliation pictures



Example for a neutral picture



Example for a scrambled picture

Questionnaires

Die Social, Cognitive and Affective Neuroscience Unit der Fakultät für Psychologie der Universität Wien lädt zur Teilnahme an der folgenden Studie ein:

„Transkranielle Gleichstromstimulation in der RaucherInnenentwöhnung“

Der Zweck dieser Studie ist es, die Wirkungsweise der so genannten transkraniellen Gleichstromstimulation, bei der durch Polarisation/Depolarisation von Gehirnarealen, die Gehirnaktivität beeinflusst wird, auf das Suchtverhalten von Rauchern zu ergründen. Mit Hilfe dieser Technik soll letztendlich das Verlangen nach Nikotin verringert werden.

Dazu werden weibliche und männliche Versuchspersonen gesucht, die den folgenden Kriterien entsprechen:

- Alter: 18-40 Jahre
- RaucherIn (mindestens 10 Zigaretten/Tag)
- Rechtshänder

Die Studie wird an der Universität Wien durchgeführt.

Ihre Teilnahme (4 Termine, insgesamt ca. 6 Stunden) wird mit 90 € entlohnt und Sie tragen zum wissenschaftlichen Fortschritt bei.

Für Ihre Bewerbung sowie weitere Informationen schreiben Sie bitte an:
Daniela Ehgartner

E-mail: tdcs_studie@gmx.at

Probandeninformation und Einwilligungserklärung
zur Teilnahme an der psychologischen Studie

„Transkranielle Gleichstromstimulation in der RaucherInnenentwöhnung“

Sehr geehrte Teilnehmerin, sehr geehrter Teilnehmer!

Wir laden Sie ein an der oben genannten psychologischen Studie teilzunehmen. Die Aufklärung darüber erfolgt in einem ausführlichen Gespräch.

Ihre Teilnahme an dieser Studie erfolgt freiwillig. Sie können jederzeit ohne Angabe von Gründen aus der Studie ausscheiden. Die Ablehnung der Teilnahme oder ein vorzeitiges Ausscheiden aus dieser Studie hat keine nachteiligen Folgen für Sie.

Psychologische Studien sind notwendig, um unseren Wissensstand über die Psyche des Menschen zu vertiefen. Unverzichtbare Voraussetzung für die Durchführung einer psychologischen Studie ist jedoch, dass Sie Ihr Einverständnis zur Teilnahme an dieser psychologischen Studie schriftlich erklären. Bitte lesen Sie den folgenden Text als Ergänzung zum Informationsgespräch mit dem Studienleiter sorgfältig durch und zögern Sie nicht Fragen zu stellen.

Bitte unterschreiben Sie die Einwilligungserklärung nur

- wenn Sie Art und Ablauf der Studie vollständig verstanden haben,
- wenn Sie bereit sind, der Teilnahme zuzustimmen und
- wenn Sie sich über Ihre Rechte als TeilnehmerIn an dieser psychologischen Studie im Klaren sind.

1. Was ist der Zweck der psychologischen Studie?

Der Zweck dieser klinischen Studie ist es, die Wirkungsweise von transkranieller Gleichstromstimulation auf das Verlangen nach Nikotin, das Arbeitsgedächtnis sowie die emotionale Bildverarbeitung zu untersuchen. Die Erkenntnisse sollen den Einsatz dieser Methode in der Raucherentwöhnung unterstützen.

2. Wie läuft die psychologische Studie ab?

Diese psychologische Studie wird an der Universität Wien (Psychologie) durchgeführt, und es werden insgesamt 15 Personen daran teilnehmen.

Vor der Untersuchung werden sie Fragebögen ausfüllen, um sicher zu gehen, dass keines der Ausschlusskriterien für transkranielle Gleichstromstimulation auf Sie zutrifft. Des Weiteren werden durch die Fragebögen für die Studie relevante Informationen erfasst. Außerdem werden

Sie vor der Testung gebeten, diese Einverständniserklärung zu unterschreiben. Schwangere Personen und Menschen, die an einer chronischen Hautkrankheit im Kopfbereich leiden, sind von der Teilnahme ausgeschlossen.

Die Untersuchung selbst besteht daraus, dass Sie, während transkranielle Gleichstromstimulation bei Ihnen angewandt wird, Tests an einem Computer bearbeiten.

