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Neurophysiological Correlates of the Modulation of Cognitive Control via Transcranial Direct Current Stimulation (tDCS)

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Abbreviations

AC	Accuracy
BA	Brodmann area
BOLD	Blood oxygen level dependent
CC	Cognitive control
COMT	Catechol-O-methyltransferase
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
DWM	Delayed working memory task
EEG	Electroencephalography
EPN	Early posterior negativity
ERP	Event-related potential
(f)MRI	(Functional) magnetic resonance imaging
GABA	Gamma-Aminobutyric acid
ICD	International Statistical Classification of Diseases and Related Health Problems
IAPS	International Affective Picture Scale
IFC	Inferior frontal cortex
(e/l)LPP	(Early/Late) late positive potential
LTD	Long term depression
LTP	Long term potentiation
MDD	Major depressive disorder
MEP	Motor evoked potential
MWT-B	Multiple Choice Word Fluency
NMDA	N-methyl-D-aspartate
PANAS	International Positive And Negative Affect Schedule
RT	Reaction time
SCL 90-R	Symptom Check List revised
SEM	Standard error of the mean
STAI	State-Trait Anxiety Inventory
tDCS	Transcranial direct current stimulation
TMS	Transcranial magnetic stimulation
VMPFC	Ventromedial prefrontal cortex
WM	Working memory

1. Introduction

1.1. Cognitive Control

Humans have the unique ability to execute planned, motivated actions. To do so, they extract relevant information from the environment, select an internal plan and implement it even when interfering events occur. The process of regulating these complex processes has been coined cognitive control (CC) (Cohen, 2017). A conventional definition characterizes cognitive control as "*the compound of cognitive processes that aid in the pursuit of current goals and vary behavior according to interfering external stimuli*" (Niendam et al., 2012). Research has identified the prefrontal cortex (PFC) as a key brain region for CC (Coutlee & Huettel, 2012; Egner, 2009). Conflicting information increases the difficulty of selecting the most advantageous behavior, necessitating a complex decision making apparatus to decide – it is this function that the PFC is thought to perform. Miller suggested that the PFC stores and updates internal goals and determines how to act when faced with conflicting stimuli (Miller, 2000). Two cognitive processes seem to be of particular importance: First, attention has to be allocated towards the desired object, which can be either an external stimulus or an internal plan. Here, the PFC is responsible for selectively allocating attention towards a single object among many. This ability is lost when the PFC is damaged. Lhermitte found that patients with lesions in the area will display what he called "utilization behavior" (Lhermitte, 1983). That is, their behavior is triggered by stimuli around them without the ability to control it. They will drink from an empty cup or open a door they had no intention to open. This finding is supported by PFC lesion studies in monkeys (Rossi, Pessoa, Desimone, & Ungerleider, 2009). Without an intact PFC, the monkeys were still able to react to stimuli, yet they could not act according to a learned rule. Second, the PFC stores goal-relevant information while performing an action. This capacity is referred to as working memory, and has been especially associated with the dorsolateral part of the PFC (Barbey, Koenigs, & Grafman, 2013). Research in primates by Goldman-Rakic showed that the prefrontal cortex sustains neural responses during a delay period, so that they are able to respond appropriately after the delay is finished

(Goldman-Rakic, 1996). While the importance of the PFC in cognitive control is well established in the experimental literature, the exact underlying neuronal mechanisms have yet to be fully elucidated (Koechlin & Duverne, 2017; Koechlin, Ody, & Kouneiher, 2003).

1.1.1. Cognitive Control Over Emotion

Cognitive control is especially relevant in emotionally ambiguous situations (Ochsner & Gross, 2005; Ochsner, Silvers, & Buhle, 2012). Emotions are one of the fundamental forces underlying behavior and therefore interact with cognition in multiple ways. Brain structures responsible for evaluating and processing emotional information have been termed the limbic system and include the amygdala and the cingulate gyrus (Catani, Dell'acqua, & Thiebaut de Schotten, 2013; Kober et al., 2008; Ledoux, 1998; Phillips, Drevets, Rauch, & Lane, 2003). There is a body of evidence indicating that the dorsolateral prefrontal cortex (DLPFC) is involved in the modulation of these (sub)cortical networks responsible for emotion processing (Roy et al., 2009; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). According to the dual competition model from Pessoa, emotional content either facilitates or inhibits the pursuit of a desired action depending on the circumstances (Pessoa, 2009). Highly threatening stimuli preferentially attract attention and this can have useful behavioral consequences, focusing a response on the most salient stimulus. However, there are situations where the impact of emotions on behavior must be regulated and it is this intricate balance that cognitive control is responsible for (Pourtois, Notebaert, & Verguts, 2012).

Impaired cognitive control over emotion is thought to be among the factors contributing to diseases such as depression (Plewnia, Schroeder, & Wolkenstein, 2015). Thus, to understand the interaction between emotion and cognition is vital but it is also a very complex task (Mueller, 2011; Pessoa, 2017). It is of particular importance since, apart from learning more about the pathogenesis of diseases, understanding the cognitive mechanisms promises insights in new treatment options (Roiser, Elliott, & Sahakian, 2012). Many studies have provided evidence that task performance in computerized cognitive tests is worsened by the presence of distracting stimuli. Padmala and colleagues argued that task-

irrelevant, negative stimuli impair cognitive control as their processing necessitates resources that are then unavailable for optimal task performance (Padmala, Bauer, & Pessoa, 2011). Dolcos and McCarthy investigated the neuronal underpinnings of distraction by emotional stimuli (Dolcos & McCarthy, 2006). They examined female participants in a delayed working memory paradigm, using functional magnetic resonance imaging (fMRI) to measure DLPFC and amygdala activity. Participants viewed three human faces and, after a delay period, were shown another face and were asked whether it was part of the set of faces seen before. During the delay period, neutral and negative pictures were shown as distracters, while scrambled (containing only nonsensical colorful pixels) pictures served as a non-distraction condition. They found that memory performance deteriorated in trials with negative distractors (see **Figure 1A**): Participants performed significantly worse than in trials with neutral or scrambled distractors.

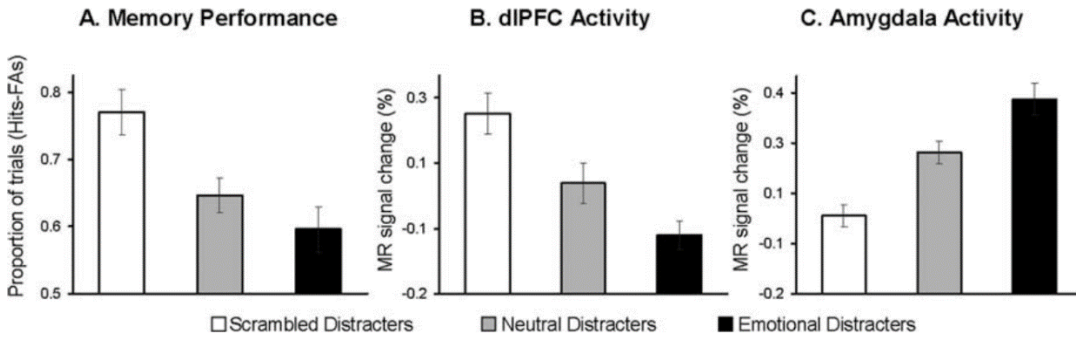

Figure 1. Memory performance and related brain activity in a delayed working memory task. Memory performance was significantly worse for negative compared to neutral and scrambled (i.e. nonsense) pictures during the delay period (A). DLPFC (B) and amygdala activity (C) were inversely related to the stimuli's valence in that DLPFC activity was highest for scrambled and lowest for negative pictures and vice versa. The figure is taken from Dolcos & McCarthy (2006).

Additionally, they were able to find neuronal correlates for the valence-specific deterioration in task performance: Emotional distractors covaried with a heightened activity in the amygdala and decreased activation in the DLPFC (See

Figure 1B and 1C). Decreased activity in the DLPFC during the delay period in turn corresponded with decreased memory performance. The authors concluded that the DLPFC participates in controlling memory and monitoring task relevant behavior. In sum, the study of Dolcos and McCarthy supported the hypothesis that emotional distractors disrupt cognitive processes, and that this is mediated by a hypoactive DLPFC, resulting in poorer task performance.

Considering these results, it is important to note that there is evidence that emotional distractors may also improve task performance (Okon-Singer, Hendler, Pessoa, & Shackman, 2015). This was demonstrated for example by Sussmann and colleagues (Sussman, Heller, Miller, & Mohanty, 2013). In agreement with previous findings, they found that highly arousing stimuli did impair performance. However, mildly arousing, task-irrelevant negative stimuli enhanced performance. Similarly, it has been found that emotions conferred beneficial effects in cognitive conflict paradigms (Kanske & Kotz, 2011) and that an active suppression of emotions resulted in diminished cognitive control (Hobson, Saunders, Al-Khindi, & Inzlicht, 2014). A study by Wessa and colleagues examined the impact of distractive negative and neutral images while subjects solved mathematical problems (Wessa, Heissler, Schonfelder, & Kanske, 2013). The authors found a worsening in reaction times for negative pictures, while accuracy was not impaired. By contrasting the functional imaging data of trials with distractive images with the activation from the math problems alone, they discovered that a task-specific heightened activation could be found in the presence of negative stimuli. This relates to findings of Egner and Hirsch, who used a cognitive conflict task (a modified stroop task) while recording fMRI (Egner & Hirsch, 2005). They found that conflict resolution was mainly accompanied by an active enhancement of task relevant information, represented by an increased activation of visual cortices and areas in the DLPC associated with cognitive control. They concluded that instead of suppressing irrelevant stimuli, cognitive control may work by enhancing relevant information and activation of relevant brain areas.

1.1.2. Impaired Cognitive Control and Depression

The interplay between cognitive and emotional function is a delicate balance, such that dysregulation can give rise to psychiatric disorders (Phillips, 2003). One of the most widespread psychiatric disease is depression, a mood disorder whose most commonly known manifestation is major depressive disorder (MDD). Lifetime prevalence is reported to be above 15 % in the United States (Kessler et al., 2005) and 8 - 12 % worldwide (Andrade et al., 2003). According to the tenth revision of the International Statistical Classification of Diseases (ICD-10), characteristic for depression are *"lowering of mood, reduction of energy and decrease of activity*" (World Health Organisation, 2010). Of note, the word depression is best seen as an umbrella term for a multitude of disorders that share common features (Gotlib & Hammen, 2014). For instance, the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) lists eight subgroups in the chapter "*depressive disorders*" (American Psychiatric Association, 2013) and offers an important summary of the diseas(es): "*The common feature of all of these disorders is the presence of sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function*" (American Psychiatric Association, 2013, p. 155). For the sake of clarity, in this dissertation the term depression will be used.

Cognitive models of depression seek to identify antecedents for the illness and examine their causal relationship with the symptoms. The aim is to be able to confirm these models empirically and use their insights to inform therapy. Possibly, the historically most influential model of depression comes from Beck (Beck, 1967). One of his hypotheses is that biased processing in favor of negative information is a prime cause of depression (Disner, Beevers, Haigh, & Beck, 2011). The model posits that negative life events, paired with genetic disposition, can lead to the construction of aberrant schemata, i.e. dysfunctional mechanisms how the world is perceived. These schemata lead to negative biases in attention, information processing and memory. In an extended version of the model (Beck, 2008), it is suggested that cognitive biases have several roles in the genesis of depression: Through deficient cognitive control, negative information is given precedence. Then, this negative information subsequently biases the way new

incoming stimuli are perceived. A vicious cycle ensues and actions are evaluated in a predominantly negative fashion. This, according to the model, ultimately gives rise to depressive symptoms (Beck, 2008). Warren et al. summarized many findings from imaging studies as well as results of pharmacological interventions in their recent model. In line with Beck they conclude that "*depression is associated with both neural and behavioural biases towards negative over positive stimuli*" (Warren, Pringle, & Harmer, 2015). They argue that pharmacological interventions normalize these biases and thus stress a negativity bias as a relevant causal factor in the disease. Along the same lines, Goschke explicitly names a failure of cognitive control as a causal factor for depression (Goschke, 2014). Also, Roiser et al. argue that "*negative information processing biases have a central causal role in the development of symptoms of depression, and that treatments exert their beneficial effects by abolishing these biases*" (Roiser et al., 2012).

Researchers have attempted to link symptoms of depression with specific, neuronal processes in the brain. Mayberg proposed a model that differentiates between the roles of ventral and dorsal compartments in the brain with regards to the occurrence of depression (Mayberg, 1997). The ventral compartment, consisting of (sub)cortical regions such as the insula, amygdala, subgenual cingulate and ventral prefrontal cortex (VPFC), is proposed to be responsible for the affective aspect of the disease. Cognitive aspects are attributed to the dorsal system that comprises the DLPFC, inferior temporal lobe, striatum and dorsal anterior cingulate. The theory poses that a *hypo*activation of the dorsal system, a breakdown of cognitive control, and simultaneous *hyper*activation of the ventral system are both characteristic of and causally responsible for the disease. The model is supported by congruent evidence from different lines of research. Siegle and colleagues for instance found hypoactivity in prefrontal areas in all of their examined depressed patients and half of them exhibited increased amygdala activity (Siegle et al., 2007). Other studies found that in depressed patients relative to healthy controls, prefrontal areas are hypoactive when negative stimuli are presented (Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013; Hamilton et al., 2012). Koenigs and Grafman commented on specific roles of the

DLPFC and ventromedial prefrontal cortex (VMPFC) in depression (Koenigs & Grafman, 2009). Evidence from lesion studies of war veterans and patients showed that DLPFC lesions were associated with significantly more severe depressive symptoms, while the opposite was true for VMPFC lesions. Moreover, they reported results of neurosurgical interventions in which patients with severe depression had the VMPFC or its associated connective circuits damaged. After such a procedure, a significant number of patients reported symptom alleviation.

To summarize, a multitude of neuroimaging studies have demonstrated hypoactivity of prefrontal areas in depression and corresponding hyperactivity in limbic areas such as the amygdala. However, there is a pivotal difference between correlation and causation. In a comment on the role of cortico-limbic dysregulation in depression, Treadway and Pizzagalli remarked that, although many abnormalities have been repeatedly associated with depression, neuroscience has to date failed to identify a reliable marker which both identifies depressive episodes or predicts their course (Treadway & Pizzagalli, 2014).

1.1.3. Excursus: Stimuli in Cognitive Neuroscience

To study functions of the brain such as perception, cognition or emotions, studies in cognitive neuroscience often rely on experiments where participants perform a standardized task on a computer. They are typically faced with a stimulus which, in most cases, consist of pictures from standardized databases. The prime example for this is the International Affective Picture Scale (IAPS) database (Lang, Bradley, & Cuthbert, 2008). These pictures were rated by healthy participants on three qualities on a 9 point Likert scale: affective valence (ranging from pleasant to unpleasant), arousal (ranging from calm to excited) and dominance (ranging from being dominated to being in control). The underlying assumption is that emotions can be categorized by these three distinct dimensions (valence and arousal were considered of primary importance). The IAPS pictures have been used extensively and have the advantage that they are easily accessible for researchers but not available to the public. Crucially, usage of these pictures with normative ratings make studies comparable. However, the mechanistic assumption that one can objectively define a picture as negative,

positive or neutral in valence has frequently been called into question (Kron, Pilkiw, Banaei, Goldstein, & Anderson, 2015). For instance, it is unclear whether neutral means the same to different people (Schneider, Veenstra, van Harreveld, Schwarz, & Koole, 2016). What is more, data suggests that the categories of valence and arousal are not distinct categories but instead have a complex relationship, depending on individual differences (Kuppens, Tuerlinckx, Russell, & Barrett, 2013).

1.2. Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that emits a weak electrical current through electrodes attached on the scalp. Alongside with transcranial magnet stimulation (TMS), it is a tool frequently used in both neuroscience research and therapy (Miniussi, Paulus, & Rossini, 2012). It is increasingly popular among researchers due to its ease of use, high level of safety and emerging evidence for reliable effects on various aspects of cognition, emotion and behavior.

1.2.1. Historical Overview

The use of electrical currents on human subjects dates back to the ancient Greeks, although the first systematic approaches started around two hundred years ago (Priori, 2003). At the beginning of the 19th century, Aldini experimented with electrical currents (see **Figure 2**) in both animals and humans (Parent, 2004).

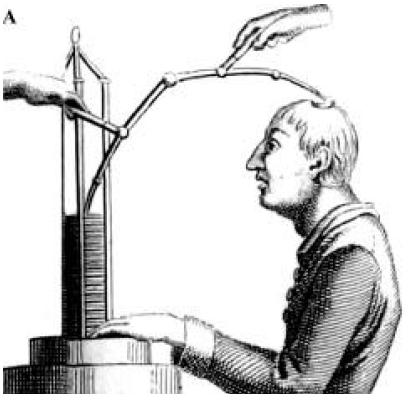

Figure 2. Experimental setup of a historical electrical stimulation device used in the laboratory of Aldini (1762-1834). The figure is reprinted from Parent (2004).

His public demonstration of how electricity made dead bodies move had a profound effect on both the spectators and society as a whole, and was capitalized on by Mary Shelley's novel *Frankenstein*, written around that time (Shelley, Macdonald, & Scherf, 1999). Aldini also examined the effect of current on psychiatric diseases and claimed to have cured patients with mood disorders (Parent, 2004).

