Transcranial Direct Current Stimulation and Cognitive Control Training for the Treatment of Depression: Investigating Stimulation Intensity and Mechanisms Underlying an Effective Training Task

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Anja Madeleine Sommer, M.Sc.

aus Stuttgart

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1. Berichterstatter:	Prof. Dr. Christian Plewnia
2. Berichterstatterin:	Prof. Dr. Jennifer Svaldi

Table of Contents

Abbreviations

BDI	Beck Depression Inventory
CC	Cognitive control
CCT	Cognitive control training
dlPFC	Dorsolateral prefrontal cortex
ERP	Event-related potential
FRN	Feedback related negativity
ISI	Interstimulus-interval
LPP	Late positive potential
MADRS	Montgomery Asberg Depression Rating scale
MDD	Major depression disorder
PASAT	Paced Auditory Serial Addition Task
PFC	Prefrontal cortex
TAU	treatment as usual
tDCS	transcranial direct current stimulation

Zusammenfassung

Transkranielle Gleichstromstimulation (tDCS) und kognitives Kontrolltraining (CCT) gelten als vielversprechende Verfahren zur Verbesserung der Behandlung von Depressionen (MDD), indem sie auf die Hypoaktivierung des dorsolateralen präfrontalen Kortex (dlPFC) und die damit verbundene beeinträchtigte kognitive Kontrolle (CC) abzielen. Da die Effektivität der tDCS eine deutliche Abhängigkeit von der Aktivität stimulierter Hirnareale aufweist, erscheint eine Kombination von tDCS und CCT sinnvoll. Bisherige Forschungen deuten auf eine synergistische Wirksamkeit einer solchen Kombination hin, jedoch stehen weitere Evaluierungen als auch Untersuchungen der optimalen Stimulationsintensität noch aus. Darüber hinaus sind trotz der Erkenntnisse über positive Effekte von CCTs die neuralen Mechanismen, die ihnen zugrunde liegen, bislang kaum bekannt. Die Ziele dieser Doktorarbeit sind daher (a) die Effektivität eines tDCS gestützten CCTs auf die Behandlung von MDD zu überprüfen, (b) eine Untersuchung zweier Stimulationsintensitäten und (c) eine Untersuchung neuraler Mechanismen, die der Wirksamkeit eines CCTs zugrunde liegen. In drei Studien wurden diese Ziele adressiert. In Studie I wurden ereigniskorrelierte Potentiale (ERP) bei gesunden Probanden während der Bearbeitung des Paced Auditory Serial Addition Task (PASAT), einem effektiven CCT zur Reduktion depressiver Symptome, abgeleitet. Größere ERP nach negativem Feedback in den drei untersuchten Verarbeitungsphasen (Feedback Related Negativity, P300, Late Positive Potential) deuten auf eine erhöhte Ressourcenallokation in Richtung negativer Inhalte hin. Zudem zeigte sich eine verarbeitungsphasenspezifische Assoziation neuraler Aktivität mit kognitiver Leistungsfähigkeit. Diese deutet auf eine initiale verstärkte Ablenkung durch erhöhte neurale Aktivierung hin, während höhere Aktivierung in späteren Phasen kognitive Kontrollprozesse widerspiegeln, die eine Aufrechterhaltung zielorientierten Verhaltens zu gewährleisten scheinen. In Studie II wurde die Effektivität eines tDCS gestützten PASAT-Trainings zur Depressionsbehandlung untersucht und zwei Stimulationsintensitäten (1 vs. 2mA) mit sham-tDCS verglichen. Insgesamt konnte eine signifikante Reduktion depressiver Symptome erreicht werden. Darüber hinaus zeigte sich jedoch für keine der beiden Stimulationsintensitäten ein zusätzlicher Effekt direkt nach dem Training. Eine nicht-signifikante Tendenz in Richtung einer größeren Reduktion der Depressivität zum Follow-up nach drei Monaten in der 1mA-Gruppe könnte vorläufige Hinweise auf günstige Langzeiteffekte der geringeren Stimulationsintensität widerspiegeln. In Studie III wurden die in Studie I identifizierten neuralen Signaturen verwendet, um die zugrunde liegenden neuralen Mechanismen der PASAT-Leistung bei MDD-Patienten zu untersuchen. Stärkere neurale

Aktivierung nach negativem als nach positivem Feedback in späten Verarbeitungsphasen, spiegelt eine typisch verzerrte Aufmerksamkeitslenkung depressiver Patienten wider. Fehlende Zusammenhänge von neuralen Signaturen mit kognitiver Leistungsfähigkeit und Depressionswerten deuten jedoch auf eine nur bedingte Aussagekraft über die dem PASAT zugrundeliegenden neuralen Mechanismen hin.

Summary

Transcranial direct current stimulation (tDCS) and cognitive control trainings (CCT) have emerged as promising tools to ameliorate the treatment of major depression disorder (MDD) by means of targeting hypoactivation of the dorsolateral prefrontal cortex (dlPFC) and the associated impaired cognitive control (CC). Based on the dependency of excitability changes by tDCS on current network activity, a combination of tDCS and CCT has been put forward. Research so far suggests synergistic efficacy of such a combination, however further evaluation as well as investigation of optimal stimulation intensity is still pending. Moreover, despite findings of beneficial effects of CCTs, neural mechanisms underlying them is still scarce. Thus, the goals of this doctoral research are (a) to investigate the effects of a tDCS enhanced CCT on MDD, (b) to expand knowledge about optimal stimulation intensity and (c) to examine neural mechanisms underlying the effectiveness of a CCT. These research questions were addressed in three studies. In study I feedback-locked event-related potentials (ERPs) were derived from healthy subjects during the paced auditory serial addition task (PASAT), an effective CCT for MDD. Larger neural activation after negative feedback in all three processing stages (feedback related negativity, P300, late positive potential) indicates an increased resource allocation towards negative content. Moreover, processing stage dependent associations of ERPs and PASAT performance indicate early distraction and late resource allocation by increased neural activation after negative feedback. In Study II we investigated the antidepressant effect of a tDCS-augmented PASAT training for MDD and compared two stimulation intensities (1 vs. 2 mA) with sham tDCS. Depression scores significantly decreased over the course of the training. However, no additional effect of tDCS augmentation was found neither for high- nor low- intensity tDCS directly after the training. A non-significant medium effect sized tendency towards a larger reduction of MDD scores at the three months follow-up in the 1mA group might reflect preliminary indications of beneficial long-term effects of low-intensity tDCS. In Study III signatures, identified in study I were utilized to investigate underlying neural mechanisms of PASAT performance in MDD patients. A larger neural activation after negative than positive feedback only in late feedback processing stages found in study III is in accordance with time frames of typical findings about attentional negativity biases in MDD. However, the lack of associations of valence-specific ERPs with PASAT performance and MDD scores indicates that by the signatures found in study I only limited knowledge about neural mechanisms underlying efficacy of PASAT training for MDD can be gained.

1. Introduction

With a 12-month prevalence rate of 6.9 % (Wittchen et al., 2011) and a lifetime prevalence of 16.6 % (Kessler et al., 2005), major depression disorder (MDD) is one of the most common mental illnesses. MDD is characterized by at least five of the following symptoms at the same time over a period of at least two weeks: (1) depressed mood, (2) loss of interest, (3) weight loss or gain, (4) hypersomnia or insomnia, (5) psychomotor agitation or retardation, (6) fatigue, (7) feeling worthless or excessive guilt, (8) diminished ability to think or concentrate or indecisiveness and (9) thoughts of death (DSM-5), with at least one of the first two symptoms included. Furthermore, the described symptoms have to cause significant distress or impairment. Thus, MDD comes with severe individual suffering. Moreover, it is associated with high societal costs (Olesen et al., 2012) and heightened mortality (Cuijpers & Smit, 2002). Additionally, it is the main cause for disability as well as suicide deaths worldwide according to the WHO[1]. Currently, psychotherapy and antidepressant medication are the most common treatment methods. Although these can be described as effective (Casacalenda et al., 2002), they do not show the desired effectiveness for all sufferers (Gartlehner et al., 2015; Malhi et al., 2019). Siegle, Ghinassi, et al. (2007) describe that only 40 to 60% of sufferers respond to current treatment methods. Thus, the development and evaluation of new interventions that augment existing therapies is an important challenge and subject of this thesis.

1.1. Cognitive Control in MDD

The ability to orchestrate purposeful and coordinated behavior in an information rich environment and in accordance with internal goals is referred to as cognitive control (CC) (Miller & Cohen, 2001). In particular, the inhibition of processing of competing, stronger, but task-irrelevant information, or reaction to it in favor of weak, but task-relevant information, i.e. nonautomatic behavior, is one of the fundamental aspects of CC. According to Roiser et al. (2012) CC specifically involves attentional control (e.g. selective attention, ignoring distractive information) and working memory processes (e.g. store and manipulate internal representations of information). Miyake et al. (2000) emphasized in particular three main

[1] World Health Organization. WHO| Depression and Other Common Mental Disorders. Available online: http://apps.who.int/iris/bitstream/handle/10665/254610/WHO-MSD-MER-2017.2-eng.pdf;jsessionid=C440641F1C1D381AB95D827C68579107?sequence=1 (accessed on 26.07.2021)

aspects of CC, which are partly interrelated and at the same time comprise independent components: Set shifting, working memory updating and inhibition of prepotent responses. Taken together, CC can be understood as functions by means of which limited cognitive resources are controlled in order to achieve internal goals.

In accordance with the cognitive impairments outlined in the diagnostic criteria (diminished ability to concentrate or indecisiveness, see above), findings so far consistently and reliably show impaired CC in depressed patients in a variety of domains, like response inhibition, set or task shifting and working memory updating (De Nooij et al., 2020; Epp et al., 2012; Goodall et al., 2018; Mondal et al., 2007; Snyder, 2013). Moreover, Cambridge et al. (2018) reviewed the relationship of cognitive impairment and psychosocial functioning. The authors found them to be negatively associated, hereby emphasizing the serious contribution of cognitive deficits to the personal suffering of patients. Furthermore, it was found that cognitive impairments persist even after remission and increase with the number of depressive episodes (Semkovska et al., 2019).

Research examining theses CC dysfunctions in MDD has gained increasing interest in the last years, especially since findings indicate that these are not epiphenomena of MDD, but rather seem to be causally related to its development and maintenance (De Raedt & Koster, 2010). This assumption is supported by findings showing that CC deficits provide predictive information about the onset of depressive symptoms. In a longitudinal study Demeyer et al. (2012) showed that diminished CC in remitted MDD patients was significantly associated with relapse one year after CC assessment. Additionally, Pe et al. (2016) found that in university students experiencing high levels of stress, difficulties in modifying affective information in working memory was positively correlated with symptoms of depression.

Mechanisms driving this causal relation of CC dysfunction and MDD are assumed to be information processing biases and dysfunctional emotion regulation strategies related to CC dysfunction. Impaired CC implies dysfunctions of important processes like inhibiting and controlling automated information processing, thus resulting in increased processing of mood-congruent (i.e., negative) content. In fact, biased processing of information is a key component of the cognitive model of depression by Beck (Beck, 1967, 1976), that postulates that *schemas*, i.e. internal representations of the self and the world, are developed due to early lifetime experiences and activated by everyday internal or external events, thereby influencing the perception of the world and oneself. Moreover, this empirically based theory assumes that due to negative early lifetime experiences, MDD patients develop negative schemas, resulting

in negative views of the world, oneself, and the future, the *negative triad* (Beck, 1976). In accordance with the cognitive model of depression *negativity biases*, described as enhanced attention allocation towards, processing and memory updating of negative information and difficulties in disengaging from negative content, have been replicated in MDD many times (for reviews, see Mathews & MacLeod, 2005; Gotlib & Joormann, 2010). Furthermore, diminished CC and the negativity bias have been linked to maladaptive emotion regulation that promotes depressive symptoms. This includes the excessive use of dysfunctional emotion regulation strategies like rumination and reduced use of adaptive emotion regulation strategies like cognitive reappraisal (for reviews, see Joormann & Vanderlind, 2014; Nolen-Hoeksema et al., 2008). Moreover, rumination has been shown to be directly associated with the development and maintenance of depression, increased relapse rates and severity of MDD symptoms (Just & Alloy, 1997; Nolen-Hoeksema, 2000; Nolen-Hoeksema & Morrow, 1991; Treynor et al., 2003). In fact, Demeyer et al. (2012) showed that the association of CC deficits and MDD relapse described above was fully mediated by rumination.

Taken together, disrupted CC in depressed patients is associated with a negativity bias, promotes dysfunctional emotion regulation strategies, and thus causally contributes to MDD development and maintenance.

1.2. Neural substrates of impaired Cognitive Control in MDD

Given the broad and prominent disruptions of experience, processing and regulation of affect in MDD, it is not surprising that depressed patients depict a variety of functional and structural changes of brain areas related to emotion and CC of emotion. These include increased and sustained activation of limbic areas, including cingulate, hypothalamus hippocampus and the amygdala. The limbic regions comprise brain areas that are closely related to the integration of external and internal information that form the basis of emotional experiencing (Mayberg et al., 1999). The amygdala in particular is a brain area strongly associated with the experience and processing of emotions. Furthermore, it is significantly involved in emotion guided attention allocation and working memory processes (Adolphs et al., 1997; Cahill et al., 1995) and thus represents an important neural basis for biased information processing in depressed patients. Findings show that faster evaluation time of negative stimuli are associated with increased amygdala activation and decreased psychological well-being (van Reekum et al., 2007). Hyperactivation of limbic areas, at rest, as well as in reaction to negative stimuli in MDD have been found (Fales et al., 2008; Siegle,

Thompson, et al., 2007) and are correlated with severity of depressive symptoms (Drevets et al., 1995; Mayberg et al., 1999; Peluso et al., 2009).

Moreover, depressed patients show significant alterations and reduced activation of neocortical regions (Mayberg et al., 1999). Most notably are robust and consistent findings about hypoactivation of the dorsolateral prefrontal cortex (dlPFC) in particular in response to emotional stimuli or attentional control over emotional cues (Beevers et al., 2010; Fales et al., 2008; Pizzagalli, 2011; Siegle, Thompson, et al., 2007). The PFC, including the dlPFC, is the phylogenetically youngest brain area in primates and known to be closely related to higher order cognitive functioning playing a crucial role for complex coordination of sensory and motor processes in accordance with internal goals forming the neural basis of CC. In healthy subjects the dlPFC is characterized by a high degree of neuroplasticity, ensuring the maintenance of demanding CC processes (Fuster, 2000; Miller & Cohen, 2001). Moreover, the dlPFC is associated with attention switching and thereby suppressing the processing of other stimuli than the attended one (Kastner et al., 1998). Kühn et al. (2014) found increases of unwanted, distressing thoughts in healthy subjects to be negatively associated with dlPFC activity pointing towards reduced control over rumination. Thus, in accordance with the well-known impairments of CC in depressed patients it is not surprising that MDD is related to disrupted dlPFC functioning. Disner et al. (2011) suggest that hypoactivation of the dlPFC in MDD in response to emotional information is linked to difficulties in disengaging from negative stimuli, resulting in prolonged exposure to negative content, therefore presumably supporting the maintenance of MDD symptoms.

Overall, MDD is characterized by hyperactivation of emotion-related limbic brain areas including the amygdala and hypoactivation of CC related neocortical brain areas including the dlPFC, suggesting that both, enhanced stimuli driven bottom-up responses as well as reduced top-down CC over emotional processing are involved in negativity biases in MDD (Fales et al., 2008). Importantly, these alterations are interconnected and form a disrupted network activation that is characterized by lack of inhibitory regulation of emotion related limbic areas, normally executed by neocortical regions (Drevets, 2001) and thus is significantly associated with MDD psychopathology (Disner et al., 2011; Siegle, Thompson, et al., 2007). Consistently, Mayberg et al. (1999) found increased activation of limbic and decreased activation of neocortical regions in response to sadness in MDD patients that changed to a reverse pattern with recovery from MDD. Moreover, MDD patients exhibit reduced connectivity between the amygdala and the dlPFC (Siegle, Thompson, et al., 2007).These

results have been interpreted as disrupted dlPFC driven inhibition of emotion related brain activity, resulting in uncontrolled activity increases in these areas, forming the neural basis of the negativity bias and disrupted affective processing (Disner et al., 2011; Mayberg, 1997).

1.3. Treatments directly targeting disrupted Cognitive Control and its Neural Basis

Considering the important role of disrupted CC for the development and maintenance of MDD, techniques to modulate CC as well as disrupted neural activity underlying impaired CC play a key role in the development of new treatment methods. In the following section transcranial direct current stimulation (tDCS) and cognitive control training (CCT) as two new treatment methods are outlined.

1.3.1. Transcranial direct current Stimulation

TDCS is a safe, inexpensive and efficient technique to modulate neural activity. By means of two rubber electrodes a weak direct current through the scalp is applied. This modifies the resting membrane potential and alters the likelihood of depolarization of neurons and thus excitability (Nitsche et al., 2009; Nitsche & Paulus, 2000). Thereby anodal tDCS predominantly facilitates and cathodal tDCS mainly decreases cortical excitability (Cambiaghi et al., 2010). Due to its critical involvement in CC the dlPFC is a typical target region for tDCS. Studies up to this point show promising effects of tDCS of the dlPFC on healthy and impaired CC (e.g. Fregni et al., 2005; Gladwin et al., 2012; Keeser et al., 2011; Zwissler et al., 2014; for a review, see Dedoncker et al., 2016). Wolkenstein and Plewnia (2013) showed improved performance in an emotional delayed working memory task in healthy and depressed participants during anodal tDCS compared to sham (i.e. placebo) tDCS. Moreover, a negativity bias in depressed patients was only present during sham, but not anodal tDCS, indicating improved CC of emotion by increased dlPFC activity. In contrast, the inhibition of dlPFC activity by cathodal tDCS has been shown to induce a depression-like negativity bias in the same task that was not present under sham tDCS in healthy subjects (Wolkenstein et al., 2014). Both studies demonstrate the significant involvement of the dlPFC in CC of emotions as well as its polarity-dependent malleability by tDCS (Plewnia, Schroeder, & Wolkenstein, 2015). Furthermore, in a training study Weller et al. (2020) found significantly larger performance gains in healthy participants receiving 1mA anodal tDCS of the left dlPFC compared to sham tDCS.

Several clinical studies have investigated tDCS for the treatment of MDD with mostly promising results (Boggio et al., 2008; Brunoni et al., 2013, 2017; Fregni et al., 2006). A recent meta-analysis found superiority of active tDCS over sham in reducing depressive symptoms (Razza et al., 2020). However effect sizes are moderate, results are not unequivocal (Loo et al., 2018) and large scale randomized clinical trials are lacking. Furthermore, a major challenge for the clinical evaluation of tDCS is that its effects are highly dependent on a wide range of parameters like stimulation configuration, polarity and intensity (Jamil et al., 2020). Thus, the investigation of optimal stimulation parameters still depicts an important objective. Nineteen of the studies in the meta-analysis used 2mA of which 11 found significant tDCS effects, whereas only four used 1 or even 0.5mA of which three showed tDCS effects (Razza et al., 2020). Debate about intensity effects is still going on and findings are unequivocal: some studies point towards efficacy gains with increased stimulation intensity (Hoy et al., 2014; Iyer et al., 2005; Schwippel et al., 2018) while others indicate non-linear tDCS effects or challenge the mechanistic concept that only high tDCS intensity leads to effects (Batsikadze et al., 2013; Weller et al., 2020; Wolkenstein & Plewnia, 2013; for a review on the complexity of dose dependent effects, see Esmaeilpour et al., 2018). Overall, research on optimal stimulation intensity is pending and particularly findings on tDCS effects on MDD with lower intensity are missing.