Sie kommen insgesamt vier Mal, damit vier verschiedene Arten der transkraniellen Gleichstromstimulation verglichen werden können. Jede Sitzung dauert etwa 60 bis 90 Minuten. Der Zeitraum zwischen den einzelnen Sitzungen beträgt mindestens zwei Tage.

Der Unterschied zwischen den vier Sitzungen liegt hauptsächlich darin, dass die Position der Elektroden verändert wird.

Schwangere sind von der Teilnahme ausgeschlossen.

Es ist für den Erfolg der Studie äußerst wichtig, dass Sie im Zeitraum von **6 Stunden** vor den Sitzungen mit der Transkraniellen Gleichstromstimulation **keine Zigaretten rauchen** und auch **in keiner anderen Form Nikotin zuführen**. Weiters dürfen Sie im Zeitraum von **24 Stunden** vor den Sitzungen **keinen Alkohol und keinerlei Medikamente** zu sich nehmen.

Um zu überprüfen, ob die Nicht-Konsumierung von Nikotin 6 Stunden vor der Testung eingehalten worden ist, werden Urinproben genommen.

Ihre Teilnahme an dieser psychologischen Studie wird also voraussichtlich vier Termine in Anspruch nehmen und insgesamt ca. sechs Stunden dauern.

Die Einhaltung der Anweisungen des Studienleiters und seiner Mitarbeiter ist dabei von entscheidender Bedeutung für den Erfolg dieser psychologischen Studie.

3. Worin liegt der Nutzen einer Teilnahme an der psychologischen Studie?

Die Ergebnisse dieser Studie sollen zeigen, ob sich Transkranielle Gleichstromstimulation auf das Verlangen nach Nikotin auswirkt. Diese Technik könnte eine wirksame neue Therapieform zur Nikotinentwöhnung darstellen und das Suchtverhalten abschwächen. Des Weiteren soll überprüft werden, welchen Einfluss die Transkranielle Gleichstromstimulation auf die emotionale Bildbewertung und das Arbeitsgedächtnis hat.

Es ist möglich, dass Sie durch Ihre Teilnahme an dieser psychologischen Studie keinen direkten Nutzen für Ihre Gesundheit ziehen.

4. Gibt es Risiken, Beschwerden und Begleiterscheinungen?

Transkranielle Gleichstromstimulation

Bei der Transkraniellen Gleichstromstimulation wirkt ein schwacher elektrischer Strom durch den Schädelknochen hindurch (transkraniell) auf das Gehirn. Er verändert die elektrische Ladung an den Nervenzellen, was ihre Erregbarkeit teilweise verstärkt und teilweise dämpft.

Transkranielle Gleichstromstimulation ist durch zahlreiche psychologische Studien erprobt, sicher und nebenwirkungsarm. Wie jede Therapie ist sie aber nicht völlig nebenwirkungsfrei. Die elektrische Stimulation führt zu einer wenige Sekunden dauernden Reizung der Kopfhaut, was von den Probanden als mehr oder weniger unangenehmes Kribbeln und Ziehen beschrieben wird. Manche Patienten berichten über leichte Müdigkeit, seltener auch über Kopfschmerzen oder Übelkeit, wobei diese Symptome, wenn sie auftreten, innerhalb von wenigen Stunden nach der Transkraniellen Gleichstromstimulation wieder vergehen.

Die Auslösung epileptischer Anfälle durch Transkranielle Gleichstromstimulation wurde noch nicht beobachtet.

Die Transkraniellen Gleichstromstimulation darf nicht mit der Elektrokrampftherapie verwechselt werden, die mit starken Stromstößen Krampfanfälle auslöst.

5. Zusätzliche Einnahme von Arzneimitteln?

Es müssen keine zusätzlichen Arzneimittel eingenommen werden (auch keinerlei Kontrastmittel). Sie dürfen nicht unter Einfluss von Psychopharmaka stehen. Bitte teilen Sie jegliche Art von Medikamenten, welche Sie zur Zeit einnehmen, dem Studienleiter und/oder seinen Mitarbeitern zur Abklärung mit.

6. Hat die Teilnahme an der psychologischen Studie sonstige Auswirkungen auf die Lebensführung und welche Verpflichtungen ergeben sich daraus?