Stimulation devices in that era were, in principle, not very different from those used today (Paulus & Opitz, 2013), but it was only towards the middle of the 20th century that noninvasive brain stimulation was rediscovered and integrated into modern neuroscience research. Bliss and Lomo showed that repeated electrical stimulation of a nerve fiber in a rabbit induced long lasting effects, in particular increasing synaptic transmission (Bliss & Lomo, 1973). This led to the discovery of long-term potentiation and depression (LTP and LTD, respectively), fundamental neuronal mechanisms that shaped the understanding of learning and memory (Miles, Poncer, Fricker, & Leinekugel, 2005; Nitsche, Muller-Dahlhaus, Paulus, & Ziemann, 2012). Moreover, animal experiments showed that direct current stimulation of the cortex resulted in elevated evoked responses to visual stimuli, as well as an increased firing rate of the stimulated neurons (Bindman, Lippold, & Redfearn, 1964). Importantly, the stimulation also resulted in long lasting after effects that shared many characteristics to LTP and LTD (Monte-Silva et al., 2013).

1.2.2. Practical Application

There are at least three characteristics that make tDCS a practical tool for research and therapy. Firstly, it is comparatively easy to implement. The typical tDCS experiment requires a direct current stimulator together with two electrodes (anode and cathode). Most studies use electrodes with sizes between 24 - 35 cm^2 (Nitsche et al., 2008). To minimize resistance with the scalp, electrodes are either put in little sponges that are soaked in saline solution or a contact paste is applied directly on the electrodes. They are then fixed on the scalp with either a cap or straps. The position of the electrode names the protocol, i.e. *anodal* stimulation means that the positive charged electrode is placed over the area to

be stimulated, while in a *cathodal* setting the negatively charged electrode has that position. For stimulation a of usually between 0.5 and 2 mA is applied over a variable period. An overview of the protocol, including a discussion of important steps and a video tutorial on the mounting of electrodes can be found in DaSilva, Volz, Bikson, & Fregni (2011).

Secondly, reliable placebo control of tDCS is feasible by applying a short period of stimulation that does not induce relevant neuronal effects. Thus, in placebo controlled studies, in the *verum* condition, the stimulation is ongoing, whereas in the *sham*, placebo condition, current is only turned on for a short period. Both result in a similar sensation for the participant. It has been shown that in 10 min of 1 mA stimulation, sham and verum conditions are indistinguishable (Ambrus et al., 2012) and also when stimulation time is extended to 20 min (Gandiga, Hummel, & Cohen, 2006). However, with increasing stimulation intensity, blinding becomes more challenging. With 2 mA, successful blinding is questionable (Wallace, Cooper, Paulmann, Fitzgerald, & Russo, 2016) and at 3 mA participants reported experiencing pain (Nitsche et al., 2008).

Thirdly, tDCS has been found to be a safe stimulation technique. While a great many tDCS experiments with a variety of protocols have been performed during recent decades, there have been very few reports of clinically relevant side effects (Bikson, Datta, & Elwassif, 2009). For standard protocols, frequently observed side effects included an itching sensation at the stimulation side, feelings of pain and a temporary reddening of the skin close to the electrode after stimulation. The latter is probably a consequence of vasodilatation (Nitsche et al., 2008). Studies using electroencephalography have not observed pathological changes caused by tDCS (Iyer et al., 2005) and any possibly detrimental cognitive changes induced by tDCS have so far been reported to be only transitory (Kuo & Nitsche, 2012). However, one has to keep in mind that the effects of tDCS found in many studies may lead to – transitory or not – impairments in other domains (Iuculano & Cohen Kadosh, 2013). Liebetanz and colleagues systematically examined upper safety limits for tDCS in rats (Liebetanz et al., 2009). In varying stimulation intensity and duration, they found that histologically observable brain damage only occurred when the overall

charge administered exceeded that used in standard experiments by a factor of one hundred. Given that, in their experiment, electrodes were located directly on the rats' brain, the current strength needed to inflict damage in humans in normal tDCS experiments would lie even higher. Notably, rats stimulated over consecutive days with lower intensities did not experience any side effects – suggesting that the repeated use of tDCS is also safe.

1.2.3. Mechanisms of Actions of tDCS

The tDCS technique functions through a weak electric current that causes shifts in the membrane potential of neurons, changing action potential frequency, which in turn alters cortical excitability (Jackson et al., 2016; Nitsche et al., 2003; Paulus, 2011; Reato, Rahman, Bikson, & Parra, 2010; Romero Lauro et al., 2014). The procedure itself does not induce action potentials, in contrast to transcranial magnetic stimulation (TMS). The effects of tDCS have generally been found to be polarity specific. Anodal stimulation increases excitability, while cathodal stimulation decreases it. Nitsche and Paulus, for example, found such a correlation for the motor cortex, where anodal stimulation resulted in a higher motor evoked potential (MEP) and cathodal stimulation in a response lower than baseline (Nitsche & Paulus, 2000). However, the reverse effect is also found, possibly resulting from different spatial orientations of neurons. Early animal experiments indicated that anodal stimulation of the cortex did excite superficial neurons while inhibiting deeper neurons, while cathodal stimulation had the opposite effect (Creutzfeldt, Fromm, & Kapp, 1962). Also, tDCS has been reported to lead to perfusion changes in stimulated areas have (Lang et al., 2005; Nord, Lally, & Charpentier, 2013; Stagg et al., 2013). In rats, these changes were found to be polarity specific (Wachter et al., 2011) in that anodal tDCS increased cerebral blood flow and cathodal tDCS decreased it. Also it has been reported that tDCS affects connectivity between different brain areas (Hunter, Coffman, Trumbo, & Clark, 2013).

Researchers have also considered tDCS effects on a molecular level, identifying neurotransmitters as important factors. Animal studies have demonstrated that tDCS effects are reflected in altered calcium concentrations (Islam, Aftabuddin,

Moriwaki, Hattori, & Hori, 1995). Nitsche and colleagues showed that the after effects are dependent on changes to neurotransmitters (Nitsche et al., 2007). For instance, tDCS response is mediated by the glutamate N-methyl-D-aspartate (NMDA) receptors, which are vital for the physiological formation of memory (Kandel & Tauc, 1964). This was demonstrated in an experiment where the NMDA receptor antagonist Memantine abolished the anodal tDCS induced after effect (Nitsche et al., 2012), showing that these receptors are a prerequisite for the effects of tDCS being more than momentary. Moreover, it has been shown that tDCS has polarity-specific effects on the concentrations on glutamate and gamma-aminobutyric acid (GABA) (Kim, Stephenson, Morris, & Jackson, 2014). GABA is released by interneurons and is responsible for inhibitory processes, while glutamate is a major excitatory transmitter and is necessary for memory formation. Studies suggested that anodal tDCS lowers GABA concentration and heightens glutamate concentration, while cathodal tDCS has the opposite effect (Stagg et al., 2009). Furthermore, there is evidence that GABA concentration predicts the effect of tDCS on motor learning (Kim, Stephenson, et al., 2014). Drawing on these findings, Krause et al. proposed that tDCS functions via modulation of an excitation/inhibition balance of the neurons, as represented by a glutamate/GABA ratio (Krause, Marquez-Ruiz, & Kadosh, 2013). Dopamine also plays a key role in the prefrontal cortex, as it is critical for neural plasticity. Monte Silva et al. demonstrated that there is a non-linear relationship between this transmitter's concentration and motor cortex plasticity (Monte-Silva, Liebetanz, Grundey, Paulus, & Nitsche, 2010). Further evidence for this comes from Plewnia and colleagues who found that in subjects with a genetic polymorphism leading to higher dopamine concentration in the DLPFC, anodal tDCS actually resulted in a deterioration in task performance (Plewnia et al., 2013).

1.2.4. Parameters Determining Stimulation Effects

The effect of tDCS depends on several parameters, including current strength, current duration, the size of the electrode, and the positioning of the reference electrode. **Table 1** displays key results from selected studies.

Table 1*:*
A summary of studies reporting on influences on tDCS effects sorted by topic (left column)

Electrode size	*Nitsche et al. (2007):* Decreasing the size of the stimulation electrode heightened stimulation focality. Increasing the size of the electrode in turn did not alter stimulation results, but diminished unwanted activation of the cortex below the reference electrode.
Reference electrode position	*Moliadze, Antal, & Paulus (2010):* The distance between reference and active electrode correlated negatively with the induced after effect.
Amount of electrodes	*Kuo et al. (2013)*: A montage using four stimulation electrodes and one reference electrode significantly increased focality. Using computational modelling, it was possible to create a montage that targeted the desired brain region more precisely.
Stimulation intensity	*Batsikadze, Moliadze, Paulus, Kuo, & Nitsche (2013)*: Non-linear effects of 1 and 2 mA, cathodal and anodal stimulation on motor cortex excitability were found. While both 2 mA cathodal and anodal stimulation increased excitability, 1 mA of cathodal tDCS decreased excitability and 1 mA of anodal stimulation had no effect.
Stimulation duration	*Nitsche & Paulus (2000):* Increasing stimulation duration in the range of 1-4 min lead to a longer duration of its after effects. *Monte-Silva et al. (2010):* 26 min of anodal tDCS abolished the initially excitatory after effects.
Stimulation polarity	*Weiss & Lavidor (2012):* Cathodal but not anodal stimulation facilitated task performance by suppressing the noise of the complex task environment. *Jacobson, Koslowsky, & Lavidor (2012)*: Effects of anodal/cathodal tDCS may be domain- specific.
Timing of stimulation	*Antal, Begemeier, Nitsche, & Paulus (2008)*: Both anodal and cathodal stimulation over the motor cortex improved task performance, but only when it was applied at the beginning of the practice session. The beneficial effect was significantly lower when stimulation started 10 -15min after the task began. *Antal, Terney, Poreisz, & Paulus (2007)*: TDCS effects varied according to the activity of the brain. Motor evoked potentials (MEPs) were lower when participants engaged in a demanding task compared to MEPs at rest. *Dockery, Hueckel-Weng, Birbaumer, & Plewnia (2009)*: In a mental planning task over three sessions, cathodal stimulation helped planning performance in the earliest session, whereas anodal stimulation improved reaction times and accuracy in later sessions.
Cognitive state of participants	*Benwell, Learmonth, Miniussi, Harvey, & Thut (2015)*: A complex non-linear interaction exists between baseline performance and tDCS effects. *Grundey et al. (2012)*: Nicotine severely altered tDCS effects.
Anatomical variation between subjects	*Krause & Cohen Kadosh (2014)*: Anatomy of the skull (such as thickness) and brain (spatial orientation of gyri, sulci and targeted brain areas) substantially impacted tDCS efficacy. *Kim, Kim, et al. (2014)*: Differences of stimulation effects in a working memory task could partly be explained through anatomical variations across participants.

Studies differ in the way they address the factors presented in **Table 1** and it is important to keep this in mind when analyzing results (Horvath, Carter, & Forte, 2014). Also, it is important to minimize possible confounding factors. However, a tradeoff has to be made between precision on the one hand and practicality on the other. For instance, looking at anatomical variations, it would likely improve results if each participant had an fMRI scan prior to an experiment, alongside an extensive pre-examination with an individualized current intensity and electrode montage. With such extra measures, however, one would lose the great advantage of tDCS, its ease of use.

Concerning stimulation intensity and duration, it is common to assume a mechanistic relationship in the form that the higher the intensity and the longer the stimulation, the higher the effect. This, within limits, seems to be true at the motor cortex (Brunoni et al., 2012; Nitsche et al., 2008; Nitsche et al., 2003). However, as can be drawn from **Table 1**, a non-linear relationship is also found with tDCS, highlighting that research has not until now fathomed the whole complexity of tDCS (Jackson et al., 2016). The same is true for the timing of the stimulation. For instance, it makes a difference whether stimulation is applied *online*, that is while the participant is performing a task or *offline,* i.e. before the task (Antal et al., 2008; Benwell et al., 2015). Here, it is important to note that most studies examine offline effects of tDCS, meaning that the actual task starts after tDCS has been performed. Especially when other techniques such as EEG are used, it is methodologically challenging to stimulate and record in parallel which only few studies have attempted so far (Cunillera, Brignani, Cucurell, Fuentemilla, & Miniussi, 2015).

1.2.5. Modulating Cortical Excitability with tDCS

The early research into tDCS effects in humans focused on the motor cortex (Nitsche et al., 2008). In a seminal study, Nitsche and Paulus reported four experiments that examined the influence of tDCS on the human motor cortex, as measured by the amplitude of the motor evoked potential (MEP) (Nitsche & Paulus, 2000). They tested stimulation intensities between 0.2 - 1 mA and durations between one and five minutes. Stimulation of at least three minutes at 1 mA lead to an amplitude change in MEP of up to 40 %. Importantly, the effects

were only observed when the electrode was placed over the motor cortex and no other cortical areas. Moreover, the effects were polarity specific, with anodal tDCS increasing and cathodal stimulation decreasing cortical excitability.

Other studies have shown that these effects transfer to other domains such as perception, working memory, and learning (Kuo & Nitsche, 2012). For perception, anodal tDCS has been reported to enhance visual contrast perception, whereas cathodal stimulation diminishes it. Auditory perception has been shown to be enhanced by anodal, and diminished by cathodal tDCS. Motion perception has been altered in often contradictory ways, with probable task interferences accounting for these results. The same holds true for somatosensory perception where for example cathodal stimulation could diminish temperature and pain perception (all taken from: Kuo & Nitsche, 2012). Concerning working memory task performance, there is evidence of variable effects of tDCS. In a systematic review, Brunoni and Vanderhasselt concluded that tDCS significantly improved reaction time (RT) but not accuracy (AC) (Brunoni & Vanderhasselt, 2014). Dedoncker and colleagues analyzed 233 within-subject trials of single-session tDCS and found that anodal tDCS significantly decreased RT in healthy participants and increased AC in neuropsychiatric patients (Dedoncker, Brunoni, Baeken, & Vanderhasselt, 2016). Hill et al. also found that tDCS improved AC in neuropsychiatric populations (Hill, Fitzgerald, & Hoy, 2016). Also, tDCS also has been shown to enhanced working memory training (Ruf, Fallgatter, & Plewnia, 2017). Finally, tDCS also has been shown to modulate higher cognitive processes such as planning (Dockery et al., 2009).

1.2.6. Effects of tDCS on Cognitive Control over Emotion and its Use in Depression

As described in the **chapter 1.1**, the DLPFC is a key brain area in mediating cognitive control over emotion and it is therefore no surprise that research of tDCS over the DLPFC has attracted much attention as it promises to both study and modulate cognitive control (Plewnia et al., 2015). Wolkenstein and Plewnia examined the effects on cognitive control in patients that suffered from major depressive disorder and healthy controls (Wolkenstein & Plewnia, 2013).

Participants performed a delayed working memory task (DWM) that was also used in the study presented here (see **material and methods**). Given the research on attentional distractibility of emotional stimuli (Dolcos & McCarthy, 2006), they surmised that task performance would worsen in trials with emotional distractors. The authors further hypothesized that tDCS would ameliorate this effect. The results supported both hypotheses: Firstly, MDD patients' task performance in terms of reaction time and accuracy was significantly worse when emotional pictures appeared during the delay period. The authors interpreted this as an emotional bias, in line with neurocognitive models of depression (Warren et al., 2015). Secondly, this bias disappeared under anodal stimulation, indicating that cognitive control was enhanced through anodal tDCS (see **Figure 3**).

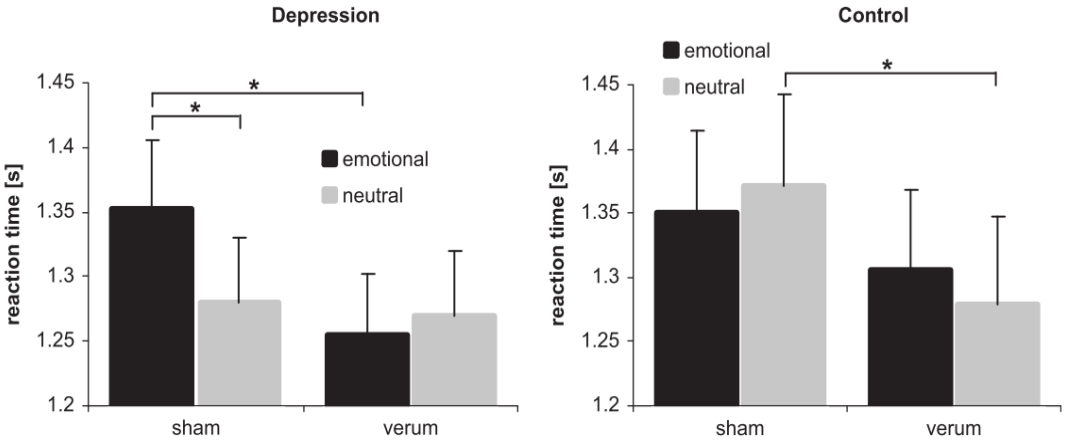

Figure 3. Results of reaction time in a delayed working memory task. Under sham (placebo) condition, only participants suffering from depression (left) exhibited longer RTs in trials with emotional pictures in the delay period. This disappeared under stimulation (verum condition). Both patients and healthy controls (right) reacted faster under stimulation. Asterices indicate p-values below 0.05. The figure is reprinted from Wolkenstein & Plewnia (2013).