Moreover, it has to be considered that tDCS itself does not induce neuronal activity like e.g. transcranial magnetic stimulation, but merely increases the probability of neuronal firing by modifying the neuronal membrane potential (Nitsche & Paulus, 2000). Therefore, the current activity of the stimulated neuronal networks is regarded to have a major influence on whether there is an actual change in brain activity resulting from this shifted membrane potential which is supported by several studies (Boroda et al., 2020; Fritsch et al., 2010). Kronberg et al. (2017) for example found that direct current stimulation of synapses of hippocampal rat slices showed long term potentiation only when stimulated synapses were already active. Moreover, Gill et al. (2015) tested if cognitive load during tDCS influenced post stimulation performance in a transfer task and found significantly better performance after tDCS during high than low cognitive load. However, most clinical studies so far stimulate patients at rest, thus missing to exhaust effectiveness of tDCS for the treatment of MDD.

Taken together, tDCS has the potential to effectively improve treatment for MDD. However, findings about optimal stimulation protocols are still missing and neuroplastic efficacy of

tDCS can be promoted using synergistic effects of simultaneous activation of stimulated brain areas.

1.3.2. Cognitive Control Training

CCTs have been put forward as interventions improving disrupted CC functioning in MDD and thus directly targeting vulnerability factors underlying depression (Siegle, Ghinassi, et al., 2007). By repeatedly performing tasks that demand CC functions, like working memory updating, inhibition, mental set shifting or performance monitoring, lasting improvement of CC is targeted. Overall, research so far suggests beneficial effects of CCT for MDD concerning global functioning, cognitive functions and depressive symptoms (for a review, see Motter et al., 2016).

A task commonly used for CCT in depressed patients is an adaptive version of the *paced auditory serial addition task* (PASAT; Gronwall, 1977; Siegle, Ghinassi, et al., 2007; Tombaugh, 1999). In the PASAT digits are presented auditorily and patients add the current digit to the one before and indicate the result by mouse or keyboard entry. Task difficulty is adapted according to the participants performance: after several correct trials speed of digit presentation increases. Although this ensures that task difficulty is feasible for all participants, the adaptive nature is associated with frustration (Holdwick & Wingenfeld, 1999; Plewnia, Schroeder, Kunze, et al., 2015): participants will never reach a pace at which they can outperform the task. As soon as they succeed in the task, it will get more difficult. Thereby a stressful and frustrating task environment is created which is amplified by the concurrent presentation of performance feedback.

Several studies have investigated the effects of PASAT training on depressive symptoms. Siegle, Ghinassi, et al. (2007) found patients receiving CCT to depict significantly larger depression improvement than patients only receiving treatment as usual (TAU). In a study extending these findings Siegle et al. (2014) found that although CCT was not associated with larger depression improvement than TAU, rumination and participation in an outpatient treatment program during a one-year follow-up significantly decreased in the CCT group. Calkins et al. (2015) showed that participants that underwent the CCT, including the PASAT, depicted a significantly larger reduction in depressive symptoms than the group that received a control training. It has to be noted that these authors combined the PASAT training with an attention training (Wells attention training; Wells, 2000). Further studies only using PASAT

training found beneficial effects on depressive symptoms, stress reactivity and rumination (Hoorelbeke et al., 2015). In remitted patients amelioration of depressive symptoms and dysfunctional emotion regulation was found (Hoorelbeke & Koster, 2017). Although Vervaeke et al. (2021) failed to replicate these findings concerning effects on resilience and emotion regulation, the authors found larger improvement of cognitive transfer, subjective cognitive functioning and a trend towards larger improvement of depressive symptoms in the CCT group.

Overall, these findings indicate that PASAT training might be a beneficial augmentation of MDD treatment and relapse prevention. Moreover, promising effects on emotion regulation, cognitive functions and reduction in outpatient treatment (Siegle et al., 2014) indicate that PASAT training contributes to long-term changes of vulnerability factors underlying MDD.

Mechanisms of PASAT training and neural signatures of cognitive control

Considering the promising effects of PASAT training, knowledge about underlying mechanisms seems crucial for several reason like improving CCTs, identify patients who will particularly benefit from training and gaining further knowledge about vulnerability factors in depressed patients to improve treatment options in general.

The stressful task environment that is created by the adaptive nature of the PASAT is believed to be crucial for the effectiveness of the training. The activation of CC functions in a stressful and frustrating environment is assumed to strengthen CC over negative emotions (Siegle, Ghinassi, et al., 2007; Vervaeke et al., 2020). It can be hypothesized that participants experience that maladaptive emotion regulation strategies like rumination go along with performance deterioration. Indeed Lass et al. (2021) found that when stress is decreased by means of a self-paced interstimulus-interval (ISI), the training is less effective. Moreover, Plewnia, Schroeder, Kunze, et al. (2015) found significantly better PASAT performance in a healthy sample receiving active vs. sham tDCD of the left dlPFC. Additionally, only in participants that received sham tDCS a significant increase of upset feelings was found. Moreover, the authors found a significant negative correlation of upset feelings with PASAT performance. These findings in a healthy sample support the idea that CC of negative emotions, driven by dlPFC activity is a crucial factor for successful PASAT performance that might be strengthened by PASAT training in depressed patients. On a neural level PASAT training thus might strengthen disrupted connectivity between prefrontal CC networks and emotion related limbic areas in depressed patients (Siegle, Thompson, et al., 2007). Findings of a critical involvement of the dlPFC during PASAT performance bolster this assumption

(Lazeron et al., 2003). However, further findings on neural mechanisms underlying the PASAT is lacking. Especially knowledge about neural activation during the highly time dynamic PASAT processing, that is crucial for the task, is still missing. Event-related potentials (ERPs) provide excellent properties to study these, due to their high temporal resolution. Moreover, neural signatures of mechanisms underlying the PASAT identified by ERPs might be employed as markers of change during and after CCT that provide further insight into vulnerability factors and CC dysfunctions.

Three ERP components in particular seem best suited to capture both, top-down driven CC as well as emotional processing during PASAT performance and capture three different time frames and processing stages of stimulus processing. The feedback related negativity (FRN) is an early ERP peaking between 200 and 300 ms after feedback presentation and is robustly larger for negative than positive feedback (Gehring & Willoughby, 2002), probably indicating negative expectation violation and also emotional involvement (Luu et al., 2003). Findings on the FRN in MDD patients are inconclusive. Several authors found increased FRN amplitudes (Cavanagh et al., 2011; Santesso et al., 2008; Tucker et al., 2003) while others found reduced FRN amplitudes (Foti & Hajcak, 2009; Keren et al., 2018; Liu et al., 2014). Research suggests that this ambiguity results from inter-patient variability and links increases of symptom severity and symptoms of anhedonia to decreased FRN amplitudes (Liu et al., 2014; Mueller et al., 2015). The P300 peaks between 300 and 400 ms after stimulus presentation and is known to reflect attention allocation to salient and task relevant stimuli, including emotional content. Accordingly it is larger for target stimuli and emotional information (Delplanque et al., 2004). Moreover, it is assumed that larger P300 components reflect cognitive processes towards relevant or salient task information like working memory updating (Polich, 2012). P300 amplitudes are significantly decreased in depressed patients which is interpreted as reflecting cognitive dysfunctions, motivational withdrawal and also emotional alterations in MDD (Proudfit et al., 2015). The late positive potential (LPP) is a late ERP, starting at about 200 to 300 ms after stimulus presentation that can last for several seconds and captures attention allocation to emotional stimuli. Like the P300, it is larger for emotional than non-emotional stimuli (Ito et al., 1998) and known to be regulated by top-down mechanisms. In depressed patients the LPP is reduced for both, pleasant as well as unpleasant stimuli suggesting reduced emotional reactivity (Blackburn et al., 1990; Foti et al., 2010; Weinberg et al., 2016).

1.3.3. Combining tDCS and Cognitive Control Training to promote Neuroplasticity

Overall, with tDCS and CCTs two promising new treatment options are available. Both target key vulnerability factors underlying MDD, by strengthen prefrontal activation and CC. Thus, both involve the dlPFC, suggesting that a combination of tDCS and CCT holds synergistic effects. Moreover, in view of the brain state dependent properties of tDCS (see chapter 1.3.1.) a combination of tDCS with CCT might amplify neuroplasticity.

This assumption is bolstered by findings from Segrave et al. (2014). In their study, 27 depressed patients underwent one of three training schedules: active tDCS + CCT (including PASAT training), sham tDCS + CCT or sham CCT + active tDCS. The authors found a significant reduction of depressive symptoms in all training groups, however only in the combined active tDCS + CCT group this reduction was not only lasting at the three weeks follow-up assessment but was further expanded. This suggests that the combined CCT + active tDCS, but not CCT or tDCS alone supports change of underlying mechanisms that contribute to maintenance of MDD. However, this finding is rather preliminary, since the sample size is quite small with nine participants per group.

Brunoni et al. (2014) investigated the effect of combined tDCS + PASAT training on MDD in a larger sample of 47 depressed patients that were randomized into one of two training conditions: active tDCS + PASAT training or sham tDCS + PASAT training. In both groups a significant reduction of depressive symptoms was achieved with no difference between the groups. However, older patients with larger PASAT improvement did benefit more in the combined group, indicating that in certain subgroups and patients that put more effort into task performance – or have more cognitive capacity for that – tDCS might be beneficial. In a subsample of that study (33 participants) Vanderhasselt et al. (2015) have explored the effects of combined tDCS + CCT on rumination. Although improvement of PASAT performance was associated with reduced rumination, there was no additional effect of tDCS on rumination.

In summary, although results of combined tDCS and CCT trainings on depressive symptoms are promising they should be considered rather preliminary in view of the small sample size (Segrave et al., 2014) and moderate effects (Brunoni et al., 2014) thus, suggesting further research into this topic.

1.4. Open Research Questions and Objective of Doctoral Research

Taken together, tDCS and PASAT training depict new interventions that have the potential to augment existing therapies and thus improve treatment of MDD overall. However, as outlined in the previous chapters, findings so far leave several research questions open. First, effect sizes for the treatment of MDD by tDCS are moderate and findings regarding efficacy are mixed. Thus, further studies on the effectiveness of tDCS are pending. Second, most tDCS studies so far missed to exhaust neuroplastic efficacy by stimulating at rest. Only a few studies combined tDCS with CCTs and due to small sample size and limited effects their findings do not allow final conclusions about the effectiveness. Third, research about the efficacy of low intensity tDCS for the treatment of MDD are missing, leading to a lack of findings on optimal stimulation intensity. Fourth, although findings on the efficacy of PASAT training for MDD are promising, knowledge about neural mechanisms underlying PASAT performance is lacking. Following these open research questions, the main objectives of this doctoral research are (a) to investigate the effects of a tDCS enhanced CCT on MDD, (b) to expand knowledge about optimal stimulation intensity and (c) to examine neural mechanisms underlying the effectiveness of PASAT trainings. These research questions were addressed in three studies, described in the following chapters.

Please note, the following chapters are written as separately readable manuscripts. This results in overlapping contents to this introduction and between the empirical chapters and discussion.

2. Study I: "Neural Signatures of Performance Feedback in the Paced Auditory Serial Addition Task (PASAT): an ERP Study"

Author	Author position	Scientific ideas %	Data generation %	Analysis & interpretation %	Paper writing %
Anja Sommer	1	50	70	70	60
Lukas Ecker	2	10	30	20	10
Christian Plewnia	3	40	0	10	30
Title of paper:		Neural Signatures of Performance Feedback in the Paced Auditory Serial Addition Task (PASAT): an ERP Study			
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Neural Signatures of Performance Feedback in the Paced Auditory Serial Addition Task (PASAT): An ERP Study

Anja Sommer, Lukas Ecker, Christian Plewnia*

Affiliations:

Department of Psychiatry and Psychotherapy, Neurophysiology & Interventional Neuropsychiatry, University Hospital Tübingen, Tübingen, Germany

*Corresponding author

christian.plewnia@med.uni-tuebingen.de

Author ORCIDs

Christian Plewnia 0000-0003-3852-9906

Anja Sommer 0000-0003-3713-3395

Abstract

Research on cognitive control has sparked increasing interest in recent years, as it is an important prerequisite for goal oriented human behavior. The paced auditory serial addition task (PASAT) has been used to test and train cognitive control functions. This adaptive, challenging task includes continuous performance feedback. Therefore, additional cognitive control capacities are required to process this information along with the already high task-load. The underlying neural mechanisms, however, are still unclear. To explore the neural signatures of the PASAT and particularly the processing of distractive feedback information, feedback locked event-related potentials were derived from 24 healthy participants during an adaptive 2-back version of the PASAT. Larger neural activation after negative feedback was found for feedback related negativity (FRN), P300, and late positive potential (LPP). In early stages of feedback processing (i.e., FRN), a larger difference between positive and negative feedback responses was associated with poorer overall performance. This association was inverted in later stages (i.e., P300 and LPP). Together, our findings indicate stage-dependent associations between neural activation after negative information and cognitive functioning. Conceivably, increased early responses to negative feedback signify distraction, whereas higher activity at later stages reflects cognitive control processes to preserve ongoing performance.

Keywords: cognitive control, PASAT, event related potential, cognitive control training, negative information processing

Introduction

In a world full of competing information and sources of distraction, the ability to maintain coordinated and purposeful behavior is essential to sustain goal directed processes. This requires cognitive control, which comprises different cognitive functions including the ability to pay selective attention, ignore distracting information, turn attention away from stimuli when they prove irrelevant, and the ability to store and manipulate internal representations of information (Roiser et al., 2012). Especially the inhibition of irrelevant but salient information, like emotional stimuli challenges cognitive control (Iordan et al., 2013). Cognitive control is a key factor for successful human behavior. Therefore, it is not surprising that dysfunctional cognitive control is increasingly recognized as a key feature of various psychiatric disorders. In fact, research shows that in particular patients suffering from depression are prone to a heightened sensitivity toward negative stimuli, which receive more attention and working memory capacity and therefore impede the maintenance of coordinated and purposeful behavior (De Raedt and Koster, 2010). This "negativity bias" constitutes an important factor for the development and maintenance of depression as well as a central mechanism of recovery via restoration of cognitive control functioning (Roiser et al., 2012). Consistently, impairment of goal-directed behavior can be observed in healthy participants when cognitive resources are occupied by emotionally salient distractors (Dolcos and McCarthy, 2006).

A task used to investigate cognitive control is the "paced auditory serial addition task" (PASAT) (Gronwall, 1977) in which digits are presented auditorily and participants add the current digit to the digit they heard before. In its adaptive version, inter-stimulus intervals (ISI) decrease (increase) when several consecutive trials are correct (incorrect). The PASAT has been used as a cognitive control task in healthy (Siegle et al., 2014; Plewnia et al., 2015; Pope et al., 2015; Wiegand et al., 2019) as well as clinically depressed (Hoorelbeke et al., 2015; Koster et al., 2017) and at-risk participants (Van den Bergh et al., 2018). These comprehensive data indicate that this task is particularly suitable to investigate and train cognitive control in both, healthy subjects and psychiatric patients. Regarding its specific mechanism, it has been shown that the PASAT induces frustration and negative affect presumably due to receiving continuously feedback on current performance and working at the individual processing speed limit. Furthermore, the negative affective change induced by the PASAT can be correlated with a lower performance (Plewnia et al., 2015), implying that task- or feedback-related irritation must be sufficiently compensated to uphold goal directed

behavior. Therefore, the PASAT challenges cognitive control by means of emotional and cognitive responses to feedback information at a high cognitive load. On a neurophysiological level, prefrontal control on limbic areas plays a key role in overcoming this distraction caused by negative information (Plewnia et al., 2015). The dorsolateral prefrontal cortex (dlPFC) influences PASAT performance (Lazeron et al., 2003). However, more studies are needed for a better understanding of the mechanisms of action underlying the PASAT.

Therefore, the goal of the current study is to investigate the highly time dynamic neural signatures of the PASAT. Due to their high temporal resolution event related potentials (ERP) are best suited to find such neural signatures of PASAT performance. To capture the conflict of competing negative information and ongoing cognitive functioning in the PASAT, ERPs locked to performance feedback presented simultaneously with the next target digit, are derived from three different processing stages.

The feedback related negativity (FRN) is a negative deflection having its peak between 200 and 300 ms after a performance feedback stimulus was presented. It is an ERP that has been shown to be sensitive to feedback valance (Ridderinkhof et al., 2004; Hajcak et al., 2006). It is larger for negative than positive feedback and maximal at medial frontal electrode sites (Gehring and Willoughby, 2002). Besides of its informative value concerning current task performance (Holroyd and Coles, 2002; Holroyd and Yeung, 2012) it has been suggested that the FRN indicates the emotional impact of a negative expectation violation (Luu et al., 2003), implying that feedback does involve emotional processing that captures cognitive resources. Since in our study negative information is operationalized by the given feedback, we utilized the FRN to investigate early parts of negative information processing. Of note, in our study its registration conditions, however, differ from the common investigations of the FRN or feedback processing because it summarizes the processing of new information (next digit) and performance feedback (last digit).

Attention allocation to task relevant as well as subsequent memory processes is reflected by the P300. It is a positive deflection peaking between 300 and 400 ms following stimulus presentation which is maximal at midline-parietal sites (Sutton et al., 1965; Polich, 2012). Furthermore, an enhanced amplitude for emotional compared to neutral stimuli can be observed for both, positive and negative content (Johnston et al., 1986; Keil et al., 2002; Delplanque et al., 2004) probably reflecting high inherent motivational salience of emotional stimuli per se. Therefore, it seems to be best suited to study negative information processing

during a demanding cognitive task. Moreover, several studies have linked larger P300 amplitudes with performance gains in non-emotional (Daffner et al., 2011; Saliasi et al., 2013) as well as in emotional tasks (Palomba et al., 1997) making it suitable to investigate associations of neural feedback processing and PASAT performance in our study.

The late positive potential (LPP) is known to capture attention allocation toward emotional salient stimuli (Cacioppo et al., 1996; Ito et al., 1998). It is recorded at centro-parietal sites and begins as early as 200–300 ms post-stimulus. In contrast to the P300 it can outlast the stimulus presentation well beyond several seconds (Hajcak et al., 2009). Therefore, besides its sensitivity to automatic attention allocation to emotional stimuli, it reflects continued processing of emotional content and is regulated by top-down mechanisms. Moreover, the magnitude of the LPP amplitude has also been linked to task performance (Weinberg and Hajcak, 2011; Bamford et al., 2015; Faehling and Plewnia, 2016). We want to utilize the LPP in our study to capture late neural reactions to negative information in the form of feedback and moreover to investigate its associations with the PASAT performance.

Taken together, with this study, we investigate the time dynamic neural signatures (FRN, P300, and LPP) of the PASAT and aim for a better understanding of the underlying mechanisms. As negative feedback is associated with negative affect and competes with ongoing performance, we assume to find larger amplitudes for negative than positive feedback in all stages of feedback processing. Furthermore, we hypothesize to find significant correlations of PASAT performance and ERP magnitudes indicating associations of cognitive control functioning and neural activation.

Material and Methods

Subjects

Twenty-five healthy participants were recruited via internet advertisement. All participants had normal or corrected to normal vision and normal hearing. Exclusion criteria were current psychiatric disorders, neurological disorders, major head injuries or color blindness. They received a financial compensation or course credit for their participation. All participants gave their written informed consent. One participant had to be excluded due to excessive noise in the electroencephalographic (EEG) data (see section “Electrophysiological Data Processing”). The remaining 24 participants (16 female, age: M = 23.71, SD = 4.06) were

included in the analysis. See Supplementary File 1 for the data underlying the sample characteristics and Table 1 of the Supplementary Materials for demographic and neuropsychological characteristics of the sample. The study was approved by the Ethics Committee of the Medical Faculty of the Eberhard-Karls-University and at the University Hospital Tübingen and was conducted in compliance with the Declaration of Helsinki.