Sie dürfen im Zeitraum von **6 Stunden** vor den Sitzungen mit der Transkraniellen Gleichstromstimulation **keine Zigaretten rauchen** und auch **in keiner anderen Form Nikotin zuführen**. Weiters dürfen Sie im Zeitraum von **24 Stunden** vor den Sitzungen **keinen Alkohol und keinerlei Medikamente** zu sich nehmen.

Nach der Transkraniellen Gleichstromstimulation dürfen Sie für zumindest 3 Stunden kein Fahrzeug lenken.

7. Was ist zu tun beim Auftreten von Symptomen, Begleiterscheinungen und/oder Verletzungen?

Sollten im Verlauf der psychologischen Studie irgendwelche beschwerlichen Symptome, Begleiterscheinungen, Krankheiten oder Verletzungen auftreten, müssen Sie diese dem Studienleiter und/oder seinen Mitarbeitern mitteilen, bei schwerwiegenden Begleiterscheinungen umgehend.

8. Wann wird die psychologische Studie vorzeitig beendet?

Sie können jederzeit, auch ohne Angabe von Gründen, Ihre Teilnahmebereitschaft widerrufen und aus der psychologischen Studie ausscheiden ohne dass Ihnen dadurch irgendwelche Nachteile entstehen.

Ihre Studienleiterin Daniela Ehgartner wird Sie über alle neuen Erkenntnisse, die in Bezug auf diese psychologische Studie bekannt werden, und für Sie wesentlich werden könnten, umgehend informieren. Auf dieser Basis können Sie dann Ihre Entscheidung zur **weiteren** Teilnahme an dieser psychologischen Studie neu überdenken.

Es ist aber auch möglich, dass Ihr Studienleiter entscheidet, Ihre Teilnahme an der psychologischen Studie vorzeitig zu beenden, ohne vorher Ihr Einverständnis einzuholen. Die Gründe hierfür können sein:

a) Sie können den Erfordernissen der Psychologischen Studie nicht entsprechen;

b) Der Studienleiter hat den Eindruck, dass eine weitere Teilnahme an der psychologischen Studie nicht in Ihrem Interesse ist;

9. In welcher Weise werden die im Rahmen dieser psychologischen Studie gesammelten Daten verwendet?

Sofern gesetzlich nicht etwas anderes vorgesehen ist, haben nur der Studienleiter und dessen Mitarbeiter Zugang zu den vertraulichen Daten, in denen Sie namentlich genannt werden. Diese Personen unterliegen der Schweigepflicht.

Die Weitergabe der Daten erfolgt ausschließlich zu statistischen Zwecken und Sie werden ausnahmslos darin nicht namentlich genannt. Auch in etwaigen Veröffentlichungen der Daten dieser psychologischen Studie werden Sie nicht namentlich genannt.

10. Entstehen für die Teilnehmer Kosten? Gibt es einen Kostenersatz oder eine Vergütung?

Durch Ihre Teilnahme an dieser klinischen Studie entstehen für Sie keine zusätzlichen Kosten. Als Vergütung für Ihren Zeitaufwand erhalten Sie nach Teilnahme an allen vier Sitzungen einen Betrag von **90,- Euro**. Bei einem vorzeitigen Abbruch der Studie erhalten Sie ein Honorar von 15,- Euro:

Vorzeitiger Abbruch

- nach ein bis drei Sitzungen : insgesamt **€ 15,-**

Absolvierung aller vier Sitzungen: **€ 90,-**

11. Möglichkeit zur Diskussion weiterer Fragen

Für weitere Fragen im Zusammenhang mit dieser psychologischen Studie stehen Ihnen Ihr Studienleiter und seine Mitarbeiter gern zur Verfügung. Auch Fragen, die Ihre Rechte als ProbandIn in dieser psychologischen Studie betreffen, werden Ihnen gerne beantwortet.

Name der Kontaktperson: Univ.-Ass. Dr. Jürgen Pripfl

Erreichbar unter (Bürozeiten): (0043) 01 4277 47508

Name der Kontaktperson: Daniela Ehgartner

Erreichbar unter: (0043) 0650 2170103

12. Sollten andere behandelnde Ärzte von der Teilnahme an der psychologischen Studie informiert werden?

Bitte beachten Sie, dass Sie aus ethischen und rechtlichen Gründen im Zeitraum bis zu 8 Wochen vor Beginn der Studienteilnahme an keiner klinischen Studie teilnehmen dürfen.