Control participants, in turn, did not exhibit this emotional bias in the sham condition. Interestingly, for the healthy participants, their performance was enhanced for the neutral picture condition during stimulation. Finally, the authors found that anodal tDCS over the left DLPFC improved working memory performance in both healthy and depressed subjects as RT improved significantly both for neutral and emotional picture trials. In a follow-up study, they found that cathodal stimulation in healthy participants actually induced a behavioral effect

similar to the one found under sham conditions in depressed patients in the previous study (Wolkenstein, Zeiller, Kanske, & Plewnia, 2014). Accuracy results deteriorated under cathodal stimulation only when negative pictures were shown during the delay period. This lends support to the notion that tDCS over the left DLPFC modulates cognitive control under emotional distraction in a working memory paradigm. Additional evidence for the enhancing effect of tDCS on CC comes from Brunoni and colleagues (Brunoni et al., 2014). In their study, patients suffering from major depression performed an emotional stroop task, were neutral, negative and positive words served as stimuli. They found that participants exhibited longer reaction times for negative vs. positive words under baseline conditions, constituting a negativity bias. Anodal tDCS but not sham stimulation over the left DLPFC abolished this bias.

As explained above, a processing bias that favors negative information (negativity bias) is thought to be involved in the pathophysiology of depression with a hypoactivation of the DLPFC as an underlying neuronal correlate. The findings discussed thus present evidence that with tDCS, a possibly causal factor of depression may be improved. As Plewnia and colleagues argue in a review article, the deliberate modulation of DLPFC activity via tDCS is a promising therapeutic option (Plewnia et al., 2015). This is further supported by growing evidence that tDCS over the DLPFC is able to alleviate symptoms of depression (Kuo, Paulus, & Nitsche, 2014). Several meta-analyses and reviews underline this. Shiozawa and colleagues reported that tDCS is superior to sham stimulation in alleviating symptoms in acute depression (Shiozawa et al., 2014). Similar results were found by Kekic et al., who systematically analyzed 66 studies in which tDCS was used to ameliorate symptoms of psychiatric diseases and concluded that overall, tDCS had a positive effect both on acute and long term symptomatology (Kekic, Boysen, Campbell, & Schmidt, 2016). Meron and colleagues concluded that tDCS might be superior to placebo but studies with larger sample sizes will be needed for definitive conclusions (Meron, Hedger, Garner, & Baldwin, 2015). Brunoni et al. found in their analysis that tDCS is comparable in effect with TMS and pharmacological interventions (Brunoni et al.,

2016). In a summary of several meta-analyses and reviews, Palm and colleagues remarked that tDCS is potentially superior to sham in alleviating symptoms of depression but that results across studies are inconsistent (Palm, Hasan, Strube, & Padberg, 2016). Already, tDCS is widely used off-label in many countries (Fregni et al., 2015). Ongoing clinical trials, such as the ELECT-tDCS trial in Brazil (Brunoni et al., 2015) will shed further light on tDCS effectiveness and aim at establishing it in routine medical practice.

1.3. Electroencephalography (EEG) and Event-Related Potentials (ERPs)

Electroencephalography (EEG) is a well established technique to trace electrical activity of the brain. Developed by the German neurologist Berger, it is still frequently used today despite the rise of imaging techniques such as fMRI (Berger, 1929). EEG recording is comparatively inexpensive and easy to use. Through conductive electrodes on the scalp, tiny electrical fields are detected. Commonly, electrodes are arranged following the international 10-20 system (Jasper, 1958) that names electrodes according to the cortical areas on which they are placed (see **Figure 4**).

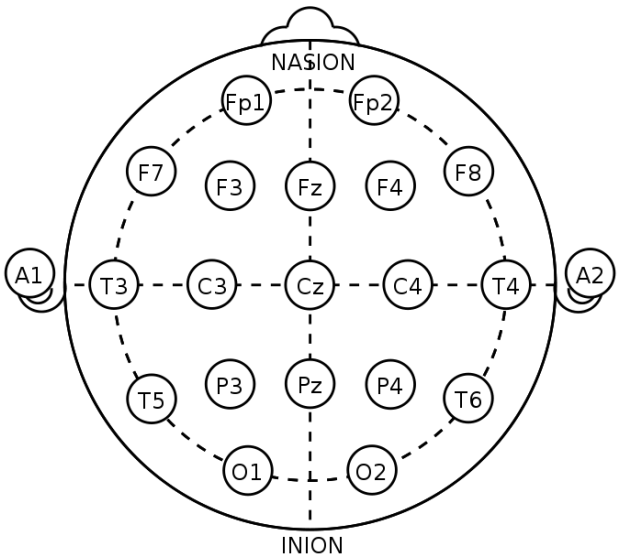

Figure 4. Sample electrode arrangement according to the international 10-20 system. For instance, “P” stands for parietal, “O” for occipital and so forth. The figure is reprinted from *https://en.wikipedia.org/wiki/10-20_system_(EEG)* and was retrieved on 07/12/2016.

The voltage changes detected by EEG originate from synchronized activity of postsynaptic-potentials and have characteristic patterns (Jackson & Bolger, 2014; Nunez & Srinivasan, 2006), which enable researchers to attribute them to cognitive processes such as sleep, concentration and also diagnose conditions such as an epileptic seizures. EEG has a high temporal precision and detects fluctuations in the range of milliseconds. In contrast, fMRI has a poor temporal resolution as it uses blood oxygen level dependent (BOLD) contrast imaging that is an indirect and more inert signature of cognitive activity (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). That said, fMRI has a very high spatial resolution, much greater than that of EEG (Banaschewski & Brandeis, 2007). This is an inherent shortcoming of EEG: It measures electrical fields that are arise from overlapping currents distributed across the brain, and so source localization is difficult.

1.3.1. Event Related Potentials (ERPs)

To better examine neuropsychological processes, researches began to average time-locked EEG waves across several experimental trials under specific conditions, such as the repeated viewing of an image. These were called event-related potentials (ERPs) (Luck & Kappenman, 2012). In the study presented in this dissertation, ERPs are particularly useful, as they allow for a behavior independent measure of psychological processes. ERPs have been called the "*reaction time of the 21st century*" (Luck, 2014, p. 22), because they enable researches to image the temporal dynamics of psychological processes. The advantage of ERPs is that they may tell researches *what* process is going on at a specific time point – compared to fMRI that is better able to describe the *where*. Also, as Luck points out, ERPs may be used to observe brain processes *before* they are observable as behavior (Luck, 2014). Several specific ERPs have been associated with emotion regulation in general and attention in particular - notably the N1, early posterior negativity (EPN), P300 and the late positive potential (LPP). The P300 (also named P3 or P3b) is a positive deflection in voltage that is registered on midline and parietal electrode sites and typically peaks between 250 - 500ms after stimulus onset (Luck & Kappenman 2012, p.448). Many studies used an oddball paradigm to examine the P300, and associate it with both

stimulus novelty and the task relevance of the stimuli (Squires, Squires, & Hillyard, 1975). Moreover, the P300 has been shown to be modulated by emotional content of stimuli (Olofsson, Nordin, Sequeira, & Polich, 2008).

A heightened ERP amplitude to emotional stimuli has also been observed starting at and exceeding the latency of the P300. Researchers have named this continuation of the P300 the *late positive potential (LPP)*, as it is a positive deflection starting around 200 - 300ms after stimulus onset and continuing for several seconds. Most studies analyzed time windows between 300 ms -1000 ms and record the LPP from centro-parietal electrode sites (Luck & Kappenman, 2012, p.449). Of note, the LPP is can be registered for the whole duration of the stimulus presentation (MacNamara, Ferri, & Hajcak, 2011). A body of empirical data shows that the amplitude of the LPP is higher for negative stimuli than for neutral (Hajcak, MacNamara, Foti, Ferri, & Keil, 2013; Schupp, Junghofer, Weike, & Hamm, 2004). It has also been shown that the LPP increases in amplitude for stimuli that are motivationally relevant to a person (Schupp et al., 2000). Research into emotion regulation has often used the LPP to index attention to emotional stimuli (Hajcak, MacNamara, & Olvet, 2010). Hence, the LPP has been described as a "*biomarker of visual attention to salient stimuli*" (Hajcak, MacNamara, et al., 2010). Due to the overlap in time and electrode sites, the LPP and P300 are sometimes difficult to differentiate (Ramchurn, De Fockert, Mason, Darling, & Bunce, 2014). Thus, it has been proposed that the two components be treated as part of a single continuum (Olofsson et al., 2008).

There are three main reasons why the LPP is an ideal target for studying cognitive control of emotion: Firstly, as a methodological reason, it is a very stable measure of attention to emotional stimuli. Whereas physiological measures such as heart rate and pupil dilation habituate, the LPP response remains stable even after many repetitions of stimulus presentation (Codispoti, Ferrari, & Bradley, 2007). Secondly, several studies have linked emotion regulation strategies as well as emotion cognition interactions to the variation of the LPP amplitude and in turn the amplitude of the LPP with behavior measures. Thirdly, through imaging

studies it has been shown that the neuronal “origin” of the LPP overlap with areas involved in emotion processing and cognitive control over emotion.

1.3.2. The LPP as a Marker of Emotion Regulation

As it is sensitive to the emotional salience of stimuli, the LPP has been used to study the effect of both implicit and explicit emotion regulation strategies (Schönfelder, Kanske, Heissler, & Wessa, 2014). Dunning and Hajcak demonstrated that directing attention towards non emotional areas in negative pictures stimuli reduced the amplitude of the LPP (Dunning & Hajcak, 2009). Participants were asked to passively view negative or neutral IAPS pictures or actively focus attention towards non-arousing or arousing parts of the negative pictures. As can be seen in **Figure 5**, the LPP amplitude was reliably higher for negative pictures than for neutral pictures in the passive viewing condition.

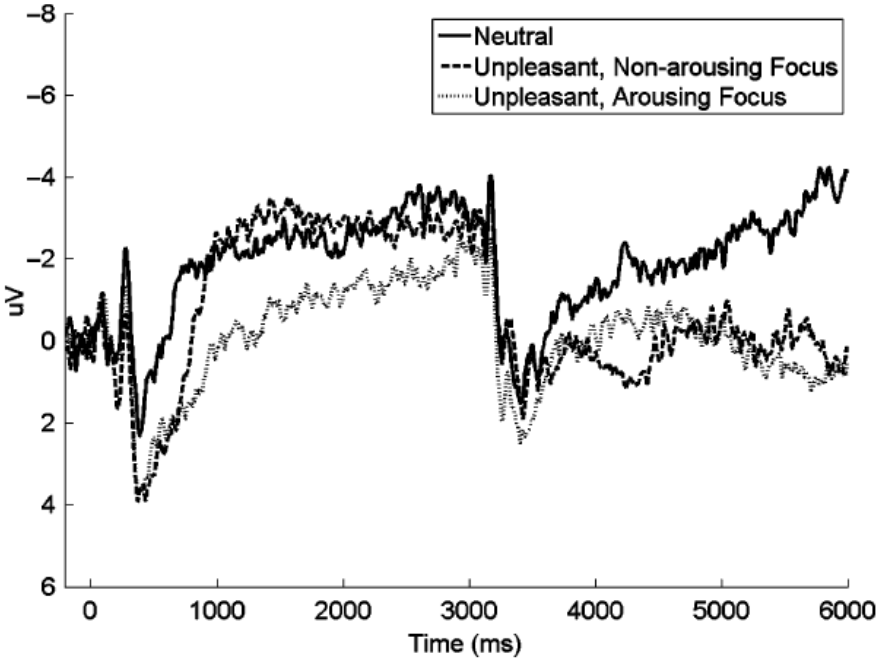

Figure 5. Grand-averaged LPP waves elicited by either negative or neutral pictures. Participants either directed their attention towards or away from arousing portions of negative pictures (first three seconds) or only looked at them (last three seconds). The figure is reprinted from Dunning & Hajcak (2009).

However, negative pictures elicited lower LPP amplitudes when participants directed their attention to non-arousing parts of the picture (**Figure 5**, dotted black line). In turn, focusing on arousing aspects of negative pictures lead to a higher LPP amplitude (**Figure 5**, dotted gray line). The authors concluded that the LPP reflects emotion regulation strategies such as directed attention modulation.

Also, the LPP has been used in several studies examining the impact of emotion on cognitive functioning. As explained in **Chapter 1.1**, holding information in working memory is a major component of cognitive control. Van Dillen and Derks found that a high working memory load corresponded with reduced LPP amplitudes for angry versus happy faces (Van Dillen & Derks, 2012). Along these lines, MacNamara et al. examined the effect of working memory load on the LPP from task irrelevant pictures (MacNamara et al., 2011). Participants were required to memorize and reproduce either two (low load condition) or six (high load condition) letters while they were distracted by either negative or neutral pictures in a delay period. They found a measurable effect for valence in accuracy: Participants performed significantly worse in trials with negative pictures. Trials on the high load condition were characterized by both worse reaction time and accuracy results. Of note, negative pictures had a more deleterious effect on task performance when the task demand was high. In the ERP data, they found that negative stimuli reliably elicited a higher LPP amplitudes than neutral stimuli and the LPP amplitude was higher for the low load condition across valence conditions (see **Figure 6**). In the high load condition in contrast, the LPP was reduced regardless of the picture type. The authors argued that the LPP is sensitive not specifically to negative versus neutral, but to salient stimuli in general. They concluded that the activation of the DLPFC through the working memory task lead to a general decrease in emotional processing which was reflected in a decreased LPP amplitude. Another point of interest in the study was the identification of a link between state anxiety (measured by the STAI-Inventory, see **material and methods**) and the LPP amplitude. Increased anxiety was associated with a decreased difference between the high and low load condition.

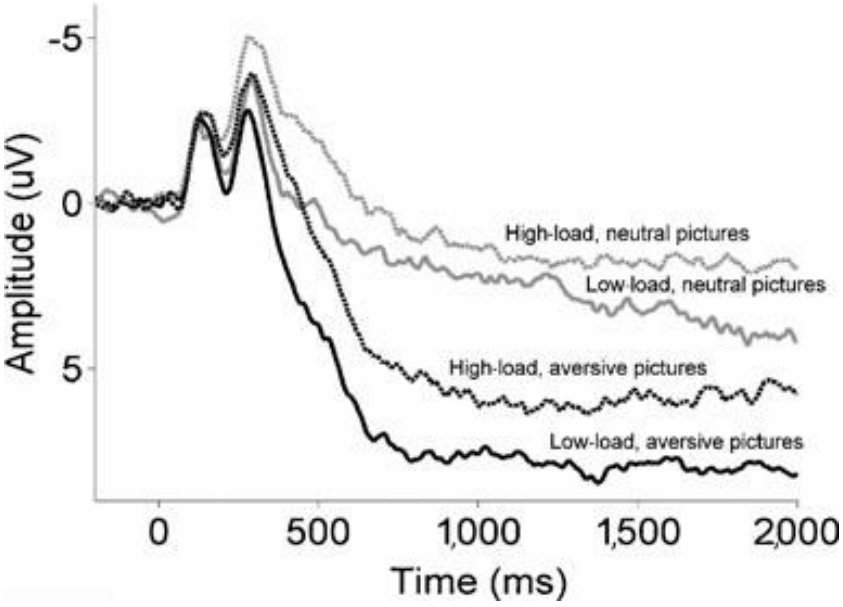

Figure 6. Grand-averaged LPP waves elicited by pictures of negative/neutral emotional content with either high or low memory load. The figure is reprinted from MacNamara et al. (2011).

Weinberg and Hajcak found a link between the LPP, as a marker of attention towards emotional stimuli, and reaction time (RT), as a marker of task performance (Weinberg & Hajcak, 2011). Participants were presented with a picture (negative, positive or neutral content) and then a target figure appeared. They then indicated whether the seen target was either a circle or a square. The authors surmised that the higher the emotional engagement to the preceding picture, the worse the performance in the following response to the target would be. To analyze this, they used three ERP components as an index for the emotional reaction to the picture: early posterior negativity (EPN), P300 and the LPP. Principal component analysis, a dimensionality reduction technique, was used to obtain peak measurements for each component. To examine the relationship between the neuronal response to the picture and task performance for each subject, they also constructed separate ERP waves for trials with slow and fast RTs. They found that negative and positive pictures evoked higher EPN, P300 and LPP amplitudes than neutral pictures and that there was no difference in the neuronal response for positive vs. negative pictures. Additionally, RTs were generally slower following emotional pictures. Interestingly, the LPP robustly

predicted RT across subjects: For each subject, trials with slow reaction time were preceded by larger LPP to pictures and vice versa. Thus, both intra- and inter-subject analysis provided evidence for the LPP as a reliable marker for attention allocation. The authors argued that the three ERP components represent different stages of visual processing, with the EPN and P300 representing the early, and the LPP a more elaborate response. The LPP, they concluded, was the most relevant amongst them. For the present study, Weinberg & Hajcak's findings have important implications: Firstly, they confirmed that the LPP is a reliable marker for visual attention to emotionally salient stimuli. What is more, they could link the LPP to subsequent target processing. A higher LPP, reflecting a higher emotional response, corresponded to slower RTs in a subsequent unrelated task.