Tasks

The tasks *PASAT, color presentation* and *feedback-neutral PASAT* outlined below were computer-based and implemented using PsychoPy2 v1.80.02 (Peirce, 2007, 2008). They were presented on a 17-inch monitor.

Paced Auditory Serial Addition Task (PASAT)

We used a 2-back version of an adaptive Paced Auditory Serial Addition Task (PASAT). Participants sat in front of a monitor (distance: approximately 65 cm) and heard digits (1–9, duration of presentation: 433–567 ms) via in ear headphones. The task was to add the current digit to the digit they heard before the last one (2-back). Results were indicated by pressing the corresponding key on a keyboard that was equipped with the response letters 2–18. Feedback was given after each trial simultaneously with the presentation of the new digit by presenting green (red) light after correct (incorrect) responses. In order to make the feedback highly salient the whole monitor was filled with the corresponding feedback color (e.g., 17 inch). The duration of the feedback presentation was 433 ms (matched to the presentation duration of the shortest number). Initially the ISI was set to 3 s. The ISI thereby refers to the time in between presented digits as well as feedback, since it was presented simultaneously. The ISI was decreased (increased) after four consecutively correct (incorrect) trials by 100 ms. This causes the PASAT to adapt to the capability of each participant while remaining challenging. The task comprised three blocks each with a duration of 5 min with 30 s of break in between. The total number of correct trials was used as the main outcome variable. Because the PASAT is highly demanding both to WM and processing speed, it is challenging to stay focused throughout the duration of the task and to not get distracted by the feedback provided. According to our hypothesis, lack in cognitive control would result in fewer consecutive correct responses. Therefore, we calculated the proportion of consecutive correct relative to the overall correct responses as a second outcome variable (subsequently referred to as “performance stability”). Moreover, for the ERPs of the PASAT, only

feedback following a response was used (e.g., trials with red feedback for a missing response were excluded from analysis).

Control Task "Color Presentation"

Since we aimed to test the differential neural responses to feedback valence as indicated by red and green screen color in contrast to the neural activation to red and green color as such, we conducted a control task "color presentation" (CP). Participants were asked to sit in front of a monitor (distance: approximately 65 cm) and perceive red and green light peripheral by keeping their gaze on the keyboard just like they would do while performing the PASAT. The task consisted of two blocks each with a duration of 2.5 min. Red and green light was presented for 433 ms (as in the PASAT) in random order with a jittered inter stimulus interval (1,500–2,500 ms).

Control Task "Feedback-Neutral PASAT"

Since differences in neural activity for negative feedback from positive feedback could be due to error monitoring based on the mistake and not the processing of the negative performance feedback as such, we additionally conducted a feedback neutral version of the PASAT ("feedback-neutral PASAT"). The procedure of this feedback-neutral PASAT was exactly like for the PASAT (see section "Paced Auditory Serial Addition Task (PASAT)"), except that no feedback was presented. Furthermore, the feedback-neutral PASAT only comprised two blocks of 5 min each.

Electroencephalography Recording

The electroencephalogram (EEG) was recorded using an elastic cap (EASYCAP GmbH, Herrsching, Germany), the actiCHamp amplifier system with 32 active Ag/AgCl electrodes and the corresponding Brain Vision Recorder system (Brain Products GmbH, Gilching, Germany). EEG was registered from 27 scalp sites (FP1, F7, F3, Fz, F4, F8, FC5, FC1, FCz, FC2, FC6, C3, Cz, C4, CP5, CP1, CPz, CP2, CP6, P7, P3, Pz, P4, P8, O1, Oz, O2). Additionally, an electrooculogram (EOG) was recorded. For horizontal eye movements two electrodes were placed approximately one cm left and right of the eyes. One electrode positioned approximately one cm below the left eye and the Fp1 electrode were used to register vertical eye movements. Furthermore, electrodes were placed on the left and right mastoid. The left mastoid served as the online reference and a forehead electrode as the ground. The online sampling rate was 1,000 Hz. Impedances were kept below 10 kΩ before

initiation of the recording. To check if time locking of the EEG trace and events was correct, we additionally equipped the presentation monitor with a photo sensor (Brain Products GmbH, Gilching, Germany). There were no time differences between the signals.

Procedure

The experiment took place in a dimly lit, quiet room. After the participants gave their written informed consent, the EEG electrodes were attached to the scalp. Participants were asked to sit quietly during the EEG recording. For all participants the experiment started with the CP before the PASAT was conducted. Although this could lead to a confounding of the data by order effects, we refrained from balancing the order of the two tasks since we feared that if participants performed the CP task after the PASAT they would have learned the specific association of color and feedback. Deriving neural signatures of the mere color presentation, which was the goal of the CP, would thus not be possible anymore as the signal would be confounded by learned associations and it can be assumed that this would lead to a stronger confound of the data than a non-mixed task order. After the CP, participants carried out the PASAT. To make sure participants understood the instruction of the task, they completed 30 practice trials, which were excluded from analysis. To control for affective effects of the PASAT, participants completed the 20 item positive and negative affect schedule (Krohne et al., 1996) immediately before and after the PASAT. That followed a resting phase of 7 min during that heart rate measures were obtained, which are not subject of the current paper. Afterward participants completed the control task “feedback-neutral PASAT.”

Electrophysiological Data Processing

We analyzed the EEG data using the EEGLAB toolbox (Delorme and Makeig, 2004) running on MATLAB 9.2 R2017a (The MathWorks, Natick, MA, United States) and the EEGLAB toolbox ERPLAB (Lopez-Calderon and Luck, 2014). The raw EEG was resampled offline to 250 Hz and re-referenced to an average of the left and right mastoids. Band-pass filters with a low and high cutoff of 0.1 and 35 Hz, and a notch-filter at 50 Hz were applied. Ocular artifacts were removed manually using independent component analysis (JADE algorithm; Cardoso, 1999). Subsequently feedback locked epochs were extracted ranging from - 100 to 1,000 ms relative to feedback (PASAT), color (CP), respectively. For the feedback-neutral PASAT the epochs were locked to the digit presentation, which is exactly the same time the feedback would have been presented in the PASAT. Just like for the PASAT and CP, epochs of the feedback-neutral PASAT ranged

from -100 to 1,000. Artifact correction was conducted in the epoched EEG. Epochs containing EEG signals exceeding an amplitude of 65 µV within a 100 ms moving window or exceeding - 65 to + 65 µV within the epoch were considered artifacts and were rejected (using the ERPLAB implemented automated artifact detection). Participants with more than 25% of rejected epochs were excluded from further analysis (n = 1). In the PASAT on average M = 4.12% of the green feedback trials (SD = 5.50%) and M = 4.60% of the red feedback trials (SD = 5.27%) were rejected. In the CP M = 2.57% of the green color trials (SD = 4.67%) and M = 3.25% of the red color trials (SD = 6.76%) were rejected. In the feedback-neutral PASAT on average M = 3.98% of the correct trials (SD = 6.53%) and M = 5.62% of the incorrect trials (SD = 7.83%) were rejected. Overall, 2,610 green and 1,245 red feedbacks of the PASAT, 1,796 green and 1,771 red color trials and 1,874 correct and 1,467 incorrect trials of the feedback-neutral PASAT were included in the ERP analysis. In sum, there were six conditions for the calculation of the ERPs: green color after a correct trial in the PASAT (green feedback), red color after an incorrect trial in the PASAT (red feedback), green color in the CP, red color in the CP, incorrect trials in the feedback-neutral PASAT and correct trials in the feedback-neutral PASAT. ERPs for the analysis of the PASAT results were constructed by separately averaging trials in the four conditions (green feedback, red feedback, green color, red color). Subsequently we calculated difference waves: positive feedback = green feedback (PASAT) - green color (CP), negative feedback = red feedback (PASAT) - red color (CP). All further ERP analyses refer to these difference waves (see Supplementary Figures 1–6 in the Supplementary Materials depicting the raw waveforms and scalp maps separately for the PASAT and CP for the FRN, P300 and LPP). ERPs for the analysis of the feedback-neutral PASAT were constructed by separately averaging trials in the two conditions correct and incorrect trials.

We chose the electrode sites and time windows to measure the FRN, P300, and LPP according to previous literature. The FRN was defined as the mean amplitude within a time window between 200 and 300 ms following feedback at Fz (Gehring and Willoughby, 2002). The P300 was scored as the average of three centro-parietal sites (Cz, CPz, Pz) (Sutton et al., 1965; Johnson, 1993). According to visual inspection there is a large shift in the P300 waveforms due to the FRN (see Figure 2). Therefore, we defined the P300 as the averaged ERP waveform for each participant as the base-to-peak difference in voltage between the most negative peak between 200 and 300 ms post feedback and the most positive peak 300–400 ms post feedback (Fabiani et al., 1987; Polich, 1991; Polich and Kok, 1995). The LPP was scored as the average of five centro-parietal sites (Cz, CP1, CPz, CP2, Pz) and defined

as the mean amplitude within a time window between 400 and 1,000 ms following feedback (Hajcak et al., 2009; Weinberg and Hajcak, 2010).

Data Analysis

All statistical analyses were performed using SPSS Statistics for Microsoft Windows (version 24.0). See Supplementary File 1 for the data underlying the results. To examine changes in mood after the PASAT, PANAS scores from before the PASAT were compared to after processing the PASAT using paired t tests. Furthermore, associations of the PANAS with PASAT scores were examined using bivariate correlation analyses using Pearson correlation coefficient. Additionally, it could be assumed that a better PASAT performance would be associated with fewer incorrect trials and therefore with less negative feedback. In turn, the mere difference in the presentation frequency of good vs. bad performers could lead to a differential neural reaction to negative feedback and we would not know if an association of the valence-specific neural activation (Δ = negative-positive feedback) and the PASAT performance could just occur due to this difference and not due to differences in cognitive control functions. Therefore, we additionally calculated the correlation of the number of incorrect trials and the PASAT performance (number of correct trials). To analyze a differential neural activation after correct vs. incorrect trials in the feedback-neutral PASAT we performed paired t-tests separately for the FRN, P300 and the LPP. To analyze a differential neural activation to positive vs. negative feedback we performed paired t-tests separately for the FRN, P300, and the LPP. To further analyze associations of the valence-specific neural activation (Δ = negative-positive feedback) and changes in the affect ratings with the PASAT performance (number of correct trials and performance stability) we calculated bivariate correlation analyses using Pearson correlation coefficient. For all analyses, two-tailed tests were used, and a 0.05 level of significance was employed.

Results

Changes in Affect and Behavioral Data

After the PASAT, overall affect deteriorated significantly as indicated by the PANAS: positive affect ratings decreased [before: $M = 29.13$, $SD = 5.06$; after: $M = 26.21$, $SD = 5.67$; $t(23) = 2.41$, $p = 0.025$] and negative affect ratings increased [before: $M = 13.29$, $SD = 2.93$;

after: M = 20.96, SD = 9.51;$t_{(23)}$ = -4.86, $p < 0.001$]. There were no significant correlations of the affect ratings with the PASAT performance (all $p \geq 0.472$). Furthermore, there was no significant correlation of the number of incorrect trials and the PASAT performance (number of correct trials) [$r_{(22)}$ = - 0.089, p = 0.681]. Concerning the PASAT performance, on average, participants gave 113.04 (SD = 31.32) correct, and 52.42 (SD = 19.68) incorrect responses with 239.54 (SD = 31.45) trials overall (including trials without a response).

Electrophysiological Data

Feedback Related Negativity

Figure 1 displays the grand average waveform (A) of the FRN and the mean voltage distribution across the scalp (B) for negative and positive feedback separately (note that higher negative values indicate a larger FRN). The mean amplitude FRN for negative feedback was significantly larger (M = - 0.817, SD = 3.223) than for positive feedback [M = 0.846, SD = 2.843; $t_{(23)}$ = 2.671, p = 0.014]. The correlation analysis for the valence-specific neural activation of the FRN (ΔFRN = negative-positive feedback, e.g., a more negative value indicates that the FRN for negative feedback was larger than for positive feedback), revealed a significant association between the ΔFRN and the number of correct trials in the PASAT [see Figure 1(C), note that for all scatterplots the Y-axis is ordered ascendingly according to the values indicating larger ERPs, e.g., for the FRN values are ordered from positive to negative]. A smaller ΔFRN (e.g., more positive ΔFRN) was linked to a larger amount of correct trials over all [$r_{(22)}$ = 0.425, p = 0.038]. In addition, we found a significant correlation of the ΔFRN and the performance stability. A smaller ΔFRN (e.g., more positive ΔFRN) was linked to a higher performance stability [$r_{(22)}$ = 0.433, p = 0.034].

P300

Figure 2 displays the grand average waveform of the P300 (A) and the mean voltage distribution across the scalp (B) for negative and positive feedback separately. Note that to avoid carry over effects of the shifts in the waveform in the time range of the FRN to the P300, we conducted base-to-peak analyses to define the P300 amplitudes. A paired t-test revealed a significant difference between the P300 for positive and negative feedback. The P300 was significantly larger for negative feedback (M = 10.648, SD = 4.047) than for positive feedback [M = 8.812, SD = 3.464; $t_{(23)}$ = 3.64, p = 0.001]. For the valence-specific

neural activation of the P300 (ΔP300 = negative-positive feedback), we found a significant correlation between the ΔP300 and the number of correct trials in the PASAT [see Figure 2(C)]. We observed that a larger P300 elicited by negative as compared to positive feedback (e.g., a more positive ΔP300) was linked to more correct trials [$r_{(22)} = 0.422$, $p = 0.040$]. In addition, we found a significant correlation of the ΔP300 and the performance stability [$r_{(22)} = 0.465$, $p = 0.022$]. A larger P300 by negative as compared to positive feedback was linked to increases in performance stability.

Late Positive Potential

The grand average waveform of the LPP (A) and the mean voltage distribution across the scalp (B) for negative and positive feedback separately, are depicted in Figure 3. We found a significant difference between the mean amplitude LPP for positive and negative feedback. The LPP for negative feedback was significantly larger ($M = 3.125$, $SD = 3.118$) compared to positive feedback [$M = 2.368$, SD = 3.026; $t_{(23)} = 2.215$, $p = 0.037$]. Further, there was a medium effect sized correlation of the valence-specific neural activation of the LPP (ΔLPP = negative - positive feedback) and the number of correct trials, which failed to reach significance [$r_{(22)} = 0.300$, $p = 0.155$]. However, we found a significant correlation of ΔLPP and performance stability in the PASAT [$r_{(22)} = 0.407$, $p = 0.049$, see Figure 3(C)]. A larger LPP by negative as compared to positive feedback was linked to increases in performance stability.

Control Task Feedback-Neutral PASAT

Moreover, there was no difference in neural responses after errors and correct trials in the control task feedback-neutral PASAT for the FRN [correct trials $M = -0.857$, $SD = 1.125$, incorrect trials $M = -0.633$, $SD = 1.624$, $t_{(23)} = -0.872$, $p = 0.392$], P300 [correct trials $M = 5.550$, $SD = 2.029$, incorrect trials $M = 5.607$, $SD = 2.348$, $t_{(23)} = -0.154$, $p = 0.879$] nor LPP [correct trials $M = 0.399$, $SD = 1.191$, incorrect trials $M = 0.329$, $SD = 1.641$, $t_{(23)} = -0.219$, $p = 0.828$]. These results indicate that potential differences in neural reactions to feedback are not due to error monitoring processes but feedback valence (descriptive data, waveforms, and scalp maps for the ERPs of the feedback- neutral PASAT can be found in Supplementary Table 2 and Supplementary Figures 7–9 of the Supplementary Materials).

Discussion

In this study, we examined electrophysiological characteristics of cognitive control processes and their relation to task performance by means of a challenging and adaptive PASAT. The main findings are (a) that positive and negative feedback induce a differential neural activation throughout the time course of feedback processing (b) that the valence-specific neural activation (negative-positive feedback) is associated with the PASAT performance, and (c) that the direction of this association is critically dependent on the stage of feedback processing.

We found that negative information in the form of performance feedback produced similar neural signals for the FRN time range as in common studies investigating feedback processing (Gehring et al., 2012). Thus, in line with our hypothesis, the FRN was larger for negative feedback than for positive feedback. This observation for the FRN is frequently interpreted as a stronger neural reaction of the anterior cingulate cortex (ACC) for negative than for positive feedback. Since the posterior medial frontal cortex including the ACC is known to reflect the motivational value of stimuli (Ridderinkhof et al., 2004) this further suggests that in early stages of feedback processing in the PASAT, negative feedback is probably perceived as more salient than positive feedback. This makes sense, concerning the fact that negative feedback contains important information to adapt behavior according to changing task demands. Therefore, it could be assumed that a more pronounced reaction to errors is beneficial for task performance. In accordance with this assumption several authors describe a beneficial effect of larger FRN and error-related negativity amplitudes on task performance (Frank et al., 2005; Cohen et al., 2007; Unger et al., 2012; Meyer et al., 2014). For example, when learning a sequence of button presses by trial and error the FRN was significantly larger for trials that were followed by a correct response indicating that a larger FRN was associated with a better learning efficacy (Van Der Helden et al., 2010). However, in our study we found that a larger valence-specific FRN amplitude was associated with poorer task performance, indicating that in the PASAT the feedback plays a different role compared to common studies investigating the FRN. To understand this, it must be considered that in the present study, besides of its informational value, the negative feedback had also the potential to fundamentally distract from task performance, since it was presented simultaneously with the next target. Therefore, we interpret the FRN as a neural signature of attention allocation toward a distractive negative information as opposed to the task relevant target. This is in line with the assumption that the FRN indicates the emotional impact of negative expectation

violation (Luu et al., 2003). In accordance with the well-established evidence of a negativity bias linked to a decreased cognitive control in depression, it has been shown that the FRN is enhanced in patients suffering from current as well as remitted depression indicating a hypersensitivity to loss, punishment or negative related stimuli in depression (Tucker et al., 2003; Santesso et al., 2008; Cavanagh et al., 2011) which reflects reduced cognitive control over emotions. This is consistent with our finding of a poorer PASAT performance (number of correct trials as well as the performance stability) in healthy participants with larger FRNs. Moreover, this finding suggests that a larger neural activation following negative than positive feedback is linked to an enhanced sensitivity to negative stimuli, which leads to increased distraction, by the valence-specific neural activation in this early stage of feedback processing.

For the P300 we could also confirm our hypothesis of a stronger neural activation for negative than for positive feedback. Consistent with findings showing that the P300 reflects attention allocation toward motivationally and/or emotionally relevant content, this indicates that negative feedback in the PASAT is associated with greater resource allocation than positive feedback. This assumption is bolstered by the correlation of the ΔP300 (negative-positive feedback) and the PASAT: in contrast to the FRN a larger P300 to negative than positive feedback was associated with a larger number of correct trials and a higher performance stability. This finding is in accordance with previous studies showing comparable associations. For instance it has been observed that a better performance in an n-back working memory task was associated with a larger P300 amplitude (Daffner et al., 2011; Saliasi et al., 2013). Moreover, a larger P300 was found to be associated with more remembered stimuli of emotional content (Palomba et al., 1997). Therefore, our finding adds further evidence that the additional recruitment of neural activity at this stage of processing leads to performance gains and the maintenance of goal-oriented behavior.