Bitte informieren Sie uns über alle aktuellen ärztlichen Behandlungen vor Studienbeginn bzw. sobald diese beginnen.

14. Einwilligungserklärung

Name des/der ProbandenIn in Druckbuchstaben: .....

Geb.Datum: ..... Code: .....

Ich erkläre mich bereit, an der psychologischen Studie „Transkranielle Gleichstromstimulation zur RaucherInnenentwöhnung“ teilzunehmen.

Ich bin von Frau Daniela Ehgartner ausführlich und verständlich über die Transkranielle Gleichstromstimulation informiert worden. Ich bin über mögliche Belastungen und Risiken, sowie über Wesen, Bedeutung und Tragweite der psychologischen Studie, sich für mich daraus ergebenden Anforderungen aufgeklärt worden. Ich habe darüber hinaus den Text dieser Probandenaufklärung und Einwilligungserklärung, die insgesamt 6 Seiten umfasst, sorgfältig gelesen. Aufgetretene Fragen wurden mir vom Studienleiter und/oder seinen Mitarbeiter/-innen verständlich und genügend beantwortet. Ich hatte ausreichend Zeit, mich zu entscheiden. Ich habe zur Zeit keine weiteren Fragen mehr.

Ich werde den Anordnungen, die für die Durchführung der psychologischen Studie erforderlich sind, Folge leisten, behalte mir jedoch das Recht vor, meine freiwillige Mitwirkung jederzeit zu beenden, ohne dass mir daraus Nachteile entstehen.

Ich bin zugleich damit einverstanden, dass meine im Rahmen dieser Studie ermittelten Daten aufgezeichnet werden. Um die Richtigkeit der Datenaufzeichnung zu überprüfen, dürfen Beauftragte des Auftraggebers und der zuständigen Behörden beim Studienleiter Einblick in meine personenbezogenen Daten nehmen. Weiters bezeuge ich, dass ich im Zeitraum bis zu 8 Wochen vor der Teilnahme an dieser Studie an keiner klinischen Studie teilgenommen habe.

Beim Umgang mit den Daten werden die Bestimmungen des Datenschutzgesetzes beachtet.

Eine Kopie dieser Probandeninformation und Einwilligungserklärung habe ich erhalten. Das Original verbleibt beim Studienleiter.

.....
(Datum und Unterschrift des Probanden)

.....
(Datum, Name und Unterschrift des verantwortlichen Studienleiters)

(Der/die ProbandIn erhält eine unterschriebene Kopie der Probandeninformation und Einwilligungserklärung, das Original verbleibt im Studienordner des Studienleiters.)

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
_____

Edinburgh Händigkeits- Inventar

Instruktion:

Bitte geben Sie an, welche Hand Sie für die folgenden Aktivitäten bevorzugt verwenden, indem sie ein „x“ in die entsprechende Spalte schreiben. Markieren Sie bitte die Fälle, in denen Sie nie die andere Hand verwenden würden, außer Sie wären absolut dazu gezwungen, mit „xx“. Für Fälle, in denen Sie keine Hand bevorzugt verwenden, schreiben Sie „x“ in beide Spalten.

Einige der Aktivitäten erfordern beide Hände. In diesen Fällen wird auf den Teil der Aufgabe des Objekts, für den Sie die bevorzugte Hand angeben sollen, in Klammern hingewiesen.

Bitte bemühen Sie sich **alle Fragen** zu beantworten. Lassen Sie eine Frage nur dann aus, wenn Sie gar keinen Erfahrung mit der Aufgabe oder dem Objekt haben.

		LINKS	**RECHTS**
1	Schreiben		
2	Zeichnen		
3	Werfen		
4	Schere		
5	Zahnbürste		
6	Messer (ohne Gabel)		
7	Löffel		
8	Besen (obere Hand)		
9	Streichholz anzünden (Streichholz)		
10	Schachtel öffnen		

Fagerströmtest für Nikotinabhängigkeit (FTND)

Gehen Sie die Fragen einfach der Reihe nach durch, und kreuzen Sie das Kästchen, das mit Ihrer Antwort übereinstimmt mit einem „x“ an.