Dennis and Hajcak postulated that the LPP can be used as a clinical biomarker for mood dysregulation in children (Dennis & Hajcak, 2009). Twenty children viewed age adjusted, negative IAPS pictures preceded by either a neutral or negative interpretation of the picture. The authors measured the late positive potential on various electrode sites and in three time windows: early (< 600 ms), middle (600 – 1000 ms) and late window (1000 – 2000 ms). They hypothesized that successful emotion regulation would be reflected in a lower LPP amplitude following neutral versus negative interpretations, and unsuccessful regulation would be mirrored by a higher amplitude following neutral interpretations. They found that LPP amplitudes were reduced in the middle window when the picture followed a neutral description, although this was only true for boys. Moreover, they could link the early and middle LPP window with maternal reports about the children: Higher amplitudes following a neutral interpretation (i.e. an unsuccessful regulation) in the early window significantly correlated with maternal reports of anxious symptoms in the children. In turn, a higher valence-specific cortical response ($LPP_{neg\text{-}neu}$, see **material and methods**) was associated with less symptoms of anxiety and depression. Moreover, LPP amplitudes following negative interpretations in the middle window corresponded to maternal reports of emotional dysregulation. The late LPP window exhibited no significant effects. The authors concluded that the early window of the LPP indexed swift emotion

regulation strategies and more elaborate strategies were represented by the middle window. On a methodological note, results showed that the LPP was maximal over centro-parietal-regions in the early and middle windows, and at anterior sites in the late window.

Schönfelder and colleagues examined two emotion regulation strategies, distraction and reappraisal, and linked them with the LPP (Schönfelder et al., 2014). They found that both strategies lead to attenuated LPP amplitudes following negative pictures. "*Using the LPP as a neuronal marker, Bamford et al. (2015) studied the influence of emotional stimuli in an approach avoidance paradigm. Pictures of negative or neutral content were presented and participants had to either "approach" or "avoid" these by pressing buttons. Here, larger LPP amplitudes were associated with faster RTs, regardless of the condition of the task. Moser, Most, & Simons (2010) found that the instruction to increase the emotional response to a negative picture was associated with a higher LPP amplitude and a significant improvement in a subsequent cognitive control ('stroop') task"* (Faehling & Plewnia, 2016).

Adding to the information of the LPP in healthy subjects, some studies have revealed impacts of psychiatric diseases on the LPP. Foti and colleagues used a passive viewing paradigm to evaluate the cortical response to emotional face stimuli in participants with major depression (Foti, Olvet, Klein, & Hajcak, 2010). Healthy participants exhibited a significantly higher LPP response to threatening faces than neutral faces. For the group suffering from depression in turn, there was no significant difference in the LPP response towards threatening versus neutral faces. The authors saw this valence-specific difference as evidence for a decreased reactivity towards negative stimuli in depression. For anxiety, McNamara and Proudfit found that participants suffering from general anxiety disorder exhibited greater cortical reactivity to negative pictures than healthy control subjects (MacNamara & Proudfit, 2014).

1.3.3. Neural Generators of the LPP

Since ERPs represent voltage deflections with various origins throughout the brain, and locating the origin to a high degree of spatial accuracy is a difficult task.

Luck called this the "*inverse problem"* of ERP research (Luck, 2014). To investigate the neural origins of the LPP, some studies have therefore opted for parallel EEG/fMRI recording.

Building on research that associated the LPP with widespread activation throughout visual cortices, Sabatinelli et al. searched for a relationship between the LPP and the BOLD response in a between-group study (Sabatinelli, Keil, Frank, & Lang, 2013). Each group watched the same set of pictures, varying in emotional content between trials. In one group, EEG was recorded while fMRI was used in the other group. They found that the LPP for emotional pictures was associated with activation in visual cortices that are sensitive to emotional content. In contrast, no emotion specific activation was found in the primary visual cortex. Moreover, they found activation in the amygdala and ventral anterior cingulate. Liu and colleagues extended the work of Sabatinelli, also using a passive viewing paradigm, yet in their study EEG and fMRI were recorded in parallel (Liu, Huang, McGinnis-Deweese, Keil, & Ding, 2012). They then identified brain regions that were active during picture viewing and correlated the activation with LPP amplitudes from a trial by trial ERP measurement. The LPP significantly correlated with BOLD activation in the occipito-temporal junctions, insula, amygdala, hippocampus, temporal lobes and left orbitofrontal cortex. Interestingly, they found different results for neutral, negative and positive pictures. For neutral pictures, no relationship between the LPP amplitude and BOLD activation in the fMRI was found. For positive pictures, the LPP amplitude correlated with activation in occipito-temporal junctions, amygdala, temporal poles, precuneus, right nucleus accumbens, medial prefrontal cortex and cerebellum. For negative pictures, the LPP amplitude correlated with activation in the ventrolateral prefrontal cortex, insula, temporal poles, left middle temporal cortex and left postcentral cortex. Using magnetoencephalography and novel source localization approaches, another research group found occipito-parietal-frontal coupling underlying the LPP (Moratti, Saugar, & Strange, 2011). They argued that this interaction between parietal and occipital regions, that are responsible for early processing of stimuli, and right prefrontal cortex, involved in

higher cognitive control mechanisms, underlie the observed bottom-up and respectively top-down characteristics of the LPP.

1.4. Combining tDCS and ERPs to Study Cognitive Control

Exploiting the temporal accuracy of EEG recordings together with tDCS is a promising method for examining the effect of tDCS on cognitive control. However, the combination of the two techniques has not been used often. This may be due to technical difficulties of a parallel set up, as tDCS currents interfere with the recording of the subtle currents registered by EEG.

Vanderhasselt et al. sought to examine cognitive control using anodal tDCS and ERP recording (Vanderhasselt et al., 2013). In the task, participants were instructed to react by pressing a button to either the actual or the opposite emotion of a face presented to them. Faces were either happy or sad, leaving four combinations of stimulus and response: actual/happy, opposite/happy, actual/sad, opposite/sad. The authors assumed that cognitive control demands were higher in the “opposite” condition. There, participants would have to internally divert their attention away from the emotional picture and respond to the opposite emotion. In a within-subjects design, 22 subjects performed this task twice, once after receiving sham and once after receiving 20 min of anodal tDCS over the left DLPFC. Participants responded significantly faster after tDCS for the opposite/happy condition compared to the opposite/sad condition. This was confirmed by the ERP data of the N450, a negative deflection recorded at frontal and central sites that is thought to index conflict monitoring (Szucs & Soltesz, 2012). They found that the N450 amplitude was significantly more negative in the opposite/happy condition during stimulation compared to sham. The authors concluded that tDCS enhanced cognitive control for positive stimuli.

Hajcak et al. found that bilateral electrical stimulation of the DLPFC enhanced cognitive control for negative stimuli (Hajcak, Anderson, et al., 2010). They tested five patients suffering from severe major depressive disorder who had epidural stimulators implanted as an experimental treatment option. Stimulators where placed bilaterally over Brodmann area (BA) 46 which roughly corresponds with the DLPFC, and on BA 10 as a control condition. Patients passively viewed a set

of negative and neutral IAPS pictures in five stimulation conditions (Sham, stimulation of BA 10 with either 2 or 4 Volts, and stimulation of BA 46 with 2 or 4 V). Both during sham and active stimulation, negative pictures elicited higher (i.e. more positive) LPP amplitudes. There was no significant main effect of stimulation intensity, yet post-hoc tests showed a significant difference ($p = 0.05$, one-tailed) for the amplitude for LPP of negative pictures between the sham and the 4 V stimulation condition. The study had two important limitations. Firstly, the sample size was small (N = 5). Secondly, participants received all stimulation conditions within single experimental sessions, although breaks where included. This is a major constraint as after effects of tDCS already appear after short stimulation durations and last for several minutes (Bindman et al., 1964). It may well be that the protocol disguised stimulation effects. Still, the findings of Hajcak et al. are informative in two ways. Firstly, they suggest that it is possible to modulate the LPP as an index of attention towards negative stimuli with electrical stimulation over the DLPFC. Secondly, Hajcak and colleagues were among the first to examine the parametric influence of stimulation intensity.

As cognitive control encompasses the ability to maintain a goal even in the face of distracting stimuli, passive viewing paradigms as used in Hajcak, Anderson, et al. (2010) examine only selective aspects of the processes involved. Paradigms such as the DWM from Wolkenstein & Plewnia, where participants perform a task and are interrupted by irrelevant stimuli, may therefore be better suited to study the of cognitive control (Wolkenstein & Plewnia, 2013).

1.5. Hypotheses of This Study

Dysfunctional cognitive control, reflected in a negativity bias in attention, may be a causal factor of depression (Plewnia et al., 2015; Roiser et al., 2012; Warren et al., 2015). Anodal transcranial direct current stimulation (tDCS) over the DLPFC promises to strengthen cognitive control for emotional stimuli (Wolkenstein & Plewnia, 2013) which may posit a treatment option for depression (Goschke, 2014). To further understand the neurophysiological mechanisms, the LPP, found to index attention allocation towards emotional stimuli, seems a promising marker (Dennis & Hajcak, 2009). However, to date the systematic modulation of the LPP

by varying tDCS intensities has not been explored fully (Brunoni et al., 2012). By recording ERPs in parallel with anodal stimulation of the DLPFC, this study aimed at establishing the LPP as a neurophysiological marker for online effects of non-invasive brain stimulation on cognitive control of emotion. Drawing on the literature reviewed above, several hypotheses were formed that guided this study. Below, these hypotheses are stated, each followed by a brief explanation.

I. (**A**) Negative stimuli impair task performance in the sham group as seen by longer reaction time (RT) and decreased accuracy (AC) compared to neutral pictures, constituting a negativity bias in healthy participants.
(**B**) This is mirrored by an increase in the valence-specific cortical response as measured by LPP amplitude after negative relative to neutral images.

An emotional bias is described as a possible causal factor in the development of depression (Warren et al., 2015) and has been shown to be present in a delayed working memory task in participants with depression (Wolkenstein & Plewnia, 2013). In the present study, it is attempted to elicit such a bias in healthy subjects to the end that modulation under stimulation can be evaluated.

II. Behavioral measures of task performance (RT and AC) correlate with the LPP amplitude in response to distractive, task irrelevant stimuli in a way that a higher LPP amplitude predicts slower RTs and lower AC.

Drawing on the studies linking the LPP with performance (Dunning & Hajcak, 2009; MacNamara et al., 2011; Weinberg & Hajcak, 2011), this hypothesis aims at further elucidating the link between the LPP as a possible marker for cognitive control and its relationship with task performance.

III. Stimulation enhances cognitive control of emotion for negative but not neutral stimuli. This enhancement is seen in (**A**) faster RTs and increased AC in trials with negative distractors compared to neutral distractors in the groups receiving stimulation and (**B**) a reduction of the valence-specific cortical response as measured by the LPP amplitude after negative relative to neutral

images.

Hypoactivation of frontal cortices, especially the DLPFC, has been proposed as a causal factor for dysfunctional cognitive control in depression (Siegle et al., 2007) and a correlate of deteriorated task performance in the face of emotional distractors (Dolcos & McCarthy, 2006). It has been shown that anodal, excitability increasing stimulation of the DLPFC may ameliorate the negativity bias, i.e. improving cognitive control in patients with depression (Wolkenstein & Plewnia, 2013). Hajcak et al. found that in a passive viewing paradigm, online electrical stimulation may attenuate LPP amplitude for negative pictures in depressed patients (Hajcak, Anderson, et al., 2010). Hence, it was attempted in this study to extrapolate these results to a delayed working memory task with healthy participants and to assess the modulation of LPP amplitude as a neurophysiological signature of cognitive control over emotion.

IV. The effects of tDCS are intensity dependent. This can be seen in a differential pattern of the valence-specific LPP curves across the experimental groups.

This is an open research question that has not yet been addressed fully but is of cardinal interest. To date, it is not fully understood which relationship exists between tDCS intensity and its effects (Batsikadze et al., 2013; Jackson et al., 2016).

V. Anxiety influences the amplitude of the LPP in response to negative and neutral stimuli.

As anxiety has been shown to influence participants cortical response to especially negative stimuli (MacNamara & Proudfit, 2014), this was examined in this study as well as an exploratory hypothesis.

2. Material and Methods

2.1. Participants

Female volunteers (95 in total) were recruited via announcements and email advertisement. The gender was restricted to secure homogeneity in the sample (Dolcos & McCarthy, 2006) and to accommodate known gender differences in sensitivity to emotional tasks (Gardener, Carr, MacGregor, & Felmingham, 2013; Syrjänen & Wiens, 2013). Female participants reportedly exhibit a heightened cortical response to emotional stimuli compared to male participants (Sass et al., 2010). Detailed inclusion and exclusion criteria are listed in **Table 2**.

Table 2

Inclusion and exclusion criteria for the study population

Inclusion criteria	Exclusion criteria
Age > 18 years	Current psychiatric diseases
Female	Male
Right-handedness	Left-handedness
	Epileptic seizures in the clinical history
	Metallic objects in the head region
	Cardiac pulse generator

"*Participants received financial compensation for the experiment regardless of their performance. They were randomly assigned to one of the four stimulation conditions (sham, 0.5, 1.0, 1.5 mA tDCS). Written informed consent was obtained from all participants at the beginning of the study. The study was approved by the Ethics Committee of the Medical Faculty of the University of Tuebingen in accordance with the Declaration of Helsinki"* (Faehling & Plewnia, 2016). Several psychological variables were assessed before the beginning of the experiment. The questionnaires and tests used are described below in **Table 3**. "*Furthermore, participants were asked to indicate whether they were smokers, drank coffee in the two hours preceding the experiment, whether they used hormonal contraception and at what stage of their menstrual cycle they were at the day of the experiment"* (Faehling & Plewnia, 2016).

Table 3

List of questionaires and psychological tests (left row) with explanations (right row)

SCL 90-R	The Symptom Check List (SCL-90-R) was used to screen for possible psychiatric diseases (Franke, 2002). It is a self-report measure that consists of 90 questions concerning the subjective feeling about bodily and psychological illnesses during the last 7 days and is rated on a 4-point Likert scale. It can either be evaluated through different subscales or a global scale (GSI) that mirrors general feeling of impairment. The GSI has a high retest reliability (Franke, 2002). For the analysis of the present data, the GSI raw-score was transformed to T-values using the values of the representative sample from the manual.
PANAS	The Positive and Negative Affect Schedule (PANAS) was administered before and after participants performed the experiment to measure mood changes through the DWM. It consists of 20 affective adjectives,10 positive and 10 negative, that are rated on a 4-point Likert scale (Crawford & Henry, 2004).
MWT-B	The Multiple Choice Word Fluency Test (MWT-B) was used to generate a approximate metric of intelligence (Lehrl, 2005). It consists of 37 rows of words, each of which contains only one correct word, the others are similar in appearance but have no semantic meaning. Participants have to mark that word and the number of correctly identified words constitute a general score that can then be converted into an IQ score.
Edinburgh Handedness Inventory	The Edinburgh Handedness Inventory was used to exclude left handed participants (Oldfield, 1971). The participant reports his preferences in using his left/right hand in every-day activities such as writing. The ratings are comprised in a score, a value below 70 was considered left-handed in this study.
STAI	The State-Trait Anxiety Inventory (STAI) questionnaire is a self-report measure consisting of 40 questions that are rated on a 4-point Likert scale (Spielberger, 1983). It assesses two facettes of anxiety. The A-state scale measures state, or the momentary anxiety, and the A-trait scale meausures trait anxiety, which reflects how anxious a person feels across different situations and times.
Digit Span	A computerized version of a digit span experiment as proposed by Sternberg was used as an approximate for a participant's working memory capacity (Sternberg, 1966). It was programmed and presented in Presentation. Participants saw a sequence of digits and were asked to repeat them. The sequence increased until the participant did not recall the digits correctly. The digit span was the maximum number of digits the participant was able to recall.

"*Two participants had to be excluded due to protocol violations, five because of problems with the EEG registration during tDCS, and due to excessive noise in the EEG data (see electrophysiological data processing). In total, 87 participants were included in the analysis (sham: N = 22, 0.5 mA: N = 22, 1 mA: N = 22, 1.5 mA: N = 21)"* (Faehling & Plewnia, 2016).