In line with our hypothesis, we also found a larger amplitude for negative than for positive feedback for the LPP. Since a large body of evidence shows that the LPP is larger for emotional than for non-emotional stimuli this indicates that negative feedback was perceived as emotionally more relevant than positive feedback (Cacioppo et al., 1996). The fact that negative feedback captures more resources than positive feedback reflected by the LPP suggests that in later stages of feedback processing a negativity bias can be observed. Regarding the valence-specific neural activation of the LPP (ΔLPP = negative-positive feedback) we could observe a similar pattern as for the ΔP300. Although the medium effect

sized correlation of the ΔLPP with the number of correct trials in the PASAT failed to reach significance, we found a significant correlation of the ΔLPP and the performance stability, indicating the same association: a larger LPP by negative than positive feedback was associated with a higher performance stability. Just like the association of the ΔP300 with performance, a stronger neural reaction to negative than positive feedback in later processing stages seems to reflect the recruitment of additional cognitive resources, which increase the effective maintenance of coordinated behavior. Our data are in accordance with results showing a positive relationship between larger LPP amplitudes and task performance. This was observed for example in a delayed working memory task: larger ΔLPPs (negative – positive) evoked by emotional pictures serving as distractors were associated with better task performances (Faehling and Plewnia, 2016). Furthermore, also in an approach avoidance task it was found that larger LPP amplitudes were linked to faster RTs (Bamford et al., 2015). In contrast, there is also a finding of larger LPP amplitudes associated with performance deteriorations, indicating increased engagement with a distracting stimulus (Weinberg and Hajcak, 2011). However, it must be considered that no WM task was used in their study, but a speeded response task, focusing on the investigation of attentional processes and less demanding cognitive functions as opposed to our study. In sum, our results for the LPP and the P300 seem to be in line with the idea of an additional recruitment of cognitive resources by emotional stimuli (González-Garrido et al., 2015), at least in these late stages of feedback processing.

Consistent with previous studies, we found affect ratings significantly decreased after PASAT performance (Holdwick and Wingenfeld, 1999; Lejuez et al., 2003; Plewnia et al., 2015). However, there was no significant correlation between the PANAS affect ratings and the PASAT performance (Plewnia et al., 2015). Nevertheless, their functional association is underlined by the correlation between the evoked potentials indicating emotional processing and task performance. For that matter, the use of self-report questionnaires like the PANAS might be not sufficiently precise to detect latent affect changes.

Taken together it appears that in the early stages of feedback processing (<300 ms following feedback) in the PASAT, less automatic resource allocation toward negative than positive feedback is beneficial for task performance. Whereas in later stages (>300 ms following feedback) this association is inverted: a more extensive neural recruitment following negative feedback is linked with better performance. Conceivably, in bad performers increased early (<300 ms) activation after negative feedback interferes with successful memory updating.

Apparently, through largely bottom up driven processing, attentional resources are diverted away from target processing and toward distractive negative information, which is reflected by a large neural response to negative feedback. Accordingly, good performance is associated with the ability to engage top-down control already at early processing stages and maintaining attentional resources to targets and not negative feedback information. Opposingly, in later stages of feedback processing (>300 ms), large valence-specific amplitudes seem to reflect resource allocation toward goal directed task processing, indicating successful implementation of top-down control. Therefore, good performers are apparently capable of using the feedback information in a top down driven manner to achieve goal directed behavior, reflected by a large valence specific neural activation in late processing stages.

Overall, the ERP signatures we found contribute to a better understanding of the neural mechanisms underlying the PASAT and furthermore help to better understand why the PASAT is an efficient cognitive control training and could be a promising, innovative treatment option for patients suffering from depression. Our results could indicate that poor performance is associated with increased sensitivity to negative information in early processing stages and reduced allocation of cognitive resources in later stages. As stated above, depressed patients depict a hypersensitivity to negative feedback and negative information in general. PASAT training may help to reduce this hypersensitivity by implementing cognitive control strategies in early processing stages to cope with the frustration caused by PASAT. At the same time, these activated cognitive resources could lead to an effective use of the feedback information in later processing stages. This hypothesis is supported by findings showing a critical involvement of the dlPFC in the PASAT performance (Lazeron et al., 2003), which in turn is a neuronal structure underlying cognitive control functioning and has been found to be hypoactive in depressed patients (Siegle et al., 2007). Our results provide useful tools to test such possible training mechanisms and to determine which patients can benefit from a cognitive control training in the long run.

There are some limitations of the current study. It could be assumed that a better performance in the PASAT would be confounded by fewer incorrect trials and therefore less negative feedback. This would indicate that a differential neural reaction to negative vs. positive feedback could be a result of this difference as opposed to be a marker of cognitive control functions. However, due to the adaptive design of the PASAT, a good performance goes along with a faster stimulus presentation and as a result, participants make more mistakes. This is also reflected by the missing association of the PASAT performance and the amount

of negative feedback: good performers receive as much negative feedback as bad performers. In addition, there have been a lot of misses in the task (e.g., trials without a response) that were excluded from data analysis. Probably also these misses reflect meaningful information since they could reflect distraction by negative feedback information. However, during the experiment we observed that the cause for the misses are manifold: participants simply processed the digits not fast enough; sometimes there actually was a response, but it occurred at the same time the feedback was presented (meaning it was not recorded) or sometimes participants zoned out and did not process the stimuli at all for several trials. Unfortunately, we cannot distinguish between these cases afterward but at the same time it can be assumed that their informative value for cognitive functions and neural responses to feedback are quite different. Thus, we decided to exclude misses completely from the analysis. Moreover, it could be possible that differences of neural activation after negative feedback from positive feedback are not due to feedback valence but monitoring processes of behavior based on the mistake. However, if neural activity differences between correct and incorrect trials were based on error as opposed to feedback processing, these differences should also occur in the feedback-neutral PASAT. Yet, this was not the case, indicating that the observed results are due to feedback valence and not error monitoring. Furthermore, to avoid confounds of neural activations of the CP by previously learned associations of color and feedback, the order of performance of the CP and the PASAT was not counterbalanced but the same for all participants (CP first). Therefore, we cannot exclude that also the timing of the measurement affected the results.

To conclude, by elucidating the neural mechanisms underlying the PASAT performance, we demonstrate that enhanced neural activity in early processing stages of negative feedback indicates a diversion of cognitive resources toward negative information resulting in reduced goal-oriented behavior. In turn, additional allocation of resources after salient negative information as indicated by a higher P300 and LPP is linked with enhanced performance and may thus represent a neural signature of successful cognitive control of distractive negative information. Our results provide the basis for further studies using and investigating the PASAT as an effective cognitive control task. Based on these results, future studies will further elucidate associations and malleability of negative information processing, cognitive performance and mood regulation in sensitive population groups and psychiatric disorders.

Data Availability Statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Ethics Statement

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Faculty of the Eberhard-Karls-University and at the University Hospital Tübingen. The patients/participants provided their written informed consent to participate in this study.

Author Contributions

AS and CP conceived and designed the experiments. AS and LE collected the data. AS and LE prepared and processed the electrophysiological data. AS, LE, and CP performed the statistical analysis. AS, LE, and CP wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Supplementary Material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum. 2021.630468/full#supplementary-material

Conflict of Interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

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Figures

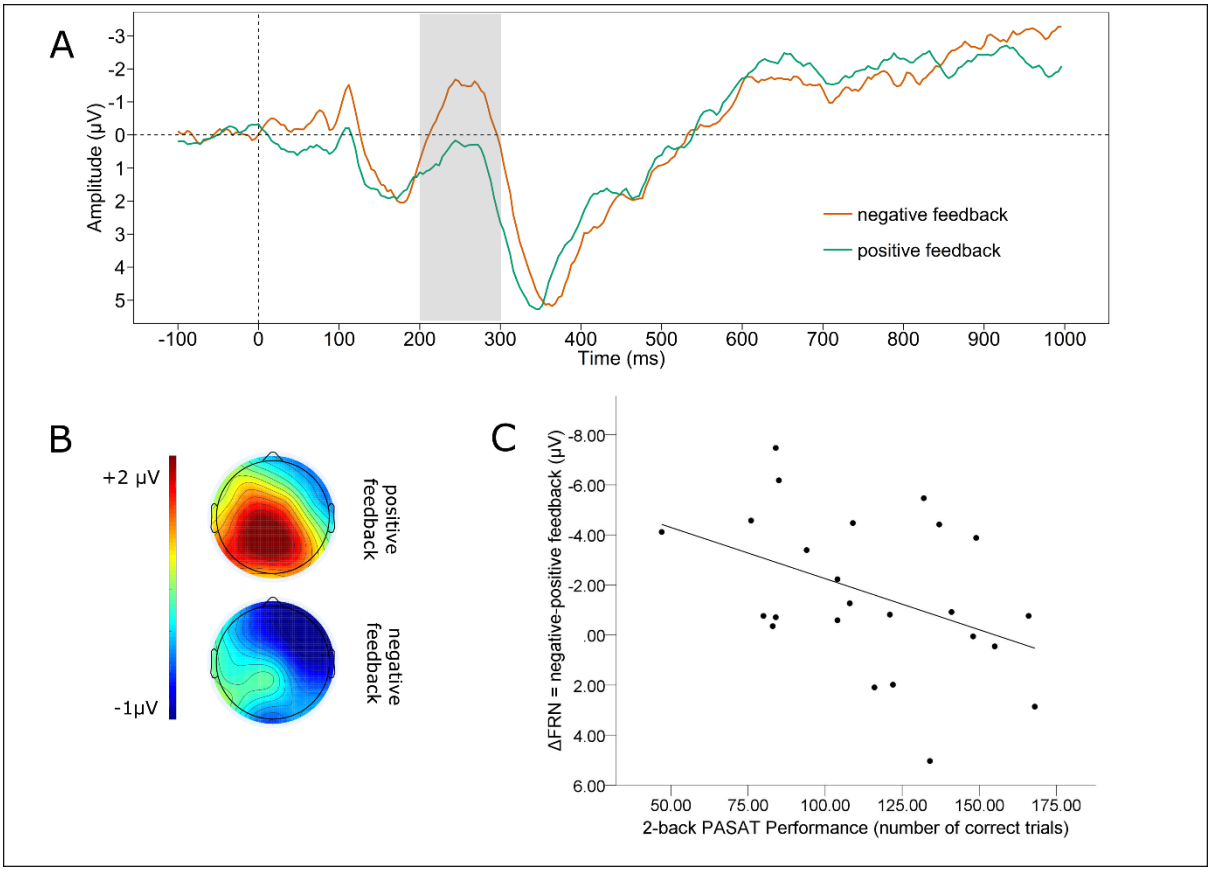

FIGURE 1. Feedback related negativity. (A) Grand average difference wave (PASAT - CP) separately for negative and positive feedback at Fz. (B) Scalp map displaying the mean voltage distribution for negative and positive feedback separately (200 - 300 ms post feedback). (C) Scatterplot displaying the PASAT performance as a function of the valence-specific FRN (ΔFRN = negative-positive feedback). Note, for the ΔFRN, more negative values indicate a larger amplitude by negative than positive feedback. Therefore, negative values are at the top of the Y-axis.

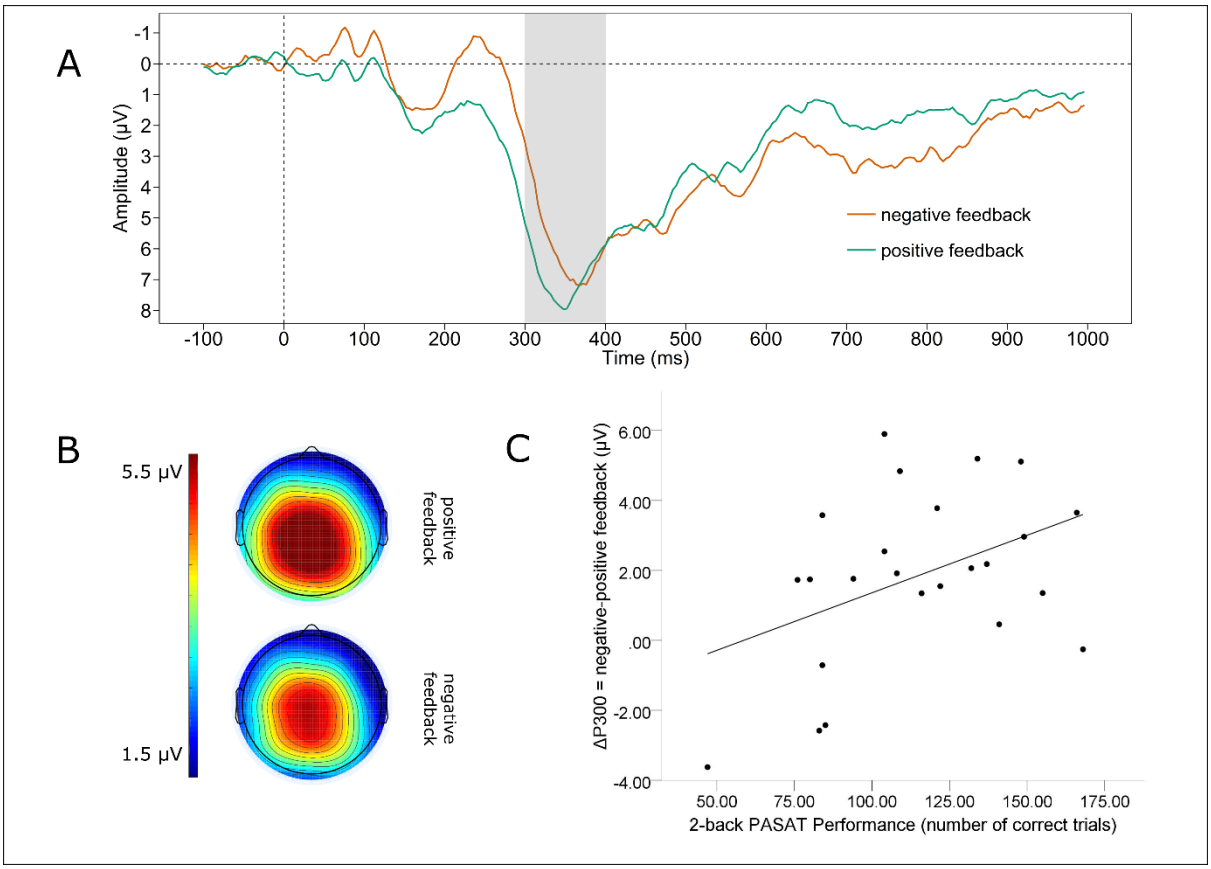

FIGURE 2. P300. (A) Grand average difference wave (PASAT – CP) of the P300 separately for negative and positive feedback averaged across Cz, CPz, Pz. Note that a base-to-peak analysis was performed for the P300. (B) Scalp map displaying the mean voltage distribution for negative and positive feedback separately (300–400 ms post feedback). (C) Scatterplot displaying the PASAT performance as a function of the valence-specific P300 (ΔP300 = negative-positive feedback).

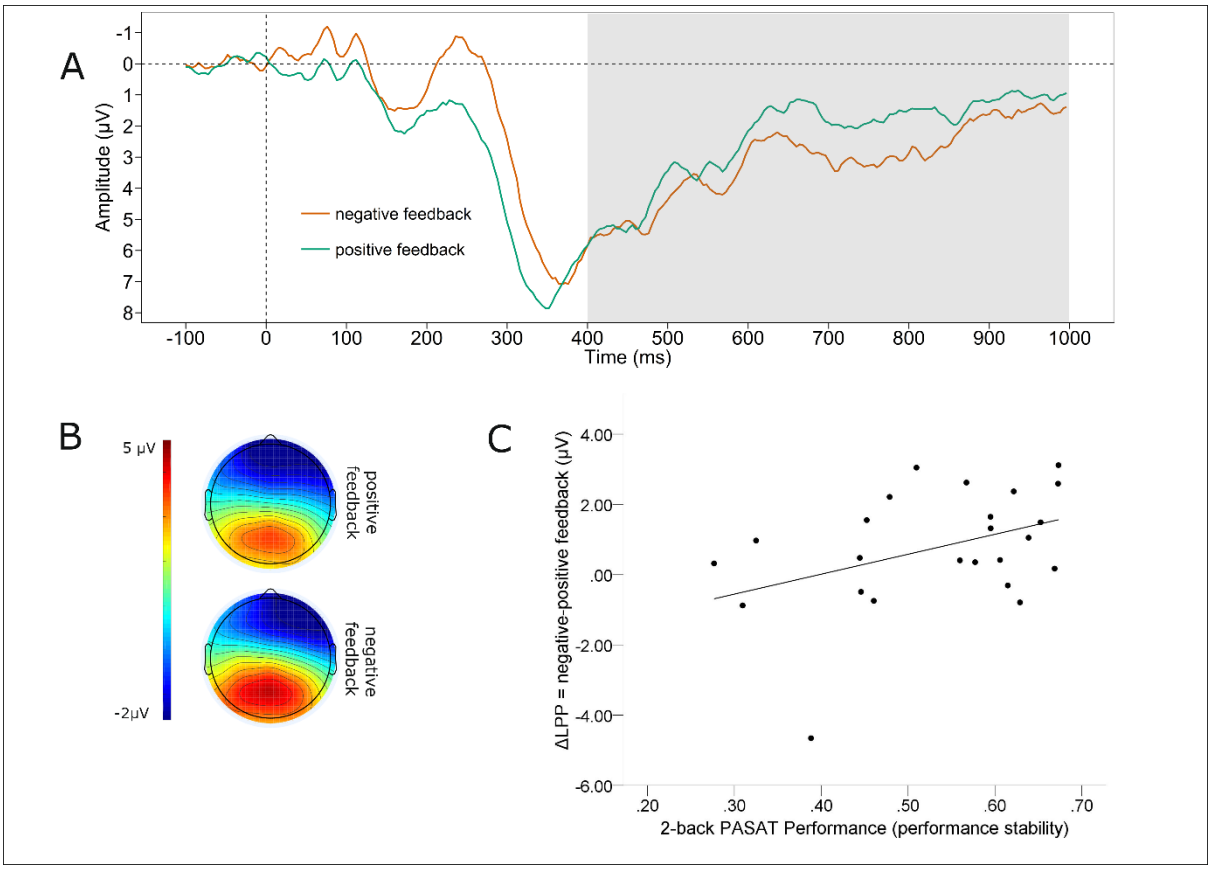

FIGURE 3. Late positive potential. (A) Grand average difference wave (PASAT – CP) of the LPP separately for negative and positive feedback averaged across Cz, CPz, Pz, CP1, CP2. (B) Scalp map displaying the mean voltage distribution for negative and positive feedback separately (400–1,000 ms post feedback). (C) Scatterplot displaying the PASAT performance as a function of the valence-specific LPP (ΔLPP = negative-positive feedback).

Supplementary Materials

Demographic and neuropsychological Characteristics of the sample

To assess neuropsychological characteristics of the participants, we measured complex attention, motor speed, visual-motor conceptual screening and executive functions with the Trail Making Test (Reitan, 1992). As a measure for approximate verbal intelligence we conducted the Multiple Choice Vocabulary Test (Lehrl, 1995). In addition, we measured participant's working memory with a short version of a digit span test of the Wechsler Adult Intelligence Scale (Wechsler, 2008). In our digit span task participants had to memorize 2-8 digits (two trials per level of difficulty, both were used for the calculation of the score) and repeat them in the same order (digit span same order) or in the reverse order (digit span reverse order).