Versuchen Sie, bei der Beantwortung der Fragen so **ehrlich** wie möglich

Wann nach dem **Aufwachen** rauchen Sie die erste Zigarette?	☐ innerhalb von 5 Min. ☐ 6-30 Min. ☐ 31-60 Min. ☐ nach 60 Min.
Fällt es Ihnen schwer, an Orten, an denen **Rauchverbot** besteht (Arztpraxen, Kino usw.) nicht zu rauchen?	☐ Ja ☐ Nein
Auf welche Zigarette würden Sie **nicht** verzichten wollen?	☐ die erste am Morgen ☐ andere
Wie viele Zigaretten rauchen Sie im Allgemeinen **pro Tag**?	☐ bis 10 ☐ 11-20 ☐ 21-30 ☐ 31 und mehr
Rauchen Sie am **Morgen** im Allgemeinen mehr als während des Tages?	☐ Ja ☐ Nein
Kommt es vor, dass Sie rauchen, **obwohl** Sie so krank sind, dass Sie den Tag überwiegend im Bett verbringen müssen?	☐ Ja ☐ Nein

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					

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

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.

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

Soziodemographisches Datenblatt

Geschlecht: Alter: _____

☐ weiblich ☐ männlich

Höchste abgeschlossene Ausbildung :

☐ noch Schüler

☐ Pflichtschule

☐ Lehre/ Berufsschule

☐ Berufsbildende mittlere Schule

☐ Berufsbildende höhere Schule/ Kolleg (Matura/ Abitur)

☐ Bachelor-Studium

☐ Master/ Diplomstudium

☐ Doktorat

Muttersprache: _____ Nationalität: _____

Aktuelle Berufstätigkeit:

☐ SchülerIn

☐ StudentIn

☐ selbstständig

☐ Angestellter

☐ Arbeiter

☐ arbeitslos/Arbeit suchend

☐ Sonstiges: _____

Rauchverhalten:

☐ Raucher ☐ Nichtraucher

Mit welchem Alter haben Sie zu Rauchen begonnen?

_____

Haben Sie schon mal versucht mit dem Rauchen aufzuhören?

☐ Ja, ein Versuch ☐ Ja, ____ Versuche (Anzahl der Versuche einsetzen!) ☐ Nein

Falls ja, welche Strategien/Medikamente haben Sie angewandt?

☐Mit Hilfsmitteln

Falls ja, mit welchen ☐Nikotinpflaster

☐Nikotinkaugummi

☐Sonstiges : _____

☐ sofort aufhören (ohne Hilfsmittel)

☐ Hypnose

☐ Akupunktur

☐ Sonstiges :_____

War einer oder mehrere dieser Versuch(e) erfolgreich, so dass Sie für länger als ein halbes Jahr das Rauchen unterbrochen haben?

☐ Nein ☐ Ja

Falls ja, wie lange hatten Sie dabei aufgehört?

_____

Falls ja, wie viele Jahre ist das her?

_____

Wie lange ist der letzte Versuch mit dem Rauchen aufzuhören her?

☐ Es gab nie einen Versuch mit dem Rauchen aufzuhören

☐ Der letzte Versuch ist weniger als 1 Monat her

☐ Der letzte Versuch ist zwischen 1 und 6 Monaten her

☐ Der letzte Versuch ist zwischen 6 und 12 Monaten her

☐ Der letzte Versuch ist über 1 Jahr her

Wollen sie derzeit mit dem Rauchen aufhören?

☐ Ja ☐ Nein

Haben sie schon mal an einer Studie zur Raucherentwöhnung teilgenommen?

☐ Ja ☐ Nein

Würden sie zukünftig an einer Studie zur Raucherentwöhnung teilnehmen?

☐ Ja ☐ Nei

Abstract

Theoretical background: Transcranial direct current stimulation (tDCS) studies over the left dorsolateral prefrontal cortex (DLPFC) have shown to decrease cue-induced craving, to change affective picture evaluation and to increase working memory performance. In most studies electrodes were used which did not only activate the DLPFC but other brain areas as well. Studies applying tDCS over the left DLPFC with small electrodes to only affect DLPFC could not replicate these results. Hence another area which is affected with tDCS over the left DLPFC using big electrodes needs to cause the effects. Brain imaging studies suggest the ventrolateral prefrontal cortex (VLPFC) to be involved in all three paradigms.