2.2. Experimental Design

*"In this single blinded, sham-controlled between-subjects design study, tDCS current intensity served as group variable with the levels sham stimulation, 0.5 mA, 1 mA and 1.5 mA. Each participant performed one DWM session with parallel anodal tDCS and EEG recording (see **Figure [7A]**). Participants were naïve to the exact purpose of the study. They were handed an information sheet at the beginning of the task, which informed them that they would participate in an experiment about attention and emotional processing, that very negative pictures would be involved and that they either would be stimulated with an electrical current or would receive sham stimulation. Importantly, participants were not aware as to which experimental condition they belonged to until after the experiment. Before they were informed whether they received stimulation, they completed a questionnaire to check if blinding was successful.*

2.3. Delayed Working Memory Task (DWM)

*The delayed working memory task was displayed on a 21-inch TFT monitor; participants sat approximately 50 cm away from the screen. The EEG recording device was connected to the monitor via photo diodes to measure the exact time of stimulus onset. The task was implemented using Presentation software (Neurobehavioral Systems, Inc., Albany, CA) and consisted of 10 training trials followed by 120 experimental trials. **Figure [7C]** depicts a sample trial from the DWM. At the beginning of the session, task instructions were given on the screen (see **Appendix A** for the exact text of the instructions). Each trial was preceded by a black screen inter-stimulus interval that jittered randomly between 1 and 1.5 s […]. Each trial then began with a white fixation cross displayed on a black background for one second. Next, a string of 8 letters was visible for 2.5 s, with*

white font on a black background. The letters were aligned in two rows of four letters and were selected randomly. A black screen was then displayed for 0.5 s. Next, a random picture of either negative or neutral content was shown for 5 s. Pictures filled the whole screen, displayed in color and each was shown only once for each participant. Next, a black screen appeared for 1 s. Then, a target letter was presented and the participant had to indicate whether the letter was part of the previously presented string by pressing the "f" key for "no" and the "j" key for yes on a commercial QUERTZ keyboard. Participants were always asked to use their right index finger to press "j" and the left to press "f", to avoid confounding effects of laterality. One trial lasted for 12 - 12.5 s.

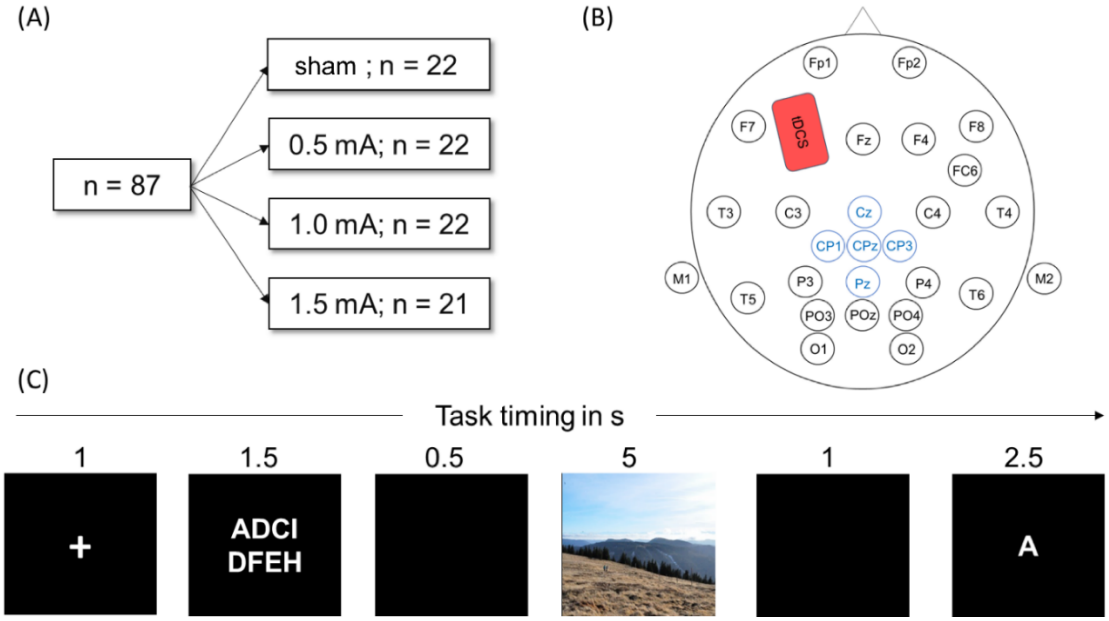

*Figure 7. "**(A)** Visualization of the experimental design. 87 healthy participants were randomly assigned to one of the four stimulation conditions. All performed the DWM. **(B)** Head map illustrating EEG and tDCS electrode placement used in this study. The anodal tDCS electrode (shown in red) was placed over F3, the cathode above the right deltoid muscle. Electrodes depicted in blue were averaged to obtain the LPP. **(C)** Schematic of one trial of the delayed working memory task (DWM). Eight letters (white on black ground) were presented and the participant had to memorize them. In a delay period, either a neutral or negative picture was shown. Next, a target letter was presented and the participant decided whether the letter was part of the string of eight letters by pressing a button. In total, the DWM comprised 80 of these trials" (Faehling & Plewnia, 2016)*. The figure is reprinted from Faehling & Plewnia (2016).

A trial was assessed as correct if the participant correctly identified whether or not the letter was part of the string seen before within the time window of 2.5 s. After every 10th trial, a black screen was shown for 15 s to let participants relax" (Faehling & Plewnia, 2016). In total, the experimental procedure lasted between 26 min 40 s to 27 min 40 s.

2.4. Stimulus Material

"*Pictures were taken from the International Affective Picture Scale (IAPS) database and normative ratings for the pictures were obtained from the online database of the IAPS. For the negative category, 40 highly arousing pictures with highly negative valence ratings were selected (Lang et al., 2008). Respectively, 40 pictures with low arousing ratings and medium valence ratings were taken for the neutral category*" (Faehling & Plewnia, 2016). See **Table 4** for the normative valence and arousal ratings of the selected pictures. "*For valence, negative pictures had significantly stronger negative ratings then neutral pictures (t(78) = -26.302, p<0.001). Ratings for arousal also differed significantly with negative pictures rated more arousing than neutral pictures (t(78) = 21.4882, p<0.001). Only scenes containing humans were used and the number of humans was matched between the categories. The negative pictures consisted of scenes of mutilated bodies (or parts of bodies such as injured hands), neutral pictures consisted of portraits of humans or everyday scenes (e,g. the inside of a supermarket). For the 10 training trials, additional 10 neutral pictures containing scenes without humans were selected (see **Appendix B** for a list of the selected pictures). Pictures were manually equated for luminance in Adobe Photoshop for Microsoft Windows. After completion of the experiment, participants rated each picture for valence and arousal on a 9-point Likert scale. The letters used in the DWM were presented at random or each trial using all 26 letters of the Latin alphabet*" (Faehling & Plewnia, 2016).

2.5. Electroencephalography Recording

"*Continuous EEG recording was performed according to standard procedure (Light et al., 2001) using an elastic cap (EASYCAP GmbH, Hersching, Germany) and the 32-channel EEG recordings system NEUROPRAX (NeuroConn GmbH, Illmenau, Germany). 25 electrodes were fixed on the scalp according to the international 10/20 system (see* ***Figure [7B]****). The locations of the electrodes were carefully cleaned with alcohol and cotton swabs to minimize resistance. Mastoid electrodes were positioned beneath each earlobe on the mastoid bone. Eye-electrodes were positioned approximately 1 cm below and above the right eye for the vertical eye movement recordings and 1 cm to the right side of the right eye and the left side of the left eye for horizontal eye movement recordings" (Faehling & Plewnia, 2016).*

Table 4

Mean values of arousal and valence normative ratings for the IAPS pictures used in the present study

	Arousal		Valence	
Negative pictures	6.71	*(2.17)*	1.59	*(1.06)*
Neutral pictures pictures	3.53	*(1.995)*	5.06	*(1.44)*

Note. Values in the table are taken from the IAPS manual (Lang et al., 2008). Ratings were performed on a nine-point Likert scale. For arousal, the scale ranged from 1 ("not at all arousing") to 9 ("very arousing") ; for valence, the scale ranged from 1 ("very negative") to 9 ("very positive"). Standard deviation is displayed in brackets.

2.6. Transcranial Direct Current Stimulation

"Except in the sham-group, anodal tDCS was applied for the whole duration of the experiment with a battery driven stimulator (NeuroConn GmbH, Illmenau, Germany) via a pair of plastic electrodes (35 cm^2 surface area) that were connected to the skin with conductive paste.

To target the left dorsolateral prefrontal cortex (DLPFC), the anodal electrode was placed on the scalp at F3 according to the international 10-20 system of electrode placement (see ***Figure [7B]****) and the reference electrode placed on the contralateral right deltoid muscle. The scalp electrode was placed under the elastic electrode cap and sufficiently fixated by the conductive paste. Stimulation was turned on after the training block and the task was started 1 min later. The current was ramped up and down for 10 s at the beginning and the end of stimulation. The impedance of the electrodes was always below 10 kΩ. The maximum duration of stimulation was 28 min, depending on the length of the randomly jittering pauses in between trials. For the sham condition, a current of 1 mA was ramped up and down for 10 s but only maintained for 30 s. This produces the same tingling sensation but does not induce sustaining effects on cortical activation (Ambrus et al., 2012; Palm et al., 2013)"* (Faehling & Plewnia, 2016). The experimenter was aware of the stimulation condition to ensure the EEG - tDCS setup worked properly.

2.7. Data Processing

"*Reaction time (RT) was measured as the time in milliseconds (ms) between picture onset and keypress. Reaction times that exceeded standard deviation (SD) by a factor of 2 were excluded. […] Mean accuracy (AC) was calculated as the proportion of correct responses [divided by …] the total number of responses. […] EEG data analysis was performed with the MATLAB (MATLAB and Statistics Toolbox Release 2012a, The MathWorks, Inc., Natick, Massachusetts, United States) based EEGLAB toolbox (Delorme & Makeig, 2004) and the EEGLAB toolbox ERPLAB (Lopez-Calderon & Luck, 2014). Raw EEG data were referenced to an average of mastoid electrodes on the left and right side. Band-pass filters with a low and high cut-off at 0.1 and 35 Hz, respectively, and a notch-filter at 50 Hz were applied. Eye blink correction was performed using the ICA-approach implemented in EEGLAB. Stimulus-locked trials were extracted ranging from 200 ms to 1000 ms relative to stimulus (i.e picture) onset. The 200 ms pre-stimulus time served as a baseline (Urbach & Kutas, 2006). A semi-automated*

artifact correction procedure was then used: Trials with a voltage step of > 50 µV between sample points, > 200 µV within a trial or > 50 µV within a 100 ms window were excluded using ERPLAB algorithms. Data were visually inspected to remove remaining artefacts. One subject was excluded after artefact detection as > 95 % of trials were rejected by the algorithm. […]

*The LPP was scored as an average from five centro-parietal sites where it was maximal in earlier studies (Hajcak, Dunning, & Foti, 2009; MacNamara et al., 2011): Pz, CPz, Cz, CP1 and CP2 [see blue electrodes in **Figure 7B**]. Following the literature on the time course of the LPP [(Dennis & Hajcak, 2009)], [the LPP was] divided in two time windows, adjusting the limits following visual curve inspection: An early window [named early LPP = **eLPP**] from 250 ms to 500 ms and a late window [named late LPP= **lLPP**] from 500 ms to 1000 ms after picture onset were selected. Trials were separated for the two picture valence categories (negative, neutral). In that way, two ERP curves per participant were generated, each consisting of an average of up to 40 stimulus-locked curves. For analysis of picture valence differences, ERP curves of all participants were then averaged. To examine stimulation effects, ERP curves for each stimulation condition were generated. […The] LPP [was measured] using the mean amplitude measurement of ERPLAP, calculating the mean amplitude for eLPP between 250-500 ms and for lLPP between 500 - 1000 ms (for a review of alternative measurements, see Luck, (2014)).*

2.8. Data Analysis

*Statistical analyses were performed with SPSS Statistics for Microsoft Windows (version 22.0). To separately account for the influence of distraction and tDCS, data from the four experimental groups were analyzed in two steps. First, […] the effects of picture valence on behavioral and electrophysiological measures in the **sham group** alone [was examined]. Then, the influence of different tDCS intensities was investigated by analysis of the **complete sample** comprising the sham, 0.5 mA, 1.0 mA, and 1.5 mA tDCS conditions.*

Paired t-tests were performed on RT, AC, eLPP, and lLPP to examine differences between negative and neutral distractor trials for the sham-stimulated subjects.

For the complete sample, a repeated measures analysis of variance (ANOVA) was conducted on RT, AC, eLPP and lLPP with valence (negative/neutral) as within-subjects factor and stimulation (sham, 0.5 mA, 1 mA, 1.5 mA) as between-subjects factor. To investigate the general association between DWM performance and brain activity [... the Pearson product-moment correlation coefficient was computed between] the LPP amplitudes and RT for negative and neutral distractors in the sham group and the complete sample.

Lastly, to examine valence-specific effects, a difference score (Δ) was calculated for RT and LPP subtracting measures of trials with neutral pictures from trials with negative pictures ($\Delta RT_{neg\text{-}neu} = RT_{neg} - RT_{neu}$, $\Delta LPP_{neg\text{-}neu} = LPP_{neg} - LPP_{neu}$,). The relationship between the amount of distraction induced by the negative valence of pictures and the corresponding valence-specific brain activity was determined by the [… Pearson product-moment correlation coefficient] *between $\Delta RT_{neg\text{-}neu}$ and the $\Delta LPP_{neg\text{-}neu}$ ($\Delta eLPP_{neg\text{-}neu}$ and $\Delta lLPP_{neg\text{-}neu}$). These analyses were performed for the sham group and the complete sample including the different tDCS intensities"* (Faehling & Plewnia, 2016).

3. Results

3.1. Characteristics of the Study Population

"*All participants were right handed healthy female (under)graduate students with normal or corrected to normal vision"* (Faehling & Plewnia, 2016). **Table 5** details the characteristics of the study population, separated by stimulation condition. As can be drawn from the table, there were no significant differences between the groups for any of the examined variables.

Table 5

Mean values of demographic data and questionnaire results of the study population

	Total	Sham	0.5 mA	1.0mA	1.5mA	*F*	*p*
N	87	22	22	22	21		
Age	23.85 *(3.03)*	24.68 *(3.38)*	23.86 (*3.40*)	22.91 (*2.24*)	23.95 (*2.95*)	1.285	*0.285*
Smoker *%*	17	22	18	13	14	0.306	*0.891*
Contra-ceptive *%*	66	77	63	63	62	0.441	*0.620*
Digit Span	5.36 *(1.28)*	5.14 *(.318)*	5.64 *(0.953)*	5.36 *(1.62)*	5.29 (0.91)	0.603	*0.615*
Handedness	84.04 *(17.86)*	87.70 *(3.12)*	87.405 *(15.08)*	80.56 *(20.02)*	79.95 *(21.25)*	1.190	*0.319*
MWTB IQ	103.05 *(11.55)*	102.73 *(10.37)*	101.91 *(10.71)*	105.77 *(12.4)*	101.71 *(12.93)*	0.570	*0.636*
STAI Trait	34.81 *(8.58)*	35.86 *(8.83)*	37.90 (7.84)	33.38 *(8.45)*	32.05 *(8.69)*	1.830	*0.148*
STAI State	31.52 *(6.47)*	32.27 *(1.57)*	33.1 *(7.15)*	31.05 *(6.18)*	29.62 *(4.71)*	1.042	*0.378*
GSI SCL-90-R	48.52 *(8.98)*	49.37 *(8.08)*	50.03 *(8.5)*	48.85 *(10.97)*	45.72 *(7.99)*	0.964	*0.414*

Note. F and *p* values are from one way ANOVA testings for differences between the experimental groups with stimulation as a factor. Standard deviation is shown in brackets.

3.2. Behavioral Results

By discarding trials without responses and those where reaction times (RT) exceeded two standard deviations of all data, 6.21 % (SEM = 0.29%) of trials containing negative and 6.47 % (SEM = 0.37%) containing neutral pictures were rejected. *"The number of trials rejected did not vary significantly for valence (F(1,83) = 0.388, p = 0.563) or stimulation (F(3,83) = 0.382, p = 0.766) nor was there an interaction effect (F(3,83) = 1.312, p = 0.276). […]*

*In subjects that received **sham** tDCS no differences between negative and neutral distractor trials were found in respect to RT (t(21) = 1.164, p = 0.258) and AC (t(21) = -0.126, p = 0.901). Analysis of the **complete sample** (sham, 0.5, 1.0, and 1.5 mA tDCS) revealed a main effect of valence on RT (F(1,83) = 3.943, p = 0.050).*

Table 6

"Mean values of reaction time (RT) and accuracy (AC) in the DWM separately for stimulation intensity

	Total		*Sham*		*0.5 mA*		*1.0mA*		*1.5mA*	
N	*87*		*22*		*22*		*22*		*21*	
RT negative	*1170.90*	*(21.73)*	*1135.21*	*(34.23)*	*1213.46*	*(42.21)*	*1164.88*	*(45.87)*	*1170.02*	*(51.81)*
RT neutral	*1151.04*	*(20.25)*	*1110.98*	*(34.62)*	*1206.59*	*(42.62)*	*1117.34*	*(38.04)*	*1170.09*	*(45.57)*
AC negative	*79.66*	*(0.76)*	*81.48*	*(1.49)*	*79.20*	*(1.61)*	*80.11*	*(1.78)*	*77.77*	*(1.02)*
AC neutral	*80.89*	*(0.81)*	*81.70*	*(1.74)*	*80.91*	*(1.66)*	*81.59*	*(1.43.)*	*79.29*	*(1.72)*

Note. RT measured in milliseconds, AC in per cent (%). Standard error of the mean (SEM) is shown in brackets" (Faehling & Plewnia, 2016).