Supplementary Table 1 - Demographic and neuropsychological characteristics of the sample

Characteristic	**%**	**M**	**SD**	**Range**
Sex (female)	66.66			
Age		23.71	4.06	20-37
University entrance diploma (yes)	95.83			
TMT-A (s)		23.12	7.55	14-51
TMT-B (s)		50.28	12.51	28-78
Digit span same order		8.33	1.95	5-12
Digit span reverse order		7.38	2.20	4-12
MWT-B		66.82	21.44	26.2-100
Notes. TMT-A = time to complete the Trail Making Test part A; TMT-B = time to complete the Trail Making Test part B; Digit span same order = number of correct remembered digits in the Digit span same order task; Digit span reverse order = number of correct remembered digits in the Digit span reverse order task; MWT-B = percentile rank in the Multiple Choice Vocabulary Test.				

Lehrl, S., Triebig, G., and Fischer, B. (1995). Multiple choice vocabulary test MWT as a valid and short test to estimate premorbid intelligence. *Acta Neurol. Scand.* 91, 335–345. doi:10.1111/j.1600-0404.1995.tb07018.x.

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Supplementary Table 2 – feedback-neutral PASAT

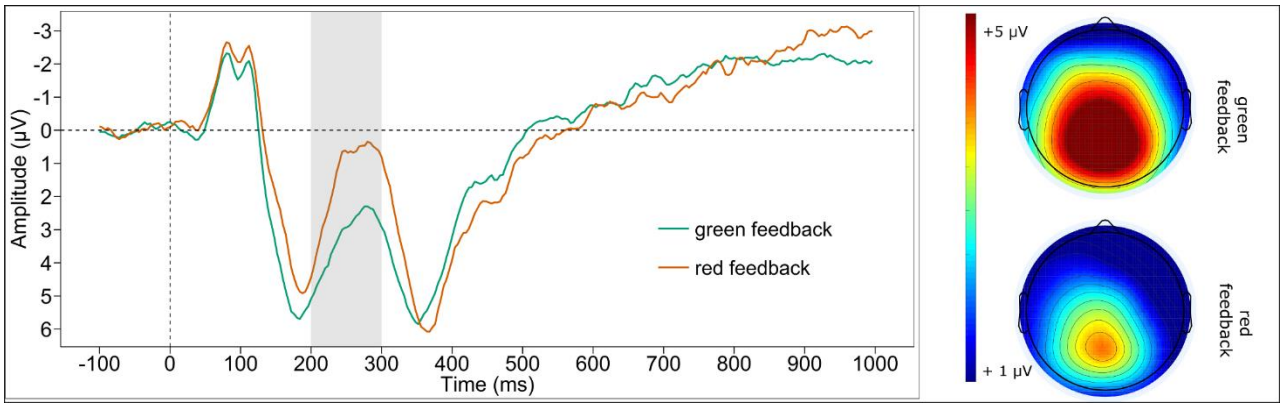
ERP	**correct trials**		**incorrect trials**		**Test statistic**
	M	SD	M	SD	
FRN	-0.857	1.125	-0.633	1.624	$t^{a}_{(23)} = -.872$, $p = .392$
P300	5.550	2.029	5.607	2.348	$t^{a}_{(23)} = -.154$, $p = .879$
LPP	0.399	1.191	0.329	1.641	$t^{a}_{(23)} = -.219$, $p = .828$

Notes. Means (M) and standard deviations (SD) of the amplitudes for the FRN, P300 and LPP separately for correct and incorrect trials in the feedback-neutral PASAT. ^{a}: paired t-Test.

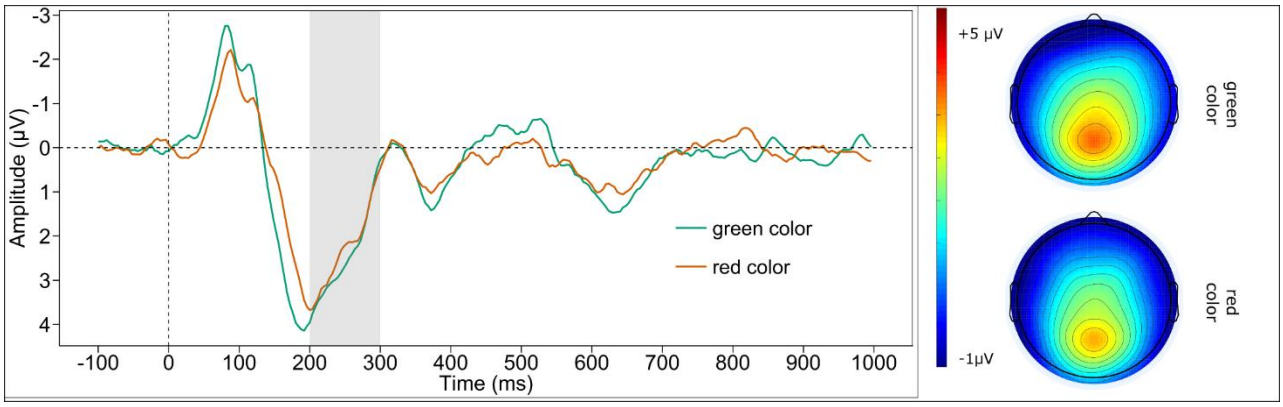
Supplementary File 1 – data underlying the study

Note: Since Supplementary File 1 is an extensive spreadsheet of data, it was not possible to be included in this this doctoral thesis. Please see https://www.frontiersin.org/articles/10.3389/fnhum.2021.630468/full#supplementary-material for Supplementary File 1.

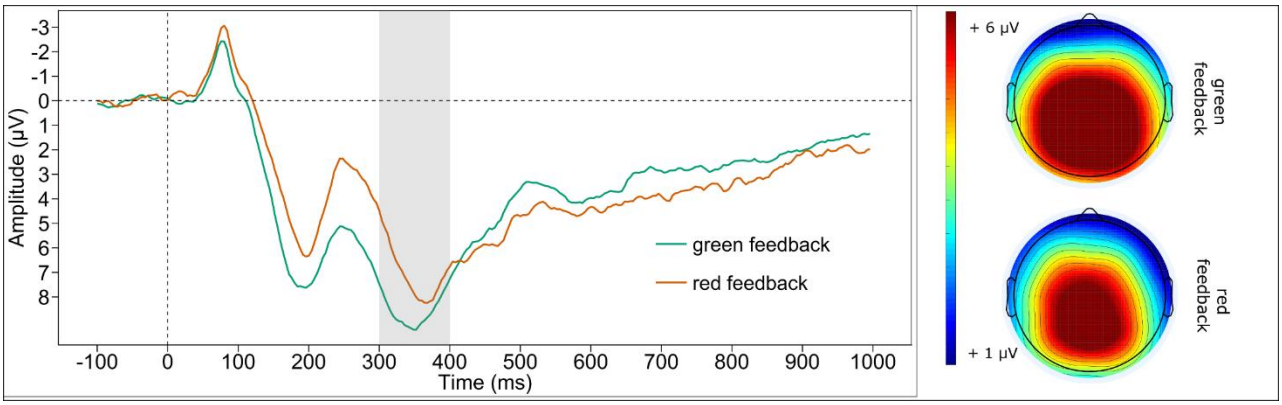
Supplementary Figures 1-9



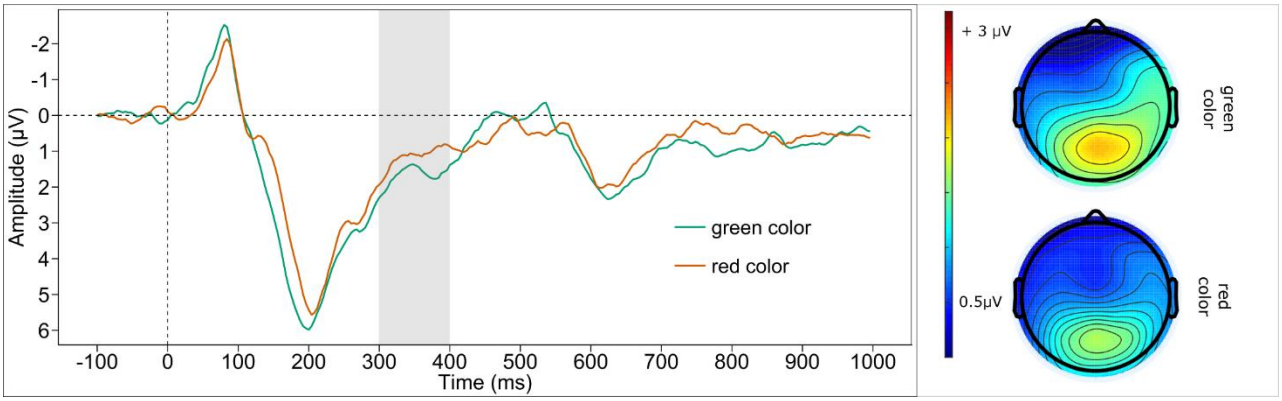
Suppl. Figure 1. Raw FRN for the 2-back PASAT. The grand average waveform separately for red and green feedback (left panel) at Fz and the scalp map displaying the mean voltage distribution for red and green feedback separately (right panel, 200 - 300 ms post feedback).



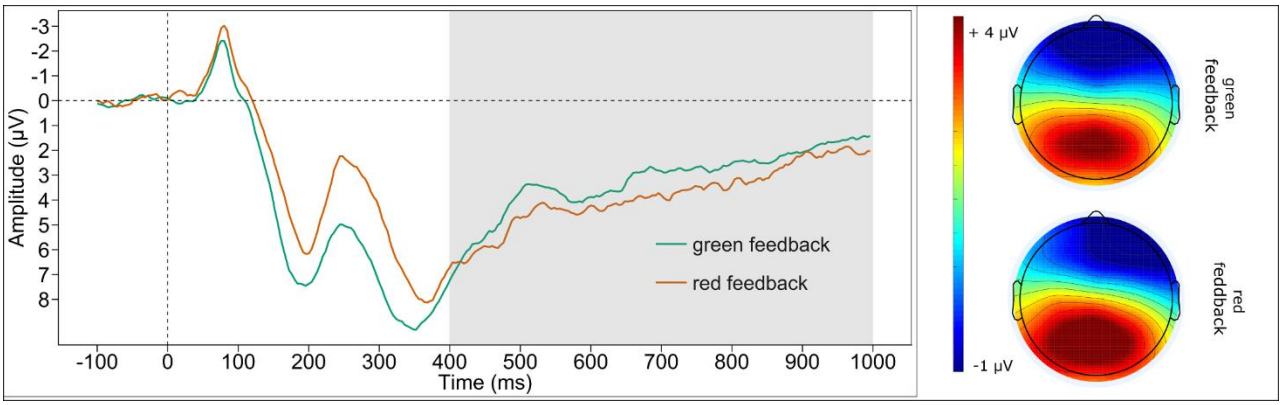
Suppl. Figure 2. Raw FRN for the color presentation task. The grand average waveform separately for red and green color (left panel) at Fz and the scalp map displaying the mean voltage distribution for red and green color separately (right panel, 200 - 300 ms post color presentation).



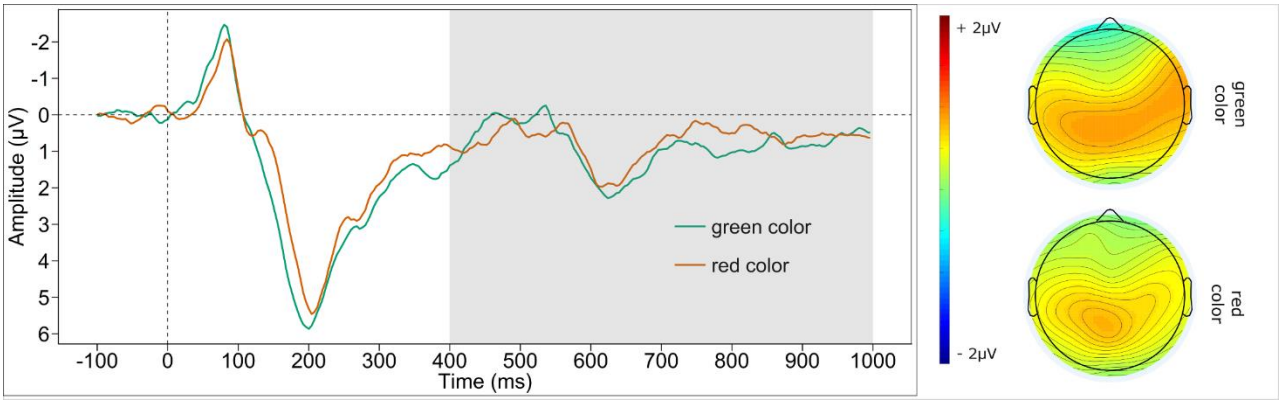
Suppl. Figure 3. Raw P300 for the PASAT. The grand average waveform separately for red and green feedback (left panel) averaged across Cz, CPz and Pz and the scalp map displaying the mean voltage distribution for red and green feedback separately (right panel, 300 - 400 ms post feedback).



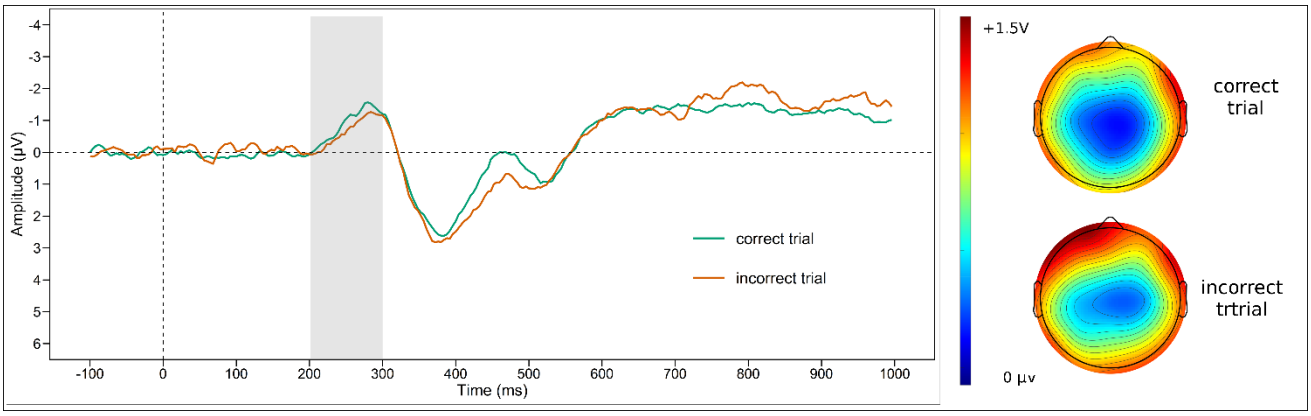
Suppl. Figure 4. Raw P300 for the color presentation task. The grand average waveform separately for red and green color (left panel) averaged across Cz, CPz and Pz and the scalp map displaying the mean voltage distribution for red and green color separately (right panel, 300 - 400 ms post color presentation).



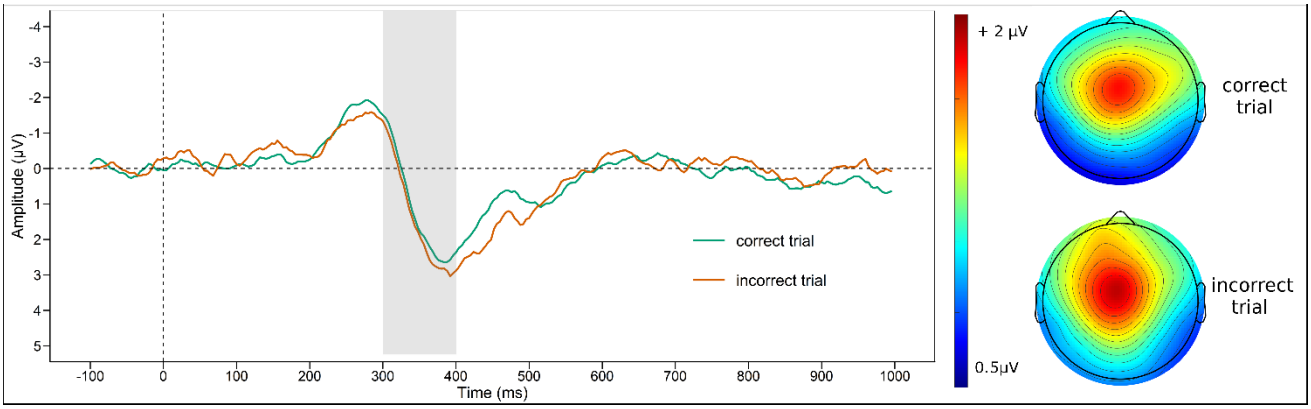
Suppl. Figure 5. Raw LPP for the PASAT. The grand average waveform separately for red and green feedback (left panel) averaged across Cz, CPz, Pz, CP1 and CP2 and the scalp map displaying the mean voltage distribution for red and green feedback separately (right panel, 400 - 1000 ms post feedback).



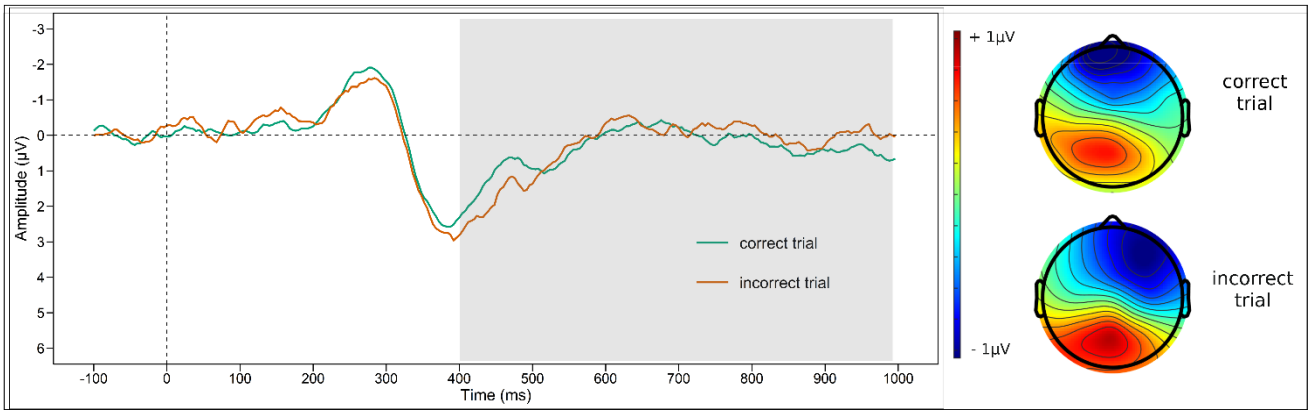
Suppl. Figure 6. Raw LPP for the color presentation task. The grand average waveform separately for red and green color (left panel) averaged across Cz, CPz, Pz, CP1 and CP2 and the scalp map displaying the mean voltage distribution for red and green color separately (right panel, 400 - 1000 ms post color presentation).



Suppl. Figure 7. Raw FRN for the feedback-neutral PASAT. The grand average waveform separately for correct and incorrect trials (left panel) at Fz and the scalp map displaying the mean voltage distribution for correct and incorrect trials separately (right panel, 200 - 300 ms post digit).



Suppl. Figure 8. Raw P300 for the feedback-neutral PASAT. The grand average waveform separately for correct and incorrect trials (left panel) at Cz, CPz, Pz and the scalp map displaying the mean voltage distribution for correct and incorrect trials separately (right panel, 300 - 400 ms post digit).



Suppl. Figure 9. Raw LPP for the feedback-neutral PASAT. The grand average waveform separately for correct and incorrect trials (left panel) at Cz, CPz, Pz, CP1 and CP2 and the scalp map displaying the mean voltage distribution for correct and incorrect trials separately (right panel, 400 - 1000 ms post digit).