Methods: Anodal tDCS was applied over the left DLPFC/VLPFC using an electrode of 35 cm^2 area. To investigate separately stimulation of left DLPFC and VLPFC, anodal tDCS was applied using an EEG electrode either over the one or the other. Additionally, sham stimulation was done as a control. To examine the effect of tDCS, a craving and affective picture evaluation task and a 3-back task were used. Whereas the craving and affective picture evaluation task measured cue-induced craving, actual craving was investigated by frequent ratings during sessions. To compare craving levels before and after stimulation, a questionnaire was used.

Results: Apart from the result that anodal tDCS over the VLPFC decreases accuracy in the 3-back task, no influence of anodal tDCS was found. Craving evaluation conducted a raise of the craving factor compulsivity in all four tDCS conditions between the beginning and the end of each session. Further craving ratings differed between smoking cues and other pictures as well as valence which was rated differently between all types of pictures (negative, positive, neutral and smoking cues). Arousal was altered between negative and neutral as well as negative and positive pictures.

Conclusion: The results of this study stand in contrast to what was proposed from previous research. Neither left DLPFC nor left VLPFC seem to be the reason for alteration in cue induced craving, picture evaluation and working memory performance in previous studies. For the lacking impact of anodal tDCS using big

electrodes in this study, the differences in tDCS parameters, study conduction and subject traits could be a reason. Further studies to get a clearer picture of tDCS are needed

Abstrakt

Theoretischer Hintergrund: Studien zur anodalen transkraniellen Gleichstromstimulation (tDCS) über dem linken dorsolateralen Präfrontalcortex (DLPFC) zeigten, dass tDCS das Verlangen/Craving nach Zigaretten senkt, die Bewertung von affektiven Bildern verändert und das Arbeitsgedächtnis verbessert. In all jenen Studien wurden große Schwammelektroden verwendet, welche neben dem DLPFC noch andere Hirnregionen aktivieren. Wird anodale tDCS mittels kleineren Elektroden nur über dem linken DLPFC angewandt, bleiben die Effekte aus bzw. sind gegensätzlich. Dies lässt darauf schließen, dass die Aktivierung des linken DLPFCs (allein) nicht der Grund für die berichteten Ergebnisse zu sein scheint. Bildgebenden Verfahren zufolge könnte die Aktivierung des ventrolateralen Präfrontalcortex (VLPFC) einen Einfluss auf Craving, affektive Bildbewertung und das Arbeitsgedächtnis haben.

Methodik: Anodale tDCS wurde mit einer 35-cm^2-Elektrode über dem linken DLPFC/VLPFC angewandt. Außerdem wurden beiden Regionen separat mit je einer kleinen EEG-Elektrode stimuliert. Als Kontrolle wurde eine vorgetäuschte tDCS eingesetzt. Zur Erhebung des Einflusses von tDCS wurde ein Task zur affektiven Bildbewertung vorgegeben, in welchem die Bilder zusätzlich nach ihrem Einfluss auf das Verlangen nach Zigaretten eingestuft werden mussten. Zusätzlich wurde ein 3-back Task durchgeführt.

Ergebnisse: Außer einem negativen Einfluss der Stimulation des linken VLPFC alleine auf die Genauigkeit im 3-back Task, konnte kein Einfluss von anodaler tDCS gefunden werden. Ein Faktor von Craving, „genauer Zwanghaftigkeit“, stieg während der Sitzungen unabhängig vom tDCS-Setting. Die Bilder im Craving und affektiven Bildbewertungstask wurden hinsichtlich Valenz und Erregung unterschiedlich bewertet. Bilder mit Bezug auf Rauchen führten zu einer höheren Craving-Bewertung.

Conclusio: Diese Studie kam zu anderen Ergebnissen als auf Grund vorangehender Forschung erwartet worden war. Da weder die Aktivierung des linken DLPFCs noch des linken VLPFCs einen Einfluss zeigten, scheinen diese in den vorhergehenden

Studien mit den großen Elektroden nicht maßgebend gewesen zu sein. Dass die vorherigen Studien durch Nutzung der großen Elektroden nicht repliziert werden konnten, kann an unterschiedlichen Studiendesigns liegen. Weiter Studien zur genaueren Erforschung von tDCS und ihrem Einfluss sind nötig.

CV

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