Subjects responded slightly faster in trials with neutral pictures (M = 1151.04 ms, SEM = 20.254) than in trials with negative pictures (M = 1170.90 ms, SEM = 21.729, see ***Table 6****). However, there was no significant effect of stimulation intensity (F(3,83) = 0.869, p = 0.461) and no interaction between picture valence and stimulation intensity (F(3,83) = 1.149, p = 0.334)"* (Faehling & Plewnia, 2016). On a descriptive level of analysis, a significant difference between reaction times for trials with negative vs. neutral pictures in the 1.0 mA condition was confirmed by paired t-test ($t(21) = -2.226$, $p = 0.037$). "*For AC, there was no main effect of valence (F(1,83) = 1.793, p = 0.184), no effect of stimulation intensity (F(1,83) = 1.05, p = 0.374) and no interaction between valence and stimulation intensity (F(3,83) = 0.137, p = 0.938)"* (Faehling & Plewnia, 2016). See **Table 6** for additional data.

3.3. Analysis of the Late Positive Potential (LPP)

3.3.1. Artifact Rejection and EEG Topography

Table 7 shows the percentage of rejected trials across stimulation conditions. *"In sum, 3221 negative and 3216 positive picture trials were included in the ERP analysis. The number of rejected trials did not vary significantly for negative vs.*

neutral pictures (F(1,83) = 0.051, p = 0.823). A significant effect was found for stimulation (F(3,83) = 106.002, p = 0.007)" (Faehling & Plewnia, 2016), with more trials rejected in the groups receiving stimulation. No interaction effect between valence and stimulation was found (*F(1*,83) = 0.847, *p* = 0.472).

Table 7

"Rejected EEG trials in per cent (%) separately for valence and stimulation intensity

	Total		*Sham*		*0.5mA*		*1 mA*		*1.5mA*	
Negative pictures	*7.44*	*(0.78)*	*5.57*	*(1.13)*	*6.70*	*(1.72)*	*5.45*	*(1.02)*	*12.26*	*(1.88)*
Neutral pictures	*7.59*	*(0.85)*	*4.66*	*(1.02)*	*7.84*	*(1.74.)*	*6.48*	*(1.39)*	*11.55*	*(2.26)*

Note. Standard error of the mean (SEM) is shown in brackets" (Faehling & Plewnia, 2016).

"*Figure [8]* *displays the grand average waveforms of the LPP for the sham* ***(A)****, 0.5 mA* ***(B)****, 1 mA* ***(C)*** *and 1.5 mA* ***(D)*** *experimental groups"* (Faehling & Plewnia, 2016) and the mean voltage distribution across the scalp for negative-neutral picture trials for the eLPP and lLPP. On a descriptive level, the voltage distributions show that the LPP was maximal at centro-parietal sites during the measurement windows. Of note, the impression of a frontal left-right asymmetry on the voltage distribution figures (**Figure 8 A-D**) resulted from the tDCS electrode placement at F3 which prevented EEG being measured at F3.

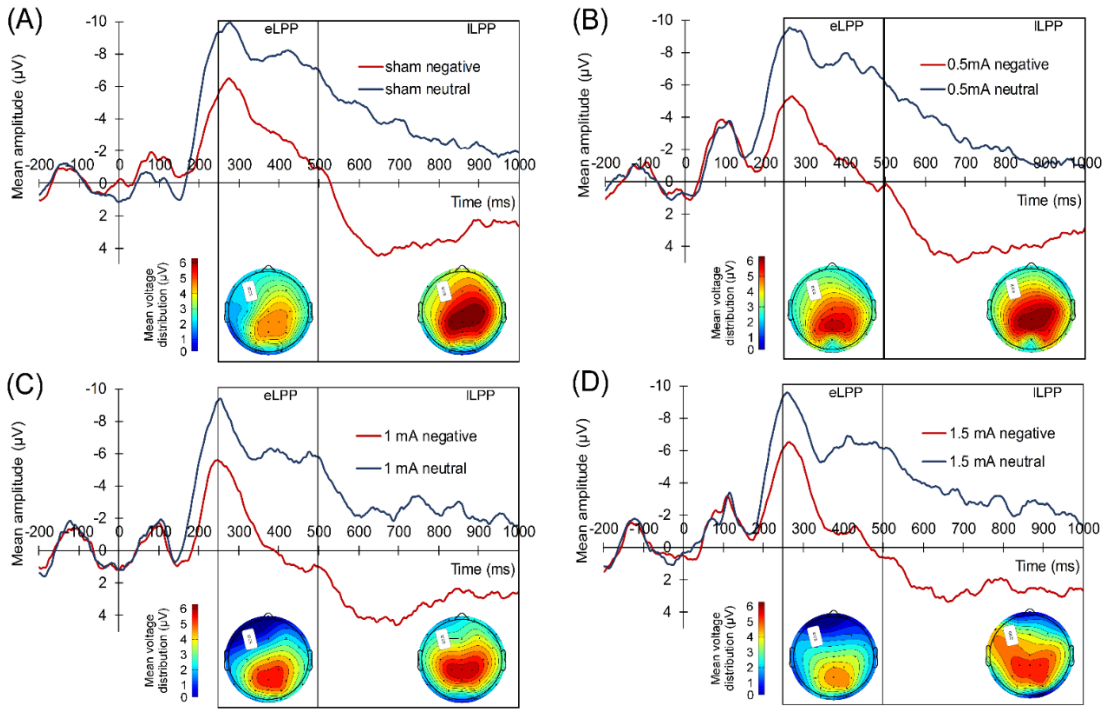

Figure 8. "Grand-averaged LPP waves separately for the experimental conditions. ***(A)*** *displays the sham,* ***(B)*** *the 0.5mA,* ***(C)*** *the 1mA and* ***(D)*** *the 1.5mA condition. Below each graph, there are two scalp maps displaying the mean voltage distribution for negative-neutral picture trials for the eLPP (250-500 ms) and lLPP (500-100 ms) time windows"* (Faehling & Plewnia, 2016). The figure is reprinted from Faehling & Plewnia (2016).

3.3.2. Early LPP (eLPP)

"*In the* ***sham group****, the difference between the eLLP amplitudes exerted by negative (M = -3.531, SEM = 1.192) and neutral pictures (M = -8.166, SEM = 1.002) was highly significant (t(21) = 7.318, p<0.001[, see* ***Table 8****]). A negative correlation was found between RT and eLPP to negative (r(20) = -0.512, p = 0.015) but not to neutral (r(20) = -0.365, p = 0.148[, see* ***Table 9****]) stimuli. Consistently, a negative correlation (r(20) = -0.429, p = 0.046 [, see* ***Figure 9A****]) between valence-specific brain activity (*$\Delta eLPP_{neg\text{-}neu}$*) and the distraction by negative stimuli (*$\Delta RT_{neg\text{-}neu}$*) indicated that the amount of additional eLPP activity elicited by negatively valenced pictures is linked with a less distractive or even beneficial influence of negative information on DWM performance.*

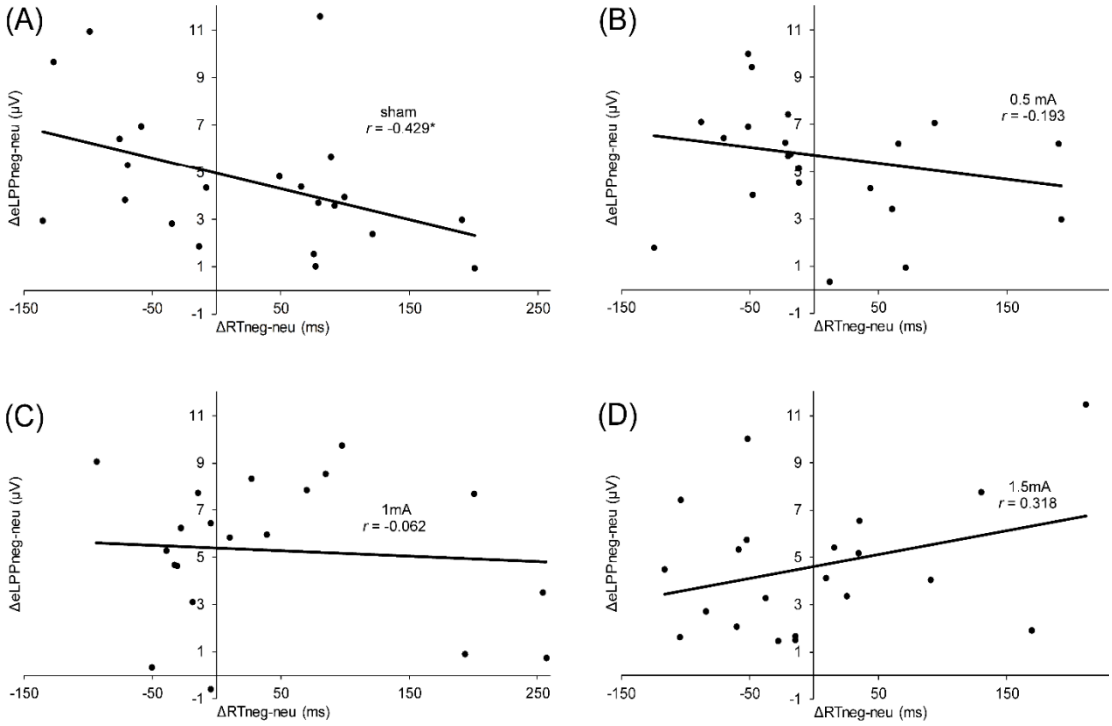

*Figure 9. "Scatter plots illustrating the correlation between ΔRT$_{neg-neu}$ and ΔeLPP$_{neg-neu}$ in the sham **(A)**, 0.5 mA **(B)**, 1 mA **(C)** and 1.5 mA **(D)** experimental conditions. In the sham group, the correlation was significant (* p = 0.046), while for the other experimental conditions no significant effect was found (0.5 mA: p = 0.389; 1 mA: p = 0.784; 1.5 mA: p = 0.160)"* (Faehling & Plewnia, 2016). The figure is reprinted from Faehling & Plewnia (2016).

*Analysis of the **complete sample** again showed a higher eLPP amplitude associated with negative as compared to neutral pictures (F(1,83) = 230.141, p<0.001, see **Table [8]**). However, no main effect of stimulation on the amplitude of eLPP (F(3,83) = 0.589, p = 0.624) was found and the valence by stimulation interaction was not significant (F(3,82) = 0.578, p = 0.631). In the complete sample, no correlation was found between RT and eLPP to negative or neutral stimuli [see **Table 9**]. Correspondingly, no correlation between ΔeLPP$_{neg-neu}$ and ΔRT$_{neg-neu}$ was present neither in the whole sample […] nor in the individual stimulation groups [… see **Figure 3 B-D**, **Table 10]**. But however, adding stimulation to the task leads to a linear modulation of correlation coefficients with increasing intensities (r(2) = 0.980, p = 0.020)"* (Faehling & Plewnia, 2016).

Table 8

"Mean amplitudes for eLPP and lLPP (in µV)

	Total		*Sham*		*0.5 mA*		*1.0mA*		*1.5mA*	
N	*87*		*22*		*22*		*22*		*21*	
eLPP negative	*-2.21*	*(0.64)*	*-3.53*	*(1.19)*	*-2.03*	*(1.34)*	*-1.07*	*(1.38)*	*-2.20*	*(1.24)*
eLPP neutral	*-7.26*	*(0.55)*	*-8.17*	*(1.002)*	*-7.68*	*(1.16)*	*-6.36*	*(1.06)*	*-6.83*	*(1.23)*
lLPP negative	*3.06*	*(0.55)*	*2.98*	*(0.98)*	*3.61*	*(1.26)*	*3.18*	*(1.15)*	*2.44*	*(1.09)*
lLPP neutral	*-2.97*	*(0.47)*	*-3.42*	*(0.89)*	*-2.63*	*(0.86)*	*-2.63*	*(0.92)*	*-3.21*	*(1.10)*

Note. Standard error of the mean (SEM) is shown in brackets" (Faehling & Plewnia, 2016).

Table 9

Correlation coefficents between mean reaction times (RT) and eLPP amplitudes for trials with negative and neutral pictures

	eLPP									
	Total		Sham		0.5 mA		1 mA		1.5 mA	
	Neg	Neu	Neg	Neu	Neg	Neu	Neg	Neu	Neg	Neu
RT negative	-0.18	-0.22	-0.51*	-0.40	-0.08	-0.03	-0.33	-0.30	-0.04	-0.18
RT neutral	-0.15	-0.19	-0.31	-0.32	-0.04	-0.03	-0.32	-0.29	-0.01	-0.20

Note. * $p < 0.05$.

Concerning the relationship between the eLPP and accuracy, neither in the **sham group** nor in the **compete sample** a significant correlation was found. A positive correlation between $\Delta eLPP_{neg\text{-}neu}$ and $\Delta AC_{neg\text{-}neu}$ in the 0.5 mA condition ($r = 0.43$, $p = 0.046$). See **Appendix C** for the correlations between eLPP and accuracy.

Table 10

Correlation coefficients between ΔRT $_{neg\text{-}neu}$ and ΔeLPP $_{neg\text{-}neu}$ separately for all experimental conditions

	ΔeLPP $_{neg\text{-}neu}$									
	Total		Sham		0.5mA		1 mA		1.5 mA	
ΔRT $_{neg\text{-}neu}$	-0.09	*(0.39)*	-0.43*	*(0.05)*	-0.19	*(0.39)*	-0.06	*(0.78)*	0.31	*(0.16)*

Note. * p< 0.05; p values are shown in brackets.

3.3.3. Late LPP (lLPP)

"*In the **sham group**, the lLPP amplitude was significantly higher (more positive) for negative (M = 2.979, SEM = 0.978) than for neutral (M = -3.423, SEM = 0.894) pictures (t(21) = 9.305, p < 0.001). The correlations between RT and lLPP to negative (r(20) = -0.311, p = 0.159) and neutral (r(20) = -0.365, p = 0.095) stimuli and between ΔlLPP$_{neg\text{-}neu}$ and ΔRT$_{neg\text{-}neu}$ (r(20) = -0.274, p = 0.217) were not significant in the sham group.*

Table 11

Correlation coefficients between mean reaction times (RT) and lLPP amplitudes for trials with negative and neutral pictures.

	lLPP									
	Total		Sham		0.5 mA		1 mA		1.5 mA	
	Neg	Neu	Neg	Neu	Neg	Neu	Neg	Neu	Neg	Neu
RT negative	-0.26*	-0.25*	-0.31	-0.29	-0.20	-0.11	-0.48*	-0.41	-0.11	-0.23
RT neutral	-0.25*	-0.25*	-0.25	-0.37	-0.16	-0.13	-0.54*	-0.42	-0.11	-0.20

Note. * p < 0.05.

*For the **[complete] sample**, the amplitude of the lLPP following negative pictures was higher than for neutral picture trials (F(1,83) = 322.773, p < 0.001, see **Table [8]**). No significant effect of tDCS on the amplitude of lLPP was found (F(3,83) = 0.174, p = 0.914) and there was also no significant valence by stimulation interaction (F(3,83) = 0.272, p = 0.845). However, across all participants, RT and lLPP were significantly correlated negatively both for negative (r(85) = -0.259, p = 0.015) and neutral picture trials (r(85) = -0.254, p = 0.018, see **Table 11**). Correspondingly, for $\Delta RT_{neg\text{-}neu}$ and $\Delta lLPP_{neg\text{-}neu}$, no relationship was found in the complete sample (r(85) = -0.077, p = 0.479) and any of the stimulation conditions [see **Table 12**]*" (Faehling & Plewnia, 2016). Concerning the relationship between the lLPP and accuracy, neither in the **sham group** nor in the **compete sample**, a significant correlation was found. See **Appendix C** for the correlations between lLPP and accuracy.

Table 12

Correlation coefficients between $\Delta RT_{neg\text{-}neu}$ *and* $\Delta lLPP_{neg\text{-}neu}$ separately for all experimental conditions

	$\Delta lLPP_{neg\text{-}neu}$									
	Total		Sham		0.5mA		1 mA		1.5 mA	
$\Delta RT_{neg\text{-}neu}$	-0.07	*(0.48)*	-0.27	*(0.22)*	-0.29	*(0.2)*	-0.06	*(0.79)*	0.43	*(0.29)*

Note. * p < 0.05; p values are shown in brackets.

3.4. Impact of Anxiety

To investigate the mediating impact of anxiety on the electro-cortical responses, correlations between the trait anxiety (A-trait) scale and the difference values for $\Delta elLPP_{neg\text{-}neu}$ and $\Delta lLPP_{neg\text{-}neu}$ were performed. For $\Delta elLPP_{neg\text{-}neu}$, the correlation with A-trait was non-significant in the **sham group** as well as in the **complete sample**. A significant correlation was found in the 0.5 mA condition.

For the ΔlLPP$_{neg-neu}$, no significant correlation was found in the **sham group** and a significant positive correlation with A-trait was found in the **complete sample** (see **Table 13**).

Table 13

Correlation coefficients between A-trait scores and ΔeLPP $_{neg-neu}$ and ΔlLPP $_{neg-neu}$

	A-trait									
	Total		Sham		0.5mA		1 mA		1.5 mA	
N	85		21		22		22		21	
ΔeLPP $_{neg-neu}$	0.20	*(0.06)*	0.34	*(0.12)*	0.48*	*(0.03)*	0.06	*(0.8)*	-0.06	*(0.78)*
ΔlLPP $_{neg-neu}$	0.22*	*(0.04)*	0.31	*(0.16)*	0.42	*(0.06)*	0.27	*(0.23)*	-0.32	*(0.16)*

Note. * p < 0.05; p values are shown in brackets. Two participants did not fill out the STAI questionnaire.