3. Study II: "Depression Treatment by tDCS-enhanced Cognitive Control Training: A Test of two Stimulation Intensities"

Contributions of the candidate and co-authors to the paper:

Author	**Author position**	**Scientific ideas %**	**Data generation %**	**Analysis & interpretation %**	**Paper writing %**
Anja Sommer	1	50	70	70	60
Christian Plewnia	2	50	*0	30	40
Title of paper:		Depression Treatment by tDCS-enhanced Cognitive Control Training: A Test of two Stimulation Intensities			
Status in publication process:		published			

Note: *30% of the data for Study II was generated in the course of student work.

Sommer, A., & Plewnia, C. (2021). Depression treatment by tDCS-enhanced cognitive control training: A test of two stimulation intensities. *Brain Stimulation*. https://doi.org/https://doi.org/10.1016/j.brs.2021.06.004

Depression treatment by tDCS-enhanced cognitive control training: A test of two stimulation intensities

Anja Sommer, Christian Plewnia*

Affiliations:

Department of Psychiatry and Psychotherapy, Brain Stimulation Center, University of Tübingen, Calwerstraße 14, 72076, Tübingen, Germany

*Corresponding author

Phone: +49 7071 29-86121

Fax: +49 7071 29-5904

christian.plewnia@med.uni-tuebingen.de

Conflict of interest: the authors declare that the research was conducted in the absence of any commercial or financial or commercial relationships that could be construed as a potential conflict of interest.

Dear editor:

Hypoactivity of the dorsolateral prefrontal cortex (dlPFC) has been described as a pathophysiological characteristic of major depression disorder (MDD) (Fales et al., 2008) which is associated with impaired cognitive control over negative emotional information, underlying the development and maintenance of MDD symptomatology (Gotlib & Joormann, 2010). DlPFC activity can be modulated by transcranial direct current stimulation (tDCS) and studies on the efficacy of tDCS for MDD are promising (Razza et al., 2020). However, the reported effect sizes are moderate and knowledge on optimal stimulation parameters, like intensity is still lacking. Since tDCS itself does not induce neuronal activity, its effect depends on concurrent brain activity. Thus, a targeted combination with cognitive control training (CCT) has been put forward as a promising approach to support antidepressive effects of tDCS (Brunoni et al., 2014; Segrave et al., 2014). Particularly trainings of the paced auditory serial addition task (PASAT, Gronwall, 1977) indicated efficacy on depressive symptoms (Siegle et al., 2007). The PASAT challenges cognitive control and negative information processing by means of continuous working memory updating in a stressful and frustrating environment (Siegle et al., 2007). Consistently, PASAT performance activates the dlPFC (Lazeron et al., 2003). Given this complementary impact of tDCS and CCT on the cognitive control network and biased information processing, synergistic effects can be expected. Therefore, we tested a tDCS supported CCT on MDD using two stimulation intensities (1 and 2mA) to investigate the most effective intensity in MDD based on previous results in healthy subjects showing a non-linear influence of stimulation intensity with a beneficial effect of 1 but not 2 mA (Weller et al., 2020).

51 depressed patients (30 female, M = 37.71 years, SD = 14.02) were randomly allocated into one of three training conditions CCT + sham tDCS, CCT + 1mA tDCS and CCT + 2mA tDCS ($N = 3 \times 17$, Sup. Tab. 1). Exclusion criteria were left-handedness, instable intake of antidepressive medication, intake of anticonvulsants, opiates, excessive benzodiazepine use (>1mg Lorazepam/ equivalent dose of other Benzodiazepines per day), bipolar disorder, schizophrenia spectrum disorder, substance use disorder, eating disorder, Cluster A, antisocial or borderline personality disorder and acute suicidality. The study was approved by the local ethics committee and was conducted in compliance with the Declaration of Helsinki. All participants gave their written informed consent. The study was registered at ClinicalTrials.gov (Identifier: NCT03518749).

All patients completed a four-week training, comprising three intermittent CCT sessions per week (Monday, Wednesday, Friday). As CCT task, we used an adaptive version of the

PASAT. One-digit numbers were presented via headphones and participants added the digit they just heard with the one before. Simultaneously with the new digit, feedback was given by presenting green (red) light after correct (incorrect) responses. An adaptive inter-stimulus interval (ISI) ensured that patients processed at their individual performance limits but are not overstrained. Starting at three seconds it was increased (decreased) by 0.1 s after four consecutive incorrect (correct) trials.

The stimulation was administered parallel to the PASAT performance for 23 minutes (5 seconds ramp up/down) using a multichannel DC Stimulator (NeuroConn GmbH, Germany) and 35cm^2 rubber electrodes placed over the left dlPFC (F3 active, anodal electrode) and the right deltoid muscle (reference, cathodal electrode). In the sham group, stimulation was terminated after 30 seconds.

Depressive symptoms were assessed using the Montgomery Asberg Depression Rating Scale (MADRS) conducted by blinded, trained psychologists at seven time points: baseline (BL), training weeks1-4, post session and three-month follow-up (FU). The study followed a randomized, sham controlled, between-subjects design. The experimenter was not blinded. Of note however, MADRS raters as well as participants were blinded.

To analyze the effect on MADRS scores, a linear mixed-effects model was conducted, comprising the factors *group* [sham (= reference), 1mA, 2mA], *week* (BL, training weeks 1-4, post), *group* × *week* and for random effects intercepts and by session random slopes for subjects: *~ 1 + week | subject*. The model showed a significant effect of *week*, demonstrating a considerable reduction of MADRS scores over the course of the training from BL to post (Fig. 1). The lack of significant interaction effects for 1mA [$t_{(51)} = 0.09$, $p = .946$, $B = 0.04$, $SE = 0.55$] and 2mA [$t_{(51)} = 0.22$, $p = .830$, $B = 0.12$, $SE = 0.55$] indicates that the reduction of MADRS scores in the active tDCS groups was not different to the sham group. Two ANCOVAs, each comprising the two-level factor *group* (sham vs. 1mA, sham vs. 2mA) and the covariate *MADRS BL score*, showed no significant effect of the factor *group* for sham vs. 2mA $F_{(2, 28)} = 0.155$, $p = .679$, $\eta^2_p = .006$ but a marginal significant effect of *group* for sham vs. 1 mA $F_{(2, 29)} = 3.281$, $p = .080$, $\eta^2_p = .102$ on change of MADRS scores from BL to FU: 1mA $M = -18.29$, $SD = 8.84$, sham $M = -12.93$, $SD = 11.51$.

These results do not support the concept of a synergistic effect of tDCS and CCT in the treatment of MDD. Considering previous studies demonstrating antidepressant efficacy of tDCS for the treatment of MDD (for a review see Razza et al., 2020), most likely specific design characteristics are responsible for the lack of difference between active and sham

tDCS. First, in contrast to previous studies, days of stimulation alternated with stimulation-free days. Although this intermitted schedule has been found to promote neuroplasticity (Ruf et al., 2017; Weller et al., 2020), this approach may have not been intensive enough for MDD patients. Second, to allow for a better understanding of the relevant mechanisms and based on previous positive results (Ruf et al., 2017; Weller et al., 2020), we refrained from integrating the right dlPFC in our stimulation protocol. This leaves room for the possibility that cathodal stimulation of the right dlPFC is critical for an antidepressive tDCS effect.

Of note, the medium effect sized tendency towards a lower score in the 1mA than the sham group at FU (Fig 1, Sup. Tab. 2), resembles similar patterns in previous studies (Brunoni et al., 2014; Segrave et al., 2014) that found significant differences between active and sham tDCS not directly after training, but only at FU.

Moreover, in accordance with previous studies (Siegle et al., 2007), showing beneficial effects of PASAT training alone on depressive symptoms, we can observe a substantial improvement in depressive symptoms across all groups in our study, which, at least in parts, is likely to be based on PASAT training effects. This aspect is most important since a small to medium effect of tDCS might have been obscured by a more prominent PASAT effect.

Taken together, our study does not add evidence for a synergistic antidepressive effect of tDCS in combination with CCT. However, modifications in treatment schedule or stimulation parameter might improve efficacy. In consideration of promising results of other studies our findings may help to inform future research on optimizing protocols for effective brain stimulation treatment of MDD.

Funding

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Author contributions

Anja Sommer: Conceptualization, Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing - original draft; Writing - review & editing.

Christian Plewnia: Conceptualization; Formal analysis; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing - original draft; Writing - review & editing.

Author ORCIDs

Christian Plewnia https://orcid.org/0000-0003-3852-9906

Anja Sommer https://orcid.org/0000-0003-3713-3395

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Figure

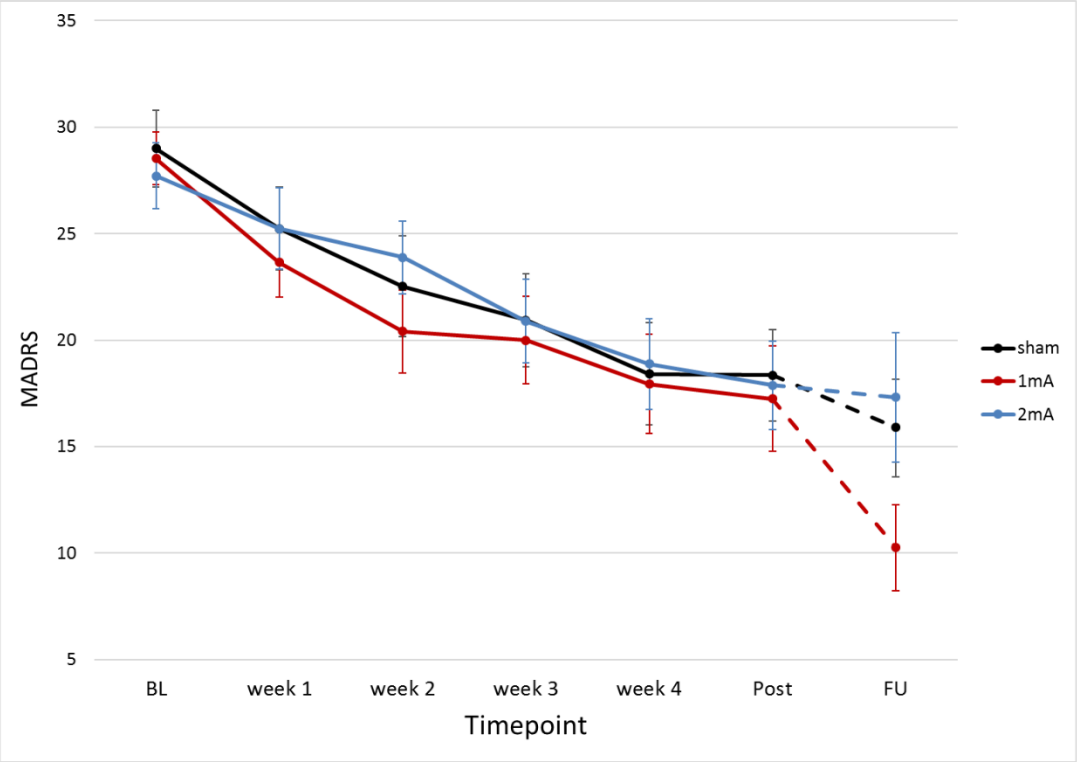

Figure 1. Means and standard errors of the MADRS scores separately for the groups from baseline to follow-up.

Supplement Tables

Supplement Table 1. Demographic and neurophysiological characteristics of the patients.

	sham + CCT (n = 17)	1mA tDCS + CCT (n = 17)	2mA tDCS + CCT (n = 17)	Test Statistic
Female Subjects	n = 10	n = 10	n = 10	[a]$\chi^2 = 0$, $p = 1$
Age (in years) (m, SD)	34.59 (13.72)	41.12 (16.18)	37.71 (11.90)	[b]$F_{(2, 48)} = 0.92$, $p = .404$
Level of education: University entrance diploma (yes)	n = 14	n = 14	n = 14	[a]$\chi^2 = 0$, $p = 1$
Current Psychotherapeutic intervention (yes)	n = 8	n = 11	n = 11	[a]$\chi^2 = 1.43$, $p = .490$
Duration of MDE in months (m, SD)	10.21 (10.84)	12.29 (8.63)	15.79 (11.22)	[b]$F_{(2, 48)} = 1.28$, $p = .288$
TMT-A (s) (m, SD)	27.82 (9.23)	30.12 (10.44)	28.24 (8.62)	[b]$F_{(2, 48)} = 0.28$, $p = .754$
TMT-B (s) (m, SD)	59.65 (24.03)	71.94 (32.95)	55.71 (14.36)	[b]$F_{(2, 48)} = 1.96$, $p = .153$
MWT-B IQ* (m, SD)	107.88 (14.11)	113 (12.37)	112.24 (13.24)	[b]$F_{(2, 46)} = 0.710$, $p = .497$
Digit Span same order (m, SD)	9.53 (1.74)	8.82 (2.56)	9.47 (1.74)	[b]$F_{(2, 48)} = 0.62$, $p = .541$
Digit Span reverse order (m, SD)	9.18 (2.33)	8.06 (2.05)	8.47 (1.38)	[b]$F_{(2, 48)} = 1.42$, $p = .252$

Notes. TMT-A (s), TMT-B (s): time to complete the Trail Making Test part A and B in seconds, respectively; Digit span same order, reverse order: number of correct remembered digits in the Digit span same order and reverse order task, respectively; MWT-B IQ = Intelligence Quotient assessed with the MWT-B (*for two participants of the 1mA group MTW-B scores are missing). a: Kruskal-Wallis H test, b: ANOVA.

Supplement Table 2. Means and standard deviations for clinical and cognitive outcomes of the patients.

	sham	1mA tDCS	2mA tDCS
MADRS BL	29 (7.45)	28.53 (5.14)	27.71 (6.37)
MADRS Post	18.35 (8.85)	17.24 (10.21)	17.88 (8.55)
MADRS FU	15.87 (8.94)	10.24 (8.34)	17.31 (12.20)
BDI BL	25.59 (6.68)	25.76 (9.12)	27.41 (7.07)
BDI Post	17.35 (7.54)	17.94 (12.52)	19.35 (8.97)
BDI FU	14.73 (8.41)	10.94 (10.43)	15.88 (11.63)
PASAT BL	179.94 (42.61)	154.18 (43.45)	176.53 (38.91)
PASAT Post	275.18 (51.71)	253.76 (61.81)	277.00 (43.20)

Notes. BL, post, FU = measurements from baseline, post and three months follow up session, respectively.

4. Study III: „Investigating Mechanisms of Cognitive Control Training: Neural Signatures of PASAT Performance in depressed Patients"

Contributions of the candidate and co-authors to the paper:

Author	**Author position**	**Scientific ideas %**	**Data generation %**	**Analysis & interpretation %**	**Paper writing %**
Anja Sommer	1	65	80	90	80
Andreas J. Fallgatter	2	10	*0	0	5
Christian Plewnia	3	25	*0	10	15
Title of paper:		Investigating Mechanisms of Cognitive Control Training: Neural Signatures of PASAT Performance in depressed Patients			
Status in publication process:		submitted			

Note: *20% of the data for Study III was generated in the course of student work.

Sommer, A., Fallgatter, A.J., & Plewnia, C. (submitted). Investigating mechanisms of cognitive control training: neural signatures of PASAT performance in depressed patients.

Investigating mechanisms of cognitive control training: neural signatures of PASAT performance in depressed patients

Anja Sommer, Andreas J. Fallgatter, Christian Plewnia*

Affiliations:

Department of Psychiatry and Psychotherapy, Tübingen Center for Mental Health (TüCMH), Neurophysiology & Interventional Neuropsychiatry, University of Tübingen, Calwerstraße 14, 72076, Tübingen, Germany

*Corresponding author

christian.plewnia@med.uni-tuebingen.de

Author ORCIDs

Christian Plewnia 0000-0003-3852-9906

Anja Sommer 0000-0003-3713-3395

Abstract

Major depression disorder (MDD) is characterized by cognitive control (CC) dysfunctions associated with increased attention towards negative information. The paced auditory serial addition task (PASAT) has been used as a targeted training of CC and studies show promising effects on depressive symptoms. However, neural mechanisms underlying its efficacy are still unclear. Based on previous findings of feedback-locked event related potentials in healthy subjects, we investigated neural signatures during PASAT performance in 46 depressed patients. We found significantly larger amplitudes after negative than positive feedback for the P300 and late positive potential (LPP). However, this difference was not significant for the feedback related negativity (FRN). Moreover, no associations of valence-specific ERPs and PASAT performance nor depressive symptoms were found. This indicates that depressed patients seem unable to use neural activation in late feedback processing stages (P300, LPP) to adapt accordingly. Moreover, lack of valence-specific neural reaction in early feedback processing stages (FRN) might point towards motivational withdrawal and emotional indifference in depressed patients.

Trial registration number: NCT03518749 Date of registration: May 8, 2018
Keywords: major depressive disorder, cognitive control, cognitive control training, PASAT, dlPFC, event-related potentials

Declarations

Funding: This work was supported by the GCBS research consortium (FKZ 01EE1403D awarded to CP) funded by the German Federal Ministry of Education and Research.

Conflicts of interest/Competing interests: the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Availability of data and material: Upon request

Code availability: Upon request

Ethics approval: The study was approved by the ethics committee of the Medical Faculty of the Eberhard-Karls-University and the University Hospital Tübingen and was conducted in compliance with the Declaration of Helsinki.

Consent to participate: All participants gave their written informed consent.

1. Introduction

Flexible adaptation of cognitive resources according to internal goals is an important prerequisite of goal directed human behavior. This top-down driven cognitive control (CC) is impaired in depressed patients, resulting in difficulties disengaging from negative thoughts, emotions and information (Baert et al., 2010). Moreover, CC deficits have been found to be associated with the development and maintenance of MDD (Gotlib and Joormann, 2010; LeMoult and Gotlib, 2019). Thus, trainings that directly target disrupted CC functions are promising new treatment methods. In cognitive control trainings (CCT) patients repeatedly perform tasks on various cognitive functions, such as working memory, processing speed or continuous attention. Studies so far show promising results concerning the clinical utility of CCTs (for an overview see Koster et al., 2017; Van den Bergh et al., 2018). A training task commonly used as CCT is the paced auditory serial addition task (PASAT; Gronwall, 1977). In the PASAT, digits have to be added serially, while difficulty adapts according to the performance of the patients (Siegle et al., 2007). Working at the individual limit of cognitive functioning while continuously receiving performance feedback results in the engagement of working memory and processing speed capacities in a stressful and emotional task context. Furthermore, the PASAT was found to activate the dlPFC (Lazeron et al., 2003) which is typically hypoactivated in depressed patients especially when it comes to tasks that require top-down driven CC of emotions (Siegle et al., 2007; Fales et al., 2008). Efficacy of the PASAT for the reduction of depressive symptoms has already been demonstrated (Hoorelbeke et al. 2015; Lass et al. 2021; Siegle et al., 2007; Siegle et al., 2014; for an overview see Koster et al. 2017 and Van den Bergh et al., 2018). However, findings about the mechanisms underlying the effectiveness of the PASAT are still scarce. It is assumed that the activation of prefrontal brain areas in a stressful and emotion inducing environment strengthens prefrontal control over emotion related limbic areas (Siegle et al., 2007). This assumption is bolstered by findings that the effectiveness of the PASAT increases with the enhancement of stress induction (Lass et al., 2021). Further insight into underlying mechanisms of the PASAT comes from a recent study from our workgroup. We examined time dynamic neural signatures during PASAT performance by the means of feedback-locked event-related potentials (ERPs) in healthy subjects. We found valence specific and stage dependent associations of PASAT performance with the feedback-related negativity (FRN), P300 and the late positive potential (LPP), that provide the basis of further research into the mechanisms underlying the PASAT in depressed patients (Sommer et al., 2021).