3.5. Participants' Mood Changes

"*Participants' mood ratings, as reflected by the PANAS, changed significantly before and after DWM task performance [See **Figure 10**].*

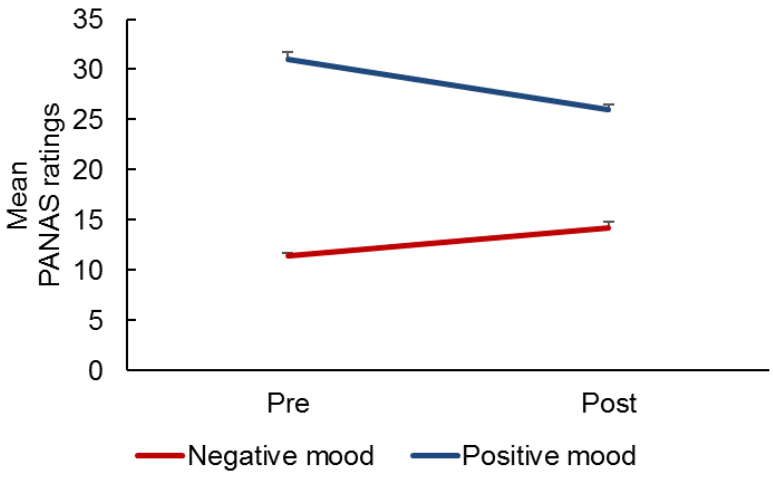

Figure 10. Participants' (N = 85) mood ratings as measured by the Positive and Negative Affect Schedule (PANAS) before (pre) and after (post) the delayed working memory task. Score were computed as a sum of 20 ratings on adjectives,10 for negative and 10 for positive mood, with a scale from 1 ("not at all") to 5 ("extremely"). Error bars indicate standard error of the mean.

After the experiment, mood was rated less positive (before: M = 31.02, SEM = 0.63; after: M = 26.05, SEM = 0.76; F(1,82) = 64.342, p<0.001) and more negative (before: M = 11.45, SEM = 0.28; after M = 14.17, SEM = 0.54; F(1,82) = 26.205, p<0.001). There was no main effect for stimulation on positive (F(3,82) = 0.661, p = 0.579) or negative mood ratings (F(3,82) = 0.669, p = 0.573).

3.6. Reports on Side Effects of tDCS and Manipulation Check

*Apart from a tingling sensation at the beginning of the session, no unpleasant side effects were reported. Blinding of stimulation condition was successful. Participants' conjecture of whether or not they receive tDCS during the task did not exceed chance level (see **Table [14]**).*

Table 14

***"**Perceived stimulation by participants in per cent (%)*

		Actual Stimulation				
		Total	*Sham*	*0.5mA*	*1 mA*	*1.5mA*
	N	*87*	*22*	*22*	*22*	*21*
Perceived Stimulation	*Sham*	*64.38*	*45.45*	*72.72*	*63.63*	*76.19*
	Verum	*35.62*	*54.55*	*27.27*	*36.36*	*23.81*

" (Faehling & Plewnia, 2016).

3.7. Participants' Valence and Arousal Ratings of the Distractive Stimuli

A significant effect was found for participants' valence ratings [of IAPS pictures that served as distractive stimuli in the DWM] (F(1,81) = 705.030, p < 0.001). Negative pictures (M = 2.14, SD = 0.89, rated on a 1 - 9 scale ranging from 1 "very negative" to 9 "very positive") were rated more negative compared to neutral pictures (M = 5.64, SD = 0.73). For arousal it was found that negative pictures (M = 6.97, SD = 1.45) were rated significantly more arousing than neutral (M = 4.19,

SD = 1.29) pictures (F(1,80) = 268.681, p < 0.001)" (Faehling & Plewnia, 2016). See **Figure 11** and **Table 15**.

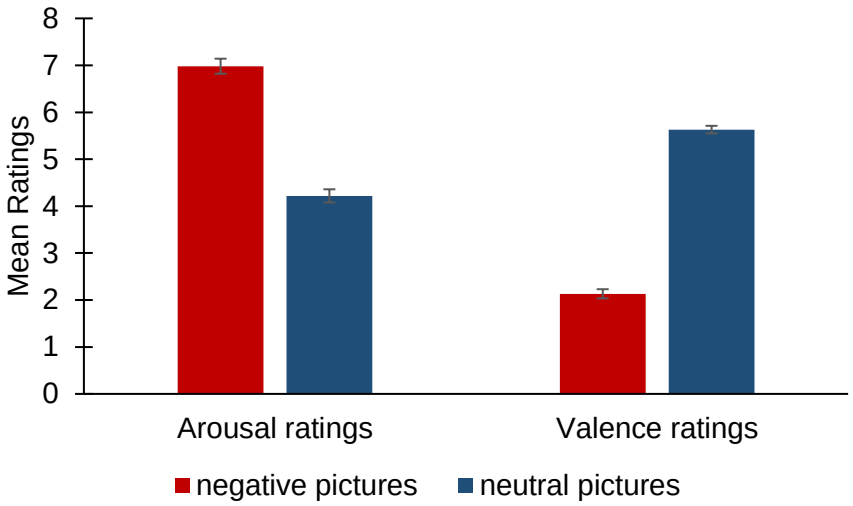

Figure 11. Participants' ratings of IAPS pictures for arousal and valence. Error bars mark standard error of the mean (SEM). The scale for arousal ranged from 1 ("not at all arousing") to 9 ("very arousing") and respectively for valence from 1 ("very negative") to 9 ("very positive").

Table 15

Mean values of arousal and valence ratings of IAPS pictures

	Arousal		Valence	
Negative pictures	6.97	*(1.45)*	2.14	*(0.89)*
Neutral pictures	4.19	*(1.29)*	5.64	*(0.73)*

Note. The ratings of three participants were missing because of technical problems. Standard deviation is shown in brackets.

4. Discussion

This study systematically assessed the effect of anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC) on the performance of healthy participants in a delayed working memory task (DWM) and the electro-cortical response elicited by distracting pictures. Parametric effects of tDCS intensity on cognitive control were investigated by using three different stimulation intensities. The study was methodologically innovative in using parallel EEG recording alongside tDCS to track online effects of stimulation. Key findings were 1) a negativity bias was present, but only when the complete sample is considered, "*[2)] without tDCS, higher valence-specific neur[on]al activation as indicated by the early phase of the LPP (ΔeLPP$_{neg-neu}$) [was] associated with less distraction by negative pictures (ΔRT$_{neg-neu}$), [3)] tDCS exert[ed] an intensity-dependent influence on this correlation, and […] a stimulation and valence-independent correlation [was] present between the later phase of the LPP (lLPP) and RT performance […, 4)] further effects of tDCS on [working memory] (WM) performance, distraction by emotional stimuli or LPP amplitudes could not be identified"* (Faehling & Plewnia, 2016).

4.1. Negativity Bias is Present Only in the Complete Sample

A negativity bias, as a sign of dysfunctional cognitive control, is thought to play a major role in the pathogenesis of depression (Plewnia et al., 2015) and has been found to be present in depressed subjects performing a delayed working memory task (Wolkenstein & Plewnia, 2013). In the present study, it was attempted to modify the DWM, so that a negativity bias would be present in healthy subjects. To this end, highly negative pictures were used in the negative picture condition and the number of letters was increased from six to eight. A valence-specific bias was visible in the **complete sample** for reaction time (RT). However, the effect was not seen in the single experimental groups and therefore, importantly, not in the **sham** condition. **Hypothesis IA** (see **chapter 1.5**) was not supported. Of note, with a lack of bias in the sham group, the probability of finding a systematic effect of tDCS was obviously diminished (see **chapter 4.4**). The negativity bias was reflected in both the early and late portion of the LPP (supporting

Hypothesis IB). The main effect of valence in the LPP replicated numerous previous findings on LPP modulations associated with salient stimuli (Hajcak, MacNamara, et al., 2010; Schupp et al., 2000). Accuracy was not affected by the presentation of negative stimuli. This may indicate that, although emotional distraction slowed the response of the participants in the **complete sample**, their cognitive system could cope with the distraction and prevent an impairment of accuracy. This is similar to the results of Wessa et al., who found that distracting emotional stimuli affected response time while not impacting accuracy (Wessa et al., 2013). In their study, this was accompanied by an increase of activity in task relevant brain regions.

4.2. The early LPP (eLPP): Neurophysiological Signature of Cognitive Control?

A key and novel finding of this study was the negative correlation between the valence-specific difference values of the eLPP and RT ($\Delta eLPP_{neg\text{-}neu}$ and $\Delta RT_{neg\text{-}neu}$). Importantly, the effect was only visible in the **sham** group. Additionally, the correlation between the amplitude of eLPP and RT was significant for negative but, importantly, not for neutral trials. This supports the hypothesis that valence-specific brain activity, as reflected by the eLPP, and the following behavioral response are related in the healthy brain (**Hypothesis II)**. The data in *"the **sham** stimulation group suggest the recruitment of additional neuronal activation as signified by a higher eLPP amplitude to compensate the influence of distracting negative information allowing for goal-directed performance. The corresponding correlation between $\Delta RT_{neg\text{-}neu}$ and $\Delta eLPP_{neg\text{-}neu}$ demonstrates that the presentation of negative pictures during the maintenance phase of the WM tasks can, in different subjects, both interfere and enhance performance. According to **Figure [9A]**, subjects with a mean negativity-related eLPP increase of less than 5 µV (as indicated by the y-intercept) were distracted by negative pictures but those with a larger valence-specific eLPP increase reacted faster in trials with negative pictures. These findings are in agreement with the existing literature on emotion-cognition interaction. It is well known that emotion can facilitate ongoing task performance by recruiting common resources [(Egner & Hirsch, 2005; Okon-Singer et al., 2015)], which is especially true for low-threat stimuli (Pessoa, 2009)*

[…]. For instance, Wessa et al. (2013) found augmented task related activation in the presence of distracting emotional stimuli in cerebral regions that were identified to be task relevant. [Two studies using the LPP as a neuronal marker found that larger LPP amplitudes may correspond with faster reaction times (Bamford et al., 2015; Moser et al., 2010). …] Together with these findings, [the present] results add evidence that the LPP [in a time window between 250-500 ms] also indexes processes which are necessary for task performance in behavioral tasks involving emotional information" (Faehling & Plewnia, 2016). This can be interpreted as a neurophysiological signature of cognitive control of emotion. Along these lines, Dennis and Hajcak found that the valence-specific LPP amplitude in a similar time window (300 - 500ms) was associated with reduced anxious depressed symptoms in children (Dennis & Hajcak, 2009).

Still, *"[the direction of the correlation …] contrasts with previous findings suggesting that high LPP amplitudes indicate high attentional involvement with a distractive stimulus resulting in poorer task performance [in a subsequent task] (Weinberg & Hajcak, 2011)"* (Faehling & Plewnia, 2016). Accordingly, in this study, the correlation was expected in the other direction (**Hypothesis II**). *"[However …,] it must be considered that in [the present] study the distractor was presented not before [as it was in the study by Weinberg and Hajcak], but during memory maintenance. Therefore, the beneficial effect of enhanced activation as reflected by a larger eLPP shown in our study is consistent with the concept of an additional recruitment of executive processes by emotional content [(Egner & Hirsch, 2005; Wessa et al., 2013)]. Remarkably, this process can, at least in some subjects, lead to an enhanced RT performance by distractive negative stimuli."* (Faehling & Plewnia, 2016). Dunning and Hajcak reported a reduction of the LPP amplitude in participants who actively focused on less arousing parts of negative pictures (Dunning & Hajcak, 2009). They concluded that the reduced LPP amplitude signaled a decrease in attentional resources towards the pictures. However, their data does not contradict the interpretation of the LPP exposed in this dissertation. By focusing on less arousing less resources may have been necessary and this could have been reflected in a decrease in LPP amplitude. Hajcak and colleagues found a reduction of the LPP through electrical stimulation

and argued that this entailed less distractibility from the pictures (Hajcak, Anderson, et al., 2010). Of note, they employed a passive viewing paradigm, which as explained above makes it difficult to draw an analogy to the results presented here.

4.3. Valence Independent Correlation Between Reaction Time and late LPP (lLPP)

"*Regarding the lLPP, [this study] found a comparable correlation between amplitude and RT performance but in this case unaffected by the emotional content (i.e. lLPPs elicited by negative and neutral pictures […] both correlated [negatively] with RT-performance [while] emotion-specific activity (ΔlLPP) and RT (ΔRT) [did] not correlate [… significantly]. This finding further exemplifies that the amount of brain activation associated with distractive pictures during the maintenance phase of a WM task is critical for performance. [Moreover], these data are also consistent with evidence that brain activity reflected by the lLPP is affected by cognitive demand, for instance memory load […] (MacNamara et al., 2011; Van Dillen & Derks, 2012), with higher load being associated with lower LPP amplitudes, both for negative and neutral distractive pictures. As [this study] used an inter-subject design, the findings may be attributed to the inter-individual variability in WM capacities. Relatively low individual WM load might be reflected by shorter RT and associated with larger lLPPs to distractive pictures. In turn, relatively high individual WM load presenting with longer RTs were linked with lower lLPPs. Since the attenuating effect of WM load has been demonstrated with positive as well as negative distractors (MacNamara et al., 2011), it is consistent that in the data presented here, emotional valence had no differential influence"* (Faehling & Plewnia, 2016).

4.4. Effects of tDCS on Cognitive Control

There is a lack of stimulation studies examining the effect of varying stimulation intensity (Brunoni et al., 2012). This study aimed to fill this gap by analyzing the effect of three different current intensities (0.5 mA, 1 mA and 1.5 mA) in a sham-controlled, single blinded, between-groups design. It was hypothesized that tDCS would lead to faster RTs and increased AC in trials with negative vs. positive

distractors in the stimulation groups contrasted with the sham group (**Hypothesis IIIA**) and a reduction in the valence-specific LPP (**Hypothesis IIIB**). This effect was hypothesized to be intensity related (**Hypothesis IV**). Neither hypothesis was supported by the data. Stimulation as a main factor had no effect on RT or the LPP, nor did there emerge a significant difference between the stimulation groups. As already stated above, a *"plausible explanation for the lack of significant effects is the rather weak negativity bias that was detected in the complete sample but* [*not in the single experimental groups]. Naturally, an absent bias cannot be ameliorated. However, the only minimal distraction by negative pictures suggests that healthy subjects are mostly able to compensate for the influence of these stimuli. Accordingly, adding anodal tDCS to basically intact cognitive control functioning seems to rather add noise to a well-balanced system without inducing meaningful effects. Moreover, in dependence of the individual conditions, anodal tDCS might have even preferentially enhanced performance under emotionally neutral distraction and thus induced a better performance in neutral as compared to negative conditions (Wolkenstein & Plewnia, 2013). Actually,the significant parametric change of the correlation between* $\Delta RT_{neg\text{-}neu}$ *and* $\Delta eLPP_{neg\text{-}neu}$ *by increasing stimulation intensity suggests that anodal tDCS might modulate or even reverse the association between negativity bias and valence-specific brain activity in healthy subjects. Of note, being independent from emotional content, the association between lLPP and RT has not been influenced by tDCS, pointing towards a preferential modulation of emotion-related cognitive control processes by prefrontal tDCS"* (Faehling & Plewnia, 2016).

One other possibility to explain the findings may be the between-groups design of the present study, especially regarding the LPP results. As discussed in **Chapter 1.2**, tDCS efficacy is mediated by a wide array of individual variables including the cognitive state of the participant, skull thickness and brain anatomy (Kim, Kim, et al., 2014). It is therefore possible that in the present study, one session of tDCS produced subtle online effects that were not detected since the inter-individual variability added too much noise. Also, "*it is important to note that previous studies showing effects of tDCS on the negativity bias applied a within-subject design that reduces the influence of inter-individual variability*

(Vanderhasselt et al., 2013; Wolkenstein and Plewnia, 2013; Wolkenstein et al., 2014)" (Faehling & Plewnia, 2016). Along these lines, three meta-analyses found reliable effects of tDCS on working memory in healthy participants (Brunoni & Vanderhasselt, 2014; Dedoncker et al., 2016; Hill et al., 2016) and almost all the studies included in the reviews were implemented as single session, within-subject studies. The lack of any effect in the present study again indicates that the between-group design was not apt to capture the differential effects of tDCS. It may be asked why this study was planned as a between-group study in the first place. A within-subject design would have entailed a repeated performance of the same task. The associated training effects were thought to be more pronounced than the interindividual differences.