The FRN is an early ERP peaking between 200 and 300 ms after feedback presentation at medial-frontal sites. It is sensitive to feedback valence and commonly found to be larger for negative than positive feedback (Ridderinkhof et al., 2004; Hajcak et al., 2006). Moreover, the FRN is assumed to reflect emotional reactions to negative feedback (Luu et al., 2003). Findings about the FRN in depressed patients are unequivocal. Some studies have found increased FRN amplitudes (Tucker et al., 2003; Santesso et al., 2008; Cavanagh et al., 2011), probably reflecting increased sensitivity and attention towards negative information, which matches a negativity bias in depressed patients. However, there are also findings pointing towards a reduced FRN amplitude in depressed patients (Foti and Hajcak, 2009; Liu et al., 2014; Keren et al., 2018). It was suggested that this ambiguity could be explained by between patient variations regarding symptom severity and especially symptoms of anhedonia (Liu et al., 2014; Mueller et al., 2015). Indeed, Mueller et al. found that anhedonia in depressed patients attenuated neural reactions to negative feedback (Mueller et al., 2015). In healthy participants we could replicate the typical finding of a larger amplitude after negative than positive feedback. Moreover, we found the valence-specific FRN (ΔFRN = negative – positive feedback) linked to task performance: larger neural activation after negative than positive feedback in the PASAT was associated with performance deteriorations pointing towards distraction by negative feedback in early feedback processing stages.

The P300 is an ERP having its peak between 300 and 400 ms after stimulus presentation at centro-parietal sites and is associated with attention allocation to task relevant and salient information, which includes content of emotional valence (Sutton et al., 1965; Polich, 2012). Moreover, it is assumed to reflect emotional involvement of the subject (Diner et al., 1985). In depressed patients commonly, a reduced P300 amplitude is found, which is associated with cognitive deficits as well as emotional and motivational abnormalities (Proudfit et al., 2015). This fits with our findings on the association of P300 amplitudes and PASAT performance in healthy subjects. Besides a larger amplitude after negative than positive feedback, we found reduced P300 activation after negative feedback to be associated with performance deteriorations. This probably reflects diminished resource allocation in later processing stages.

The LPP is a positive deflection starting at about 200 and 300ms after stimulus presentation that can persist for several seconds and is recorded at centro-parietal electrode sites (Cacioppo et al., 1996; Ito et al., 1998). The LPP is sensitive for emotional information and enhanced for stimuli of positive and negative valence (Cuthbert et al., 2000). Moreover, the LPP has been

found to be regulated by CC mechanisms. Since CC deficits as well as emotional abnormalities are commonly found in MD, the LPP is an interesting ERP to study dysfunctional information processing in depressed patients and has been shown to be reduced for both, stimuli of positive and negative emotional valence (Blackburn et al., 1990; Foti et al., 2010; Proudfit et al., 2015; Klawohn et al., 2020). This indicates blunted emotional reactivity as well as motivational withdrawal and decreased cognitive engagement in depressed patients. In line with previous findings, showing larger LPP amplitudes after negative than positive feedback, we found an enhanced LPP for negative feedback compared to positive feedback during PASAT performance, probably reflecting the emotional impact of negative information. Moreover, although the association of the number of correct trials in the PASAT failed to reach significance, we found the performance stability, a measure of CC[1] to be significantly correlated with the valence specific LPP: a smaller LPP after negative than positive feedback was associated with reduced performance stability. This probably reflects diminished resource allocation and motivational engagement.

Our findings in healthy participants raise the question if similar relationships can be found in depressed patients, which could help to gain a better understanding of the mechanisms underlying the effectiveness of PASAT training for the reduction of depressive symptoms. Thus, the goal of our study is to use the neural signatures we found in healthy participants to investigate neural mechanisms of PASAT performance in depressed patients with the long-term aim to use these as measures of change in CC over the course of a CCT.

2. Material and Methods

Note that this study is part of a larger project (Clinical Trials Registration at clinicaltrials.gov, NCT03518749). Therefore, parts of the material and methods overlap with already published manuscripts (Sommer and Plewnia, 2021; Sommer et al., 2021). The data for the current paper were collected in the baseline session of a larger training study (Sommer and Plewnia, 2021). Thus, a detailed description of the materials and methods in part has been omitted in this manuscript.

[1]Performance stability: percent of consecutive correct responses relative to the overall correct responses (see Sommer et al., 2021)

2.1. Tasks

The *PASAT* and the control task *color presentation (CP)* have been computer based and implemented using Psycho-Py2 (v1.80.02; J. Peirce, 2009; J. Peirce, 2007).

In the PASAT digits (1-9) were presented auditorily, initially with an interstimulus interval (ISI) of 3 seconds. Participants had to add the current digit to the digit they heard before and indicated the result with the use of a keyboard equipped with the corresponding numbers (2-18). Simultaneously with the presentation of the next digit, subjects received feedback about the correctness of the previous trial indicated by green (correct) or red (incorrect) screen color. Difficulty of the task was adaptive as the ISI adjusted to the performance level of the subjects: after four consecutive correct (incorrect) trials the ISI decreased (increased) by 100 ms. The task comprised three blocks, each lasting five minutes and breaks of one minute between the blocks. Before the first block, all patients underwent 11 practice trials, which were excluded from analysis. The number of correct trails ($PASAT_{corr}$) and the performance stability ($PASAT_{PS}$) were used as the dependent variables. For the EEG analysis only trials with a response were used (e.g. incorrect trials without a response were discarded).

Since the goal of the current study was to investigate neural reactions to feedback and not color information (which the feedback also contains), we additionally performed the control task *color presentation (CP)* (see Sommer et al., 2021). In the CP red and green color was presented with a jittered ISI (1,500–2,500 ms) in randomized order, while the patients were asked to keep their gaze on the keyboard, just like they would do during the PASAT. The CP comprised two blocks (each 2.5 min.).

2.2. Electroencephalography

2.2.1. EEG procedure

For the electroencephalography (EEG) recording an elastic cap (EASYCAP GmbH, Hersching, Germany) was equipped with active Ag/AgCl electrodes. EEG was registered from 27 scalp sites (FP1, F7, F3, Fz, F4, F8, FC5, FC1, FCz, FC2, FC6, C3, Cz, C4, CP5, CP1, CPz, CP2, CP6, P7, P3, Pz, P4, P8, O1, Oz, O2) using the actiCHamp amplifier system and the corresponding Brain Vision Recorder system (Brain Products GmbH, Gilching, Germany). To control for eye movements, an electrooculogram was recorded using electrodes placed on the lateral side of each eye (horizontal eye movements) and electrodes positioned approximately one cm below/ above (Fp1) the left eye (vertical eye movements). Electrodes

placed on the forehead and the left mastoid served as the ground and online reference, respectively. The online sampling rate was 1000 Hz. Impedances were kept below 10kΩ before initiation of the recording.

2.2.2. EEG analysis

We used the EEGLAB toolbox (Delorme and Makeig, 2004) running on MATLAB 9.2 R2017a (The MathWorks, Natick, MA, USA) and the EEGLAB toolbox ERPLAP (Lopez-Calderon and Luck, 2014) to analyze the EEG data. The data was resampled offline to 250 Hz and re-referenced to an average of the left and right mastoids and filtered using band-pass filters with a low and high cutoff of 0.1 and 35 Hz, and a notch-filter at 50 Hz. Independent component analysis was used to manually remove ocular artifacts. Epochs ranging from -100 to 1000, locked to the onset of feedback (PASAT) and color (CP) were extracted. The automated artifact detection implemented in ERPLAB was used for artifact correction in the epoched EEG. On average 3.82 % of the red feedback trials, 1.76 % of the green feedback trials (PASAT) and 3.17 % of the red and 2.46 % of the green color trials (CP) were rejected from analysis due to excessive noise. Participants with more than 20% rejected trials were excluded from analysis (n = 5). Moreover, for one participant the FP1 channel was removed due to excessive noise in this channel. Overall, 907 red feedback trials, 7820 green feedback trials (PASAT) and 3402 red and 3494 green color trials (CP) were used for the construction of the ERPs, which was done by separately averaging trials in the four conditions. For the analysis of the neural signatures of the PASAT, difference waves were calculated: positive feedback = green feedback (PASAT) - green color (CP), negative feedback = red feedback (PASAT) - red color (CP). All further ERP results refer to these difference waves. Time windows and electrode sites are the same as in our previous study (Sommer et al., 2021): the FRN was defined as the mean amplitude at Fz within a time window of 200 - 300 ms following feedback. The P300 was scored as the base-to-peak difference in voltage between the most negative peak between 200 - 300 ms post feedback and the most positive peak 300 - 400 ms post feedback of the average of three centro-parietal sites (Cz, CPz, Pz). The LPP was defined as the mean amplitude between 400 - 1000 ms after feedback presentation at an average of five centro-parietal electrode sites (Cz, CP1, CPz, CP2, Pz).

2.2.3. Procedure

Overall, 51 patients with a current depressive episode were enrolled. All participants gave their written informed consent. Five participants had to be removed due to excessive noise in the data during EEG recording. The data of the remaining 46 patients (age *M* = 37.50, *SD* = 14.19, 26 female) were analyzed. Demographic and clinical characteristics of the sample are depicted in **Table 1.** Study eligibility was ascertained in a separate diagnostic session (see Sommer and Plewnia, 2021 for inclusion criteria). In the EEG session (baseline session of the training), severity of depressive symptoms was assessed using a questionnaire (Beck Depression Inventory, BDI-II) and a semi structured interview (Montgomery Asberg Depression Rating Scale, MADRS; Montgomery and Asberg, 1979). Afterwards participants completed the PASAT and CP. Immediately before and after the PASAT, affect was assessed using the 20-item positive and negative affect schedule (PANAS; Krohne et al., 1996).

2.2.4. Statistical analysis

All statistical analyses were performed using SPSS (version 24.0). For all analyses, a 0.05 level of significance was employed. In line with our previous study, we analyzed the data as follows (Sommer et al., 2021): We used paired t-Tests to analyze changes in affect rating (PANAS before vs. after the PASAT) and to examine differences in neural activation after positive vs. negative feedback, separately for each ERP (FRN, P300, LPP). Relationships between variables were analyzed using bivariate correlation analyses (Pearson correlation coefficient). This was done for the associations of the valence-specific neural activation (ΔERP = positive – negative feedback) with $PASAT_{corr}$ and $PASAT_{PS}$, changes in the affect ratings with $PASAT_{corr}$ and $PASAT_{PS}$ and severity of depressive symptoms (MADRS and BDI-II) and ΔERPs. Moreover, since previous research shows associations of anhedonia and ERP magnitudes, we additionally examined correlations of ΔERP and levels of anhedonia using bivariate correlation analyses (Pearson correlation coefficient). Anhedonia was assessed by means of item 8 of the MADRS (Inability to feel).

3. Results

3.1. Changes in affect rating

Affect significantly deteriorated after the PASAT as indicated by increased negative affect [before: M = 15.02, SD = 4.33, after: M = 23.41, SD = 9.24; $t_{(45)}$ = 7.354, p < .001]. There was no significant change in positive affect (before: M = 21.83, SD = 5.69, after: M = 23.20, SD = 6.73; $t_{(45)}$ = 1.487, p = .144]. Moreover, there were no significant correlations of the affect ratings with $PASAT_{corr}$ and $PASAT_{PS}$ (all $p \geq .088$).

3.2. Electrophysiological data

3.2.1. Feedback related negativity

See **Figure 1** for the grand average waveform of the FRN and the mean voltage distribution across the scalp, separately for negative and positive feedback. There was no significant difference between neural activation after positive (M = -0.846, SD = 2.592) and negative feedback [M = -1.226, SD = 3.103, $t_{(45)}$ = 1.047, p = .300]. Additionally, there were no significant associations of ΔFRN with the $PASAT_{corr}$ and $PASAT_{PS}$ nor depression scores or symptoms of anhedonia (all $p \geq .179$, see **Table 2**).

3.2.2. P300

Figure 2 displays the grand average waveform of the P300 and the mean voltage distribution across the scalp separately for negative and positive feedback. For the P300, neural activation after negative feedback (M = 9.982, SD = 3.769) was larger than after positive feedback [M = 6.282, SD = 2.337, $t_{(45)}$ = 8.976, p < .001]. There were no significant correlations of ΔP300 with $PASAT_{corr}$ and $PASAT_{PS}$, nor depression scores or symptoms of anhedonia (all $p \geq .095$, see **Table 2**).

3.2.3. Late positive potential

See **Figure 3** for the grand average waveform of the LPP and the mean voltage distribution across the scalp separately for negative and positive feedback. For the LPP a larger activation after negative (M = 0.443, SD = 4.440) than positive feedback (M = -1.220, SD = 2.579) was found [$t_{(45)}$ = 3.573, p = .001]. There were no significant association of the ΔLPP with $PASAT_{corr}$ and $PASAT_{PS}$ nor depression scores or symptoms of anhedonia (all $p \geq .195$, see **Table 2**).

4. Discussion

The goal of the current study was to investigate neural mechanisms underlying CCTs for depressive symptoms by means of neural signatures of the PASAT found in healthy participants. We found that negative affect significantly increased after PASAT performance, this change however was not correlated with PASAT performance. Neural activation after negative feedback was larger than after positive feedback for the P300 and LPP. This difference was not significant for the FRN. Furthermore, we could not find any associations of the valence-specific ERPs (ΔFRN, ΔP300, ΔLPP) with PASAT performance, depression scores or symptoms of anhedonia.

In contrast to our findings in healthy subjects the FRN after negative feedback was not larger than after positive feedback. Such reduced FRN amplitudes are in accordance with previous findings about diminished FRN amplitudes in depressed patients (Foti and Hajcak, 2009; Liu et al., 2014; Keren et al., 2018) and might reflect emotional indifference and motivational withdrawal caused by symptoms of anhedonia in depressed patients as suggested by Mueller et al. (Mueller et al., 2015). However, in relation to our previous findings in healthy subjects this is quite unexpected, since we have found increased FRN amplitudes to be associated with performance deteriorations, indicating diminished top-down driven CC over distraction by negative feedback. Thus, it could have been assumed that reduced CC in depressed patients goes along with increased FRN amplitudes reflecting attentional engagement with negative information which distracts from goal-oriented behavior, e.g. PASAT performance. However, our results do not support this hypothesis. Rather, the lack of correlation between PASAT performance and FRN amplitudes suggests that the relationships of neural signatures with CC found in healthy subjects are not applicable to our depressed sample, probably due to pathophysiological characteristics. Moreover, previous studies have shown links of increased depression severity and symptoms of anhedonia with reduced FRN amplitudes (Mueller et al., 2015). In our study, we could not replicate this finding. In this context it has to be noted that the PASAT differs from usual tasks used to elicit FRN amplitudes in the way that feedback is presented simultaneously with the next target. Thus, the processing of the next digit might have influenced FRN amplitudes and obscured associations with depressive symptoms. Additionally, differences in measures of anhedonia might account for the missing correlation of anhedonia with the FRN. Whereas we used item number 8 of the MADRS interview, Mueller et al. used the Anhedonic Depression subscale from the Mood and Anxiety Symptom Questionnaire, which might be a more sensitive measure for anhedonia.

For the P300 and LPP larger neural activation after negative than positive feedback was found. This is in line with our hypothesis, indicating increased attention allocation towards information of negative content. However, just like for the FRN, no association with PASAT performance was found for the P300 nor LPP. Thus, increased attention allocation after negative feedback seems to be unrelated to increased resource allocation. Depressed patients seem to be unable to use the neural activation of late processing stages after negative feedback information to adapt accordingly. Moreover, previous studies have found associations of reduced P300 (Gangadhar et al., 1993; Nan et al., 2018) and LPP (Blackburn et al., 1990; Foti et al., 2010; Proudfit et al., 2015; Klawohn et al., 2020) amplitudes with depressive symptoms. This is not in line with our results since no significant correlative relationships of depression severity and P300 nor LPP amplitudes were found. A major difference to these studies is the use of performance feedback in our study as stimuli which might explain this difference. Previous studies have used words of emotional valence, pictures of pleasant or unpleasant content or monetary gains or losses. Overall, this indicates that there is no relationship between symptoms of depression and neural signatures in later stages of performance feedback processing in the PASAT.

Differences of neural signatures during PASAT performance in depressed patients compared to healthy subjects (Sommer et al., 2021) may have several causes. A pathophysiological characteristic that may be reflected by our findings is a loss of specificity of neural activation to feedback parallel to the processing of new information (i.e. new target digit) which might be related to cognitive overload in depressed patients. Thus, patients may no longer be able to process feedback in an orderly manner that allows for the best possible use of feedback information. Moreover, due to the diagnostic system for psychiatric diseases based on symptoms, not brain-based biological alterations (Fischer, 2012), there is a high between patient variability of neural activation and brain alterations that might obscure consistent pathological processes distinctive for certain types of MDD. Furthermore, besides specific pathophysiological characteristics in depressed patients, reasons for these differences for all processing stages (FRN, P300, LPP) could be differences in tasks between our studies. To avoid ceiling effects in healthy participants we used a more challenging 2-back version of the PASAT to derive ERPs during PASAT performance in our previous study. In the 2-back PASAT participants have to add the digit before the last one to the currently presented one. Therefore, cognitive functions involved differ to some extent between the tasks, which might be reflected in differences in ERPs. In contrast to the one-back PASAT, the 2-back PASAT

puts higher demands on working memory, thus increasing task difficulty. Moreover, this could also influence expectancy of negative feedback. Supposedly, in the 2-back PASAT participants often are not sure if the remembered digit is the correct one, whereas in the one-back PASAT mistakes are more often due to speeded response. It can be assumed that in the latter, participants already expect to receive negative feedback which is not the case if one is unsure if the remembered digit is the correct one. This is especially relevant for the FRN as it has been shown that its amplitude is significantly larger for unexpected than expected negative feedback (Bellebaum and Daum, 2008; Weismüller and Bellebaum, 2016).

As expected, negative affect significantly increased after the PASAT. This is in line with findings from Plewnia and colleagues (Plewnia et al., 2015) about the impact of PASAT performance on mood in healthy subjects. In addition, the authors observed a link between elevated scores of upset feelings and performance deteriorations, which was interpreted as diminished CC over negative emotions. In our previous trial (Sommer et al., 2021) and in the current study involving subjects with depression, we were not able to replicate this finding. This might indicate that the PANAS is not sensitive enough to detect latent affect changes. Moreover, in depressed patients PASAT performance might be more significantly influenced by other variables, such as lack of motivation and working memory dysfunctions, than CC over emotions. This should be investigated in future studies to gain further information on the effectiveness of PASAT training.

There are some limitations of the current study. First, the number of negative feedback trials used to build the ERPs is quite small. On average only about 20 negative feedback trials per subject were included in the analysis, possibly resulting in increased noise due to artifact-heavy trials. However, due to the highly demanding nature of the task an increasement of trials overall was not possible without overstraining our sensitive sample. Second, 58.7 % of the participants received antidepressive medication, which might have influenced neural reactivity and thus neural responses to feedback.

Taken together, due to the missing associations of ERPs, CC and depressive symptoms only limited understanding of the mechanisms underlying the effectiveness of PASAT training for the reduction of depressive symptoms can be gained. Accordingly, our results do not support the idea to use ERPs during PASAT performance as measures of change in CC over the course of a CCT. Nevertheless, despite the limited explanatory power of our results, this study makes an important contribution to the field by exploring hypotheses and open research

questions based on previous findings. Further studies are needed to investigate neural mechanisms underlying the effectiveness of the PASAT and CCTs in general.