4.5. Trait Anxiety Influences the Valence-Specific lLPP

Anxiety is thought to induce heightened attention towards - and increased processing of - threatening stimuli (MacNamara & Proudfit, 2014). In the present study, it was sought to examine the relationship between trait anxiety, as measured by the trait anxiety (A-trait) scale of the STAI questionnaire, and the cortico-electrical response towards pictures, represented by the LPP (**Hypothesis V**). The correlation with the A-trait scale was significant for the ΔlLPP$_{neg\text{-}neu}$ (r = 0.222, p = 0.041) in the **complete sample**. Hence, a heightened non-pathological anxiety was accompanied with heightened valence-specific neuronal response elicited by distractive stimuli. There is no evidence for an influence of anxiety on performance from the present data, as there was no significant correlation between the A-Trait scale and RT or AC. Still, the data is informative when viewed in in the light of present research. MacNamara et al. found that participants with increased state (A-state) anxiety ratings exhibited a heightened cortical response to negative versus neutral stimuli under increased working memory load (MacNamara et al., 2011). In a follow-up study, they substantiated this finding among participants with general anxiety disorder: Participants suffering from generalized anxiety disorder were found to have an increased LPP amplitudes for negative stimuli compared with healthy controls (MacNamara & Proudfit, 2014). In the light of the results discussed above, there

might be a functional benefit, in that non-pathological anxiety helps to recruit more resources, and allow participants to be more attentive towards the task.

4.6. Concurrent tDCS and EEG is Safe and Feasible

This study is among the first (Cunillera et al., 2015) to demonstrate parallel EEG recording during tDCS on a large sample of participants (N = 87). Results warrant that it is a feasible research approach. Stimulation did increase the amount of noise in the EEG data so that more ERP trials had to be rejected in the stimulation conditions. However, this was still within an acceptable range (5.57 % negative trials rejected in the sham and 12.26 % negative trials rejected in the 1.5 mA group), as close to 90 % of EEG data could still be used. It has been shown that the LPP is quite robust to change after at least 12 trials are included (Moran, Jendrusina, & Moser, 2013). However, the decrease in the signal to noise ratio is an important consideration for future concurrent tDCS/EEG studies.

This study used longer stimulation durations than commonly administered (Nitsche et al., 2008). As no side effects were reported, this study provides further evidence that tDCS is a safe stimulation technique. What is more, blinding was successful for all conditions, demonstrating that it is possible to conduct blinded experiments with a duration up to 28 min of stimulation and current intensity of 1.5 mA. On a descriptive note, it seems advantageous to use rubber tDCS electrodes with conductive paste rather than saline sponge electrodes when working with concurrent EEG. Moreover, it was not possible to blind the experimenter, as it was necessary to control that the EEG recording device would not shut down due to the extra current flow. In future experiments, it will be useful to think of ways to double-blind the experiment. This might be done by assigning one experimenter to control the experiment and another to analyze the EEG data. However, this is not without methodological difficulty, as the tDCS leaves characteristic artifacts in the EEG recording when the current is ramped up and down.

4.7. Limitations of the Study

"*Limitations of the study are first that, to warrant practicability, only highly arousing negative stimuli were used. This is in general agreement with the notion*

that the LPP is modulated particularly by arousing stimuli (Codispoti et al., 2007; Hajcak et al., 2013). It is actually possible that highly arousing positive pictures will yield comparable results" (Faehling & Plewnia, 2016). Results from previous studies support this conjecture, as Wolkenstein & Plewnia (2013) found effects of both positive and negative pictures and Vanderhasselt and colleagues actually found a modulation of cognitive control for positive stimuli (Vanderhasselt et al., 2013). What is more, recent research called into question the dichotomous concepts of arousal and valence, highlighting the importance of individual differences in reaction to emotional content (Kuppens et al., 2013). Also, even the category of "neutral" pictures has been questioned as it is difficult to define what "neutral" means to different people (Schneider et al., 2016). However, since there are no better options to standardize studies than these rated pictures, there are not yet practical implications to be drawn from here.

"*Second, to increase the homogeneity of our sample we only included female participants. Nevertheless, it would be interesting to assess the influence of gender, as it has previously been shown that attention allocation towards emotional stimuli as mirrored by the LPP differs with gender (Syrjänen & Wiens, 2013). Third, concerning the time windows of the eLPP and lLPP, the available literature provides variable definitions (Weinberg & Hajcak, 2010). We decided to examine one early and one late window due to evidence that modulation by valence was predominantly found in the earlier phase (Codispoti et al., 2007) and refrained from analysis beyond the 1000 ms range because previous research indicated attention modulation to be predominantly important in the first second [(Dennis & Hajcak, 2009)]"* (Faehling & Plewnia, 2016). It is possible that a focus on different time windows may have yielded other results.

4.8. Conclusions and Future Directions

The present dissertation established a link between the neuronal response (the LPP) to a task irrelevant stimulus and task performance in a concurrent working memory task. "*The findings support the notion of the LPP as a neuronal marker for cognitive control, measured by RT performance in a WM task with emotional distractors. Furthermore, they provide evidence that the LPP amplitude induced*

by a distractive stimulus mirrors allocation of neuronal resources that support task performance. Particularly, the emotion specific increment of its early portion (eLPP), signals effective compensation for behavioral distraction by negative stimuli and thus points towards a neuronal mechanism for effective control of the emotional bias. In contrast, the association of the later phase (lLPP) with RT is not emotion specific" (Faehling & Plewnia, 2016). These results add valuable evidence to the ongoing discussion on the cognition-emotion interaction (Mueller, 2011) in that under certain circumstances, task-irrelevant, negative stimuli may be beneficial for task performance. This study did not find a main effect of tDCS on task performance or on the neurophysiological response elicited by distractive stimuli. This was probably due to the chosen study design and the selection of healthy participants. As a methodological conclusion drawn from this study, a within-subjects design should be used when working with ERPs. Lastly, it was demonstrated that concurrent tDCS and ERP recording is feasible and an apt way to examine neurophysiological reflections of online stimulation effects.

The results presented here offer a departing point for new research. It will be worthwhile to investigate the relationship between the neuronal response and behavior in depressed patients, who have been shown to exhibit an emotional bias in a working memory paradigm (Wolkenstein & Plewnia, 2013). As studies have found an attenuated cortical response to pictures in patients with depression (Foti et al., 2010), further investigations may shed light on the neuronal signature underlying the loss of cognitive control of emotion. Including tDCS in such research would also allow to see what cognitive correlate gives rise to a possible better task performance (Wolkenstein & Plewnia, 2013). It would be also informative if the same paradigm was tested with patients suffering from anxiety disorder, who seem to exhibit heightened cortical reactions in response to threatening stimuli (MacNamara & Proudfit, 2014).

5. Summary

"*Cognitive control of emotional processing is essential for adaptive human behavior" (Faehling & Plewnia, 2016).* Research indicates both facilitative and inhibitory effects of emotion on task performance. *"Biased attention [as a consequence of dysfunctional cognitive control] towards emotionally salient information is critically linked with affective disorders and is discussed as a promising treatment target" (Faehling & Plewnia, 2016).* Hypoactivity of the dorsolateral prefrontal cortex (DLPFC) is suggested as a causal factor. *"Anodal (activity enhancing) transcranial direct current stimulation (tDCS) has been shown to increase healthy and impaired cognitive control over emotional distraction and is therefore widely used for the investigation and experimental treatment of this disorder. In this […dissertation], event-related potentials (ERPs) were recorded parallel to tDCS to track its online effects [on cognitive control of emotion]. Healthy volunteers (N = 87) performed a delayed working memory paradigm (DWM) with [negative …] and neutral distractors during [anodal] stimulation [of the left DLPFC] with different intensities (sham, 0.5, 1, 1.5 mA). Measuring the late positive potential (LPP), an ERP that indexes attention allocation, [it was] found that a valence-specific increase of the early portion of the LPP (eLPP, 250-500 ms) was associated with less emotional distraction in the sham group. Of note, stimulation with tDCS exerted an intensity related effect on this correlation. The later part of the LPP (lLPP, 500-1000 ms) was found to be correlated with reaction time, regardless of valence. General effect of tDCS on LPP [amplitude]s and task performance were not observed*" (Faehling & Plewnia 2016). A measure of non-pathological trait anxiety correlated significantly with the late LPP in the complete sample. "*These findings demonstrate that ERP recordings parallel to tDCS are feasible to investigate the neuronal underpinnings of stimulation effects on executive functions. Furthermore, they support the notion that the LPP induced by a distractive stimulus during a working memory task mirrors the additional allocation of neuronal resources with a specific sensitivity of the early LPP for highly arousing negative stimuli*" (Faehling & Plewnia, 2016).

Zusammenfassung

„*Kognitive Kontrolle über die Verarbeitung von Emotionen ist für das adaptive Verhalten des Menschen unerlässlich“* (Faehling & Plewnia, 2016). Untersuchungen zeigen dabei sowohl eine förderliche als auch eine hinderliche Rolle von Emotionen auf die Aufgabenleistung. „*Die systematische Aufmerksamkeitsverzerrung [, als Konsequenz dysfunktionaler kognitiver Kontrolle,] zugunsten emotional bedeutsamen Informationen ist entscheidend mit affektiven Störungen verknüpft und wird als vielversprechendes Behandlungsziel diskutiert*“ (Faehling & Plewnia, 2016). Eine Hypoaktivität des dorsolateralen Präfrontalkortex (DLPFC) scheint hierbei eine kausale Rolle einzunehmen. „*Es konnte gezeigt werden, dass anodale (aktivitätssteigernde) transkranielle Gleichstromstimulation (tDCS) physiologische sowie dysfunktional beeinträchtigte kognitive Kontrolle von Emotionen stärken kann, weshalb ihr Einsatz für die Untersuchung und experimentelle Behandlung dieser Störung weit verbreitet ist*. *In der hier vorliegenden […* Dissertation*] wurden ereigniskorrelierte Potentiale (ERPs) parallel zur tDCS registriert um online Effekte der Stimulation [auf die kognitive Kontrolle von Emotionen] zu beobachten. Gesunde Freiwillige (N=87) führten ein delayed working memory Paradigma (DWM) durch, bei dem [negative …] und neutrale Distraktoren gezeigt wurden. Dabei wurden sie [anodal über dem linken DLPFC] mit unterschiedlichen Stromstärken stimuliert (sham, 0.5, 1, 1.5 mA). Das late positive potential (LPP), ein ERP, welches Aufmerksamkeitsallokation anzeigt, wurde gemessen. Ein valenzspezifischer Anstieg in der frühen Phase des LPP (eLPP, 250-500ms) war assoziiert mit weniger Ablenkung durch [negative …] Stimuli in der sham Gruppe. Die Stimulation hatte einen intensitätsabhängigen Effekt auf diese Korrelation. Die spätere Phase des LPP (lLPP) korrelierte valenzunabhängig mit der Reaktionszeit. Haupteffekte von tDCS auf die LPP [Amplitude] oder die Aufgabenleistung wurden nicht beobachtet*“ (Faehling & Plewnia, 2016). In der gesamten Gruppe wurde ein signifikanter Zusammenhang zwischen nicht-pathologischer Eigenschaftsangst und der späten LPP Phase beobachtet. „*Diese Ergebnisse zeigen, dass ERP Aufzeichnung parallel zur tDCS eine praktikable Technik zur Untersuchung der neuronalen Grundlagen von Stimulationseffekten auf exekutive Funktionen sind. Außerdem unterstützen sie die These, dass das LPP, induziert durch einen ablenkenden Stimulus in einer Arbeitsgedächtnisaufgabe, spezifische Rekrutierung zusätzlicher neuronaler Ressourcen widerspiegelt, wobei eine spezifische Sensitivität des frühen LPP für stark erregende negative Stimuli festzustellen ist* “ (Faehling & Plewnia, 2016).

6. Appendix

(A) "*Text of the Instructions Preceding the DWM Task:*

Next, you will see a cross in the middle of the screen. Please look at it. Then eight letters will appear. Please memorize these letters. Then a picture will appear and afterwards one single letter. If you believe that the single letter already appeared in the eight previous letters, please press the J key. If you believe that it did not appear, press the F key. Hold your index fingers on the keys for the whole time of the experiment. Please answer as quickly as possible. In between, there will be breaks of 15 seconds. Among the pictures, there will be very unpleasant ones, including dead human bodies. Please do not close your eyes. If you want to end the experiment at any time, just tell the supervisor. Try to relax your face and sit relatively still. Do you have any questions?

(B) Index Numbers of Pictures Taken for the DWM From the IAPS Database:

Negative pictures:
2703,2800,3001,3010,3015,3016,3030,3051,3053,3059,3060,3064,3071,3100, 3102,3110,3120,3130,3131,3140,3150,3230,3261,3350,3400,3530,3550,6313, 6315,6350,6510,9040,9253,9250,9253,9265,9405,9410,9433,9412
Neutral pictures:
2025,2038,2039,2102,2190,2191,2200,2210,2214,2215,2221,2235,2270,2272, 2305,2372,2374,2383,2400,2411,2487,2490,2493,2500,2512,2514,2575,2579, 2590,2595,2749,2745.1,2840,2850,2870,
2890,7493,7503,7505,9210
Training pictures:
5455,7130,7140,7180,7234,7490,7491,7496,7700" (Faehling & Plewnia, 2016).

(C) Correlations Between Accuracy Results of the DWM and eLPP and lLPP

Table 16

Correlation coefficients between ΔAC $_{neg-neu}$ and ΔeLPP $_{neg-neu}$

	ΔeLPP $_{neg-neu}$									
	Total		Sham		0.5 mA		1 mA		1.5 mA	
ΔAC $_{neg-neu}$	-0.01	*(0.95)*	-0.14	*(0.53)*	0.43*	*(0.05)*	-0.330	*(0.13)*	0.156	*(0.5)*

Note. * p < 0.05; p values are shown in brackets.

Table 17

Correlation coefficients between mean accuracy and eLPP amplitudes for trials with negative and neutral pictures

	eLPP									
	Total		Sham		0.5 mA		1 mA		1.5 mA	
	Neg	Neu	Neg	Neu	Neg	Neu	Neg	Neu	Neg	Neu
AC_{neg}	-0.20	-0.2	0.15	0.40	-0.29	-0.37	-0.29	-0.33	0.04	0.02
AC_{neu}	-0.07	-0.05	-0.09	-0.01	-0.34	-0.18	0.18	-0.02	0.28	-0.06

Note. * p < 0.05.

Table 18

Correlation coefficients between ΔAC $_{neg-neu}$ and ΔlLPP $_{neg-neu}$

	ΔlLPP $_{neg-neu}$									
	Total		Sham		0.5 mA		1 mA		1.5 mA	
ΔAC $_{neg-neu}$	-0.09	*(0.47)*	-0.22	*(0.33)*	0.26	*(0.24)*	-0.34	*(0.12)*	0.03	*(0.89)*

Note. * p < 0.05; p values are shown in brackets.

Table 19

Correlation coefficients between mean accuracy and lLPP amplitudes for trials with negative and neutral pictures

	lLPP									
	Total		Sham		0.5 mA		1 mA		1.5 mA	
	Neg	Neu	Neg	Neu	Neg	Neu	Neg	Neu	Neg	Neu
AC_{neg}	-0.07	-0.04	0.23	0.46*	-0.35	-0.43*	0.04	0.02	-0.19	-0.29
AC_{neu}	0.06	0.04	0.14	-0.09	-0.09	-0.34	0.27	-0.06	0.16	0.15

Note. * $p < 0.05$.

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8. Erklärung zum Eigenanteil

Die Arbeit wurde an der Universitätsklinik für Psychiatrie und Psychotherapie Tübingen in der Arbeitsgruppe Neurophysiologie und Interventionelle Neuropsychiatrie unter der Leitung und Betreuung von Prof. Christian Plewnia durchgeführt.

Die Konzeption der Studie erfolgte durch Prof. Plewnia, ich war an der Ausgestaltung beteiligt.

Der Versuchsaufbau des Experimentes erfolgte durch mich unter der Betreuung von Prof. Plewnia. Barbara Wasserka und Prof. Plewnia arbeiteten mich in den Umgang mit der tDCS ein. Sämtliche Versuche wurden von mir mit Unterstützung von Barbara Wasserka, Paul Rehberger, Fedor Schlegel und Simone Alves durchgeführt.

Die Aufbereitung der behavioralen und EEG Daten erfolgte eigenständig durch mich. Die statistische Auswertung und Interpretation der Daten erfolgte in Zusammenarbeit mit Prof. Plewnia.

Ich versichere, das Manuskript, bis auf die gekennzeichneten Stellen der Publikation (siehe unten), selbständig verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben. Abbildungen 7 -11 wurden von mir erstellt.

Erklärung zum Eigenanteil an der Publikation

„*CP [Prof. Christian Plewnia] and FF [Florian Faehling] designed the study*

FF collected the data

FF and CP analyzed the data

FF and CP wrote to the manuscript“ (Faehling & Plewnia, 2016).

9. Publication

Major parts of the data and passages of the text of this dissertation (mainly in the **summary** and in the chapters **material and methods**, **results** and **discussion**) were published in the following article:

Faehling, F., & Plewnia, C. (2016). *Controlling the Emotional Bias: Performance, Late Positive Potentials and the Effect of Anodal Transcranial Direct Current Stimulation (tDCS)*. Frontiers in Cellular Neuroscience; 10: 159.

Text passages that are identical to those in the publication are written in quotation marks followed by the citation and formatted in *italics*. Square brackets (e.g. [word]) indicate newly inserted words/characters in the quotation while three dots ([…]) indicate omission of words.

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