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Figures

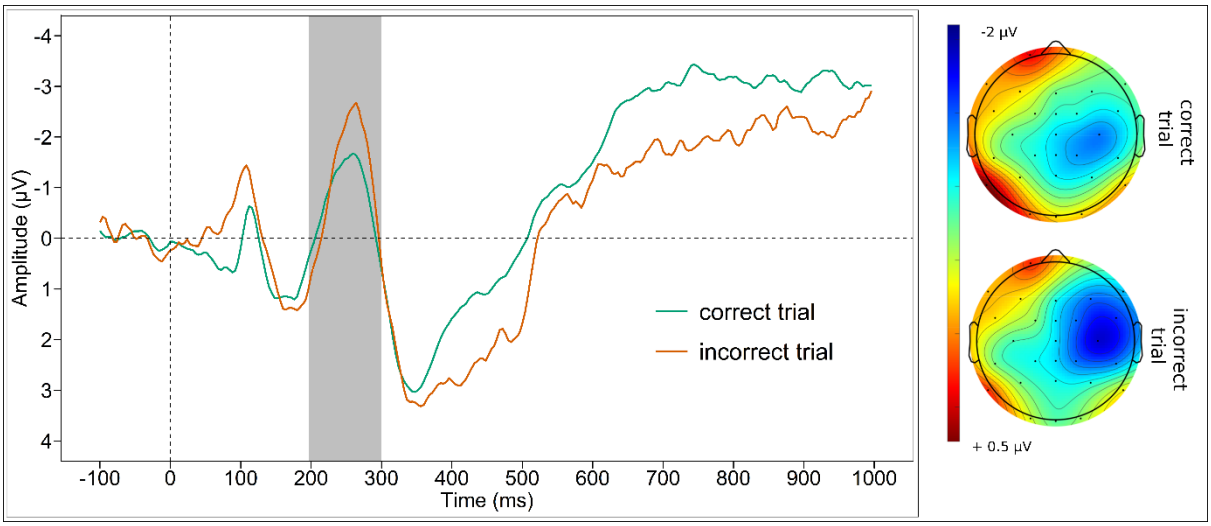

Fig 1 Feedback related negativity. Grand average waveform at Fz and scalp map displaying the mean voltage distribution (200 - 300 ms post feedback) of the feedback related negativity, separately for negative and positive feedback.

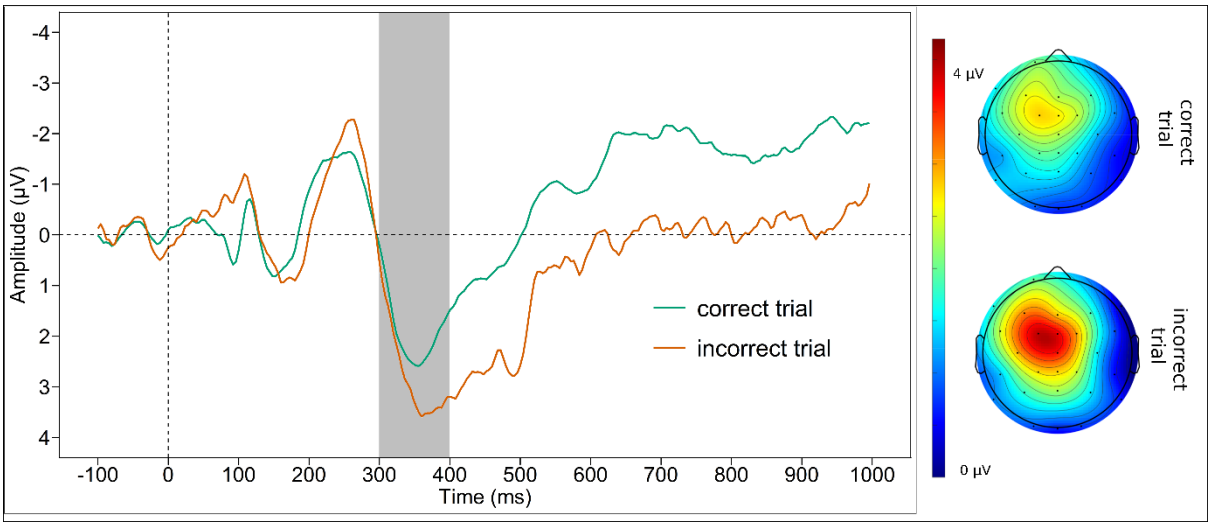

Fig 2 P300. Grand average waveform averaged across Cz, CPz, Pz and scalp map displaying the mean voltage distribution (300 - 400 ms post feedback) separately for negative and positive feedback of the P300.

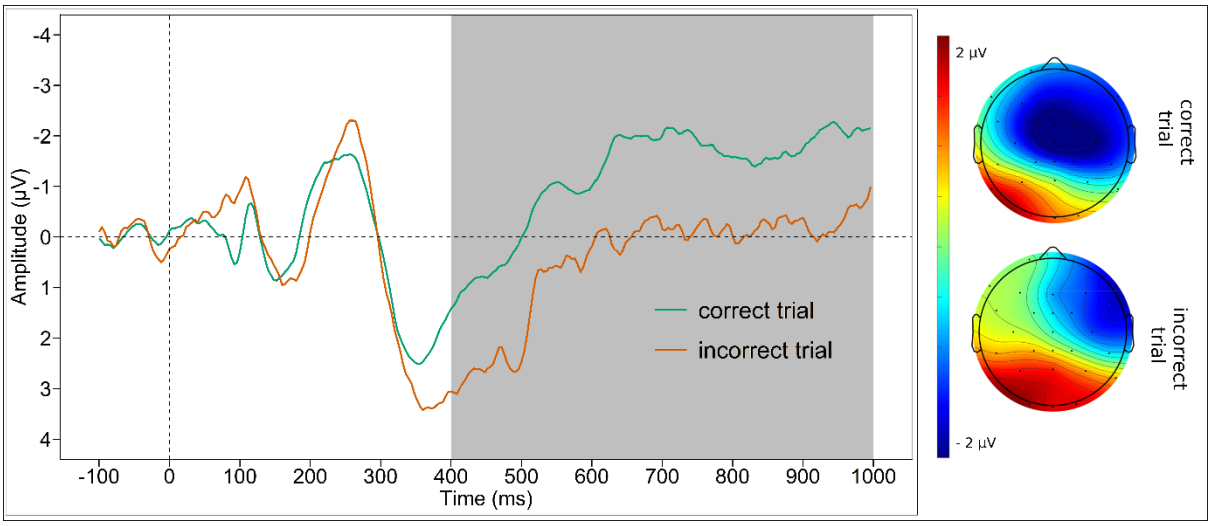

Fig 3 Late positive potential. Grand average waveform averaged across Cz, CPz, Pz, CP1, CP2 and scalp map displaying the mean voltage distribution (300 - 400 ms post feedback) separately for negative and positive feedback of the LPP.

Tables

Table 1. Demographic and clinical characteristics of the sample.

Characteristics	**N**	**M**	**SD**	**Range**
sex (female / male)	26 / 20			
Age (in years)		37.50	14.19	19 - 62
Level of education: University entrance diploma (yes / no)	39 / 7			
Current Psychotherapeutic intervention (yes / no)	27 / 19			
Duration of MDE in months		12.61	10.52	1 - 35
MADRS		27.98	6.42	15 - 45
BDI-II		25.91	7.64	12 - 47
$PASAT_{corr}$		175.43	40.84	77 - 285
$PASAT_{PS}$		58.69 %	8.25 %	32.53 % - 71.72%
Antidepressive Medication (yes/ no)	27 / 19			

Notes. $PASAT_{corr}$ = Number of correct trials in the PASAT, $PASAT_{PS}$ = Performance stability, percent of consecutive correct responses relative to the overall correct responses.

Table 2. Correlations of ΔERPs with PASAT scores and depressive symptoms.

	$PASAT_{corr}$	**$PASAT_{PS}$**	**MADRS**	**BDI-II**	**Anhedonia**
ΔFRN	r = .105, p = .486	r = .202, p = .179	r = -.110, p = .467	r = -.027, p = .860	r = -.194, p = .196
ΔP300	r = .051, p = .739	r = .035, p = .816	r = -.200, p = .182	r = -.249, p = .095	r = -.171, p = .255
ΔLPP	r = -.185, p = .219	r = .026, p = .864	r = -.194, p = .195	r = -.033, p = .828	r = -.216, p = .149

Notes. $PASAT_{corr}$ = Number of correct trials in the PASAT, $PASAT_{PS}$ = Performance stability, percentage of consecutive correct responses relative to the overall correct responses.

5. General Discussion

With the current doctoral research, I investigated the effect of a tDCS enhanced CCT and optimal stimulation intensity of tDCS for the treatment of MDD. Furthermore, ERPs of the CCT were examined with the goal to gain a better understanding of its underlying neural mechanisms and to find biological signatures to indicate change due to CCT and tDCS. An additional effect of tDCS for the treatment of MDD was found for neither of the stimulation intensities. In addition, indicative neural signatures linked to PASAT performance in healthy subjects were observed, reflecting increased attention allocation towards negative feedback and feedback processing stage dependent associations of CC and neural activation. Based on these findings an exploration of neural mechanisms of PASAT performance in MDD patients was possible. Increased attention allocation in late processing stages but no associations of neural signatures and PASAT performance or MDD symptoms in depressed patients were found. In the following, these results and their contribution to the exploration of the objectives of my doctoral research will be discussed.

5.1. Effects of tDCS for the Enhancement of PASAT Training

The results of study II do not add evidence for an additional effect of tDCS for the treatment of MDD. A conceivable reason is that the effect of tDCS on depressive symptoms is substantially smaller than expected (Brunoni et al., 2017) or even not present (Loo et al., 2018). This is contradicted by a number of positive studies demonstrating antidepressant effects of tDCS at rest (e.g., Boggio et al., 2008; Brunoni et al., 2013) and combined with CCT (Brunoni et al., 2014; Segrave et al., 2014; for a recent review, see Razza et al., 2020). However, considering the high variability of stimulation parameters, it is more likely that, in the case of this study, specific design characteristics are responsible for the lack of difference between active and sham tDCS. First, in the current study the reference electrode (cathode) was mounted to the contralateral (right) deltoid muscle whereas other studies investigating tDCS for the treatment of MDD predominantly attached the reference to the right frontal side of the scalp (F4, F8, right supraorbital; e.g., Brunoni et al., 2014, 2017; Fregni et al., 2006; Segrave et al., 2014). We chose that electrode placement based on beneficial effects in previous studies (Plewnia, Schroeder, Kunze, et al., 2015; Ruf et al., 2017; Weller et al., 2020; Wolkenstein & Plewnia, 2013). Moreover, we wanted to gain a better understanding of effects underlying tDCS effects. Yet, when the right PFC is employed as a reference, it is

cathodally stimulated, i.e., inhibitory, so that effects cannot be clearly attributed to anodal stimulation of the left dlPFC. However, it is possible that this very cathodal stimulation of the right dlPFC is crucial for the treatment of MDD. This assumption is supported by findings of increased activity in right hemisphere and reduced activity in the left hemisphere in depressed patients (Grimm et al., 2008; Hecht, 2010). Thus, the bilateral montage with cathodal right and anodal left tDCS might attenuate this hemispheric imbalance.

Second, an intermitted training design with alternating days of stimulation and stimulation free days was chosen. This was done to promote consolidation and based on beneficial findings on CC and working memory in healthy subjects (Ruf et al., 2017; Weller et al., 2020). However, due to specific pathophysiological characteristics, like decreased neuroplasticity a beneficial effect of intermitted tDCS sessions might not apply to depressed patient and result in decreased tDCS effects. Daily tDCS sessions may be essential to achieve an additional tDCS effect.

Interestingly, a substantial decrease of depressive symptoms (37 % MADRS) within the treatment period of 4 weeks has been observed over all groups, including sham. Although a relevant proportion of this effect can be attributed to the natural course of the disease under constant treatment and an unspecific effect of the treatment procedure, an efficacy of the PASAT training must also be taken into account. Previous studies have already shown that PASAT training alone can have beneficial effects on brooding rumination, stress reactivity and depressive symptoms overall (Hoorelbeke et al., 2015; Siegle et al., 2014; Siegle, Ghinassi, et al., 2007). Consistently, we can observe a substantial improvement in depressive symptoms across all groups in our study, which, at least in parts, might be based on PASAT training effects. This aspect is all the more important as a small to medium effect of tDCS in our study might have been obscured by a more prominent PASAT effect. However, the lack of a control group without PASAT training precludes clear conclusions about the antidepressive efficacy of PASAT training alone.

5.2. Stimulation Intensity

The second objective of this doctoral research was to expand knowledge about optimal stimulation intensity since findings especially on low intensity tDCS for MDD is scarce and debate about optimal stimulation intensity is still going on (e.g., Schwippel et al., 2018). In the current study neither 1 nor 2mA were superior to sham tDCS regarding reduction of

depressive symptoms over the course of the training from baseline to post. However, it is important to note that our results suggest that an increase in stimulation intensity as suggested by other studies (Hoy et al., 2014; Iyer et al., 2005; Schwippel et al., 2018) seems not sufficient based on our finding that both, 1 and 2mA tDCS did not yield effects. Moreover, at the 3-months follow-up the difference between groups showed a trend towards a medium effect sized larger reduction in MADRS score from baseline to follow-up in the 1mA but not 2mA than the sham group (see Fig. 1 of study II). Thus, this finding does not exclude the possibility of a delayed efficacy of low intensity tDCS that might be supported by changes of specific pathological mechanisms substantial for the maintenance of depressive symptoms. Additionally, it should be noted that the pattern of this result does not contradict previous studies combining tDCS and CCT in depression (Brunoni et al., 2014; Segrave et al., 2014) in which significant differences between active and sham tDCS were not found directly after training, but only at follow-up. Further research regarding optimal stimulation intensity should be conducted. Particularly in neuropsychiatric patients this represents challenge due to additional effects on neuroplasticity due to medication (Brunoni et al., 2013) and disorder related impairments of neuroplasticity (Cooke & Bliss, 2006; Noda et al., 2018).

5.3. Neural Signatures underlying PASAT Performance in healthy and depressed Subjects

In study I indicative neural signatures during PASAT performance in healthy subjects were identified that provide information regarding several mechanisms during PASAT performance. Larger neural activation after negative than positive feedback for all feedback processing stages reflects a stronger attention allocation towards negative information indicating a negativity bias. Furthermore, correlation analyses of valence specific neural activation (ΔERPs = negative-positive feedback) after feedback provide information about the effects of this biased processing. The negative correlation of ΔFRN in early feedback processing stages with PASAT performance points towards performance deteriorations due to distraction by negative feedback. Thus, fast and strong reactions to negative feedback seem to be detrimental for PASAT performance. This is not in line with previous studies showing associations of performance gains and increased FRN amplitudes after negative feedback (Cohen et al., 2007; Meyer et al., 2014; Unger et al., 2012). These studies highlight the informative value of negative performance feedback for the adaption of goal-directed

behavior. However, it has to be emphasized that in study I, feedback was presented simultaneously with the next target digit, thus besides containing performance information, representing a highly distracting stimulus. The positive correlation of neural activation with PASAT performance in late processing stages (P300, LPP) is inverse to early processing stages and in line with previous findings about amplitude magnitude and task performance (Bamford et al., 2015; Daffner et al., 2011; Faehling & Plewnia, 2016; Palomba et al., 1997). These results indicate increased attention allocation after negative feedback that supports the recruitment of additional resources and maintenance of goal-directed performance. Taken together, in study I we could identify feedback-processing stage dependent associations of neural signatures and PASAT performance that provide insight into cognitive processes during the highly time dynamic PASAT performance. With these findings, we set the basis for the investigation of neural mechanisms underlying PASAT performance and efficacy of PASAT training in depressed patients in study III, that might be employed as markers of change due to CCT and tDCS.

In study III, only in late feedback processing stages differential neural activation after negative and positive feedback was found but not for the FRN. Although there are findings of decreased FRN amplitudes in depressed patients (Foti & Hajcak, 2009), especially with increased anhedonia (Mueller et al., 2015), this finding is surprising and might reflect blunted emotional responses or motivational withdrawal. The prominent negativity bias in MDD patients is reflected by larger neural activation after negative than positive feedback in late feedback processing stages (P300, LPP). Our findings that larger neural activation for negative feedback are only present in later processing stages are consistent with results from behavioral studies in which attentional biases in MDD were found mainly in paradigms with long stimulus presentations, indicating that negativity biases in MDD occur predominantly in late processing stages (De Raedt & Koster, 2010). Opposed to the findings in healthy subjects no associations of PASAT performance and ΔERPs were found. Furthermore, although previous findings showed depression related alterations in ERPs (e.g. Foti & Hajcak, 2009; Klawohn et al., 2020; Proudfit et al., 2015) that suggest a link of ERP amplitudes with depression severity, no associations of ΔERPs with MADRS or BDI-II have been found. Thus, depressed patients seem unable to use increased neural activation after negative feedback in late processing stages (P300 and LPP) for the additional recruitment of cognitive resources. Moreover, our results suggest that the associations of CC and neural signatures during PASAT performance found in study I are not applicable to depressed patients. Besides

pathophysiological characteristics, differences in tasks between study I and III might be responsible for that. To avoid ceiling effects in healthy participants a more challenging 2-back version of the PASAT, that puts higher demands on working memory functioning, was used in study I opposed to study III. Overall, the results of our study provide only limited knowledge about neural mechanisms underlying PASAT performance in depressed patients and further research in this regard should be done.

5.4. Effects of PASAT Performance on Affect

The studies of this doctoral research showed deteriorations of affect after PASAT performance in line with previous studies (Holdwick & Wingenfeld, 1999; Plewnia, Schroeder, Kunze, et al., 2015). In contrast to Plewnia, Schroeder, Kunze, et al. (2015), though, no associations of PASAT performance and changes of affect were found, thus challenging the assumption that successful CC of emotion is associated with performance gains, since participants that were able to prevent frustration (i.e., resulting in smaller changes of affect) did not show improved task performance. However, it must be noted that there can be different causes for decreased frustration. While subjects may have used functional emotion regulation strategies like cognitive reappraisal, they also might have been simply less ambitious and unmotivated, which could also have led to less frustration by bad performance. Simply because it was not that important for the subjects. Furthermore, less commitment and/ or worse performance goes actually not along with more frequent negative feedback in the PASAT, since due to the adaptive nature of the task the ratio of negative and positive feedback stays more or less the same: good performance leads to increased digit presentation speed that in turn leads to more mistakes. Therefore, unambitious, bad performers probably are not more frustrated due to negative feedback than good performers. Nevertheless, our findings of increased negative affect after PASAT performance support the assumption that the activation of CC functions in a stressful and frustrating environment is a crucial factor for the effectiveness of PASAT training.

5.5. Limitations and future directions

5.5.1. Study II

The current diagnosis of depression refers to a relatively broad spectrum of solely visible and observable symptoms and not to underlying brain-based alterations (Fischer, 2012) resulting

in high levels of interindividual variability and inconsistent pathological processes that probably influence the malleability of MDD symptoms by tDCS. Presumably certain patients identified on the basis of biological markers, like changes in fronto-limbic network activity described in chapter 1.2., or genetic polymorphisms (Plewnia et al., 2013) could benefit to a greater extent from tDCS. Thus, the examination of further biological markers in the current study might have provided more insight into such patient populations. However, such analyses would have overstrained statistical power of our sample size. Thus, future studies, with larger sample sizes should investigate that.

Moreover, the numerical tendency in the 1mA group towards a larger reduction of depressive symptoms might suggest that the low-intensity stimulation contributes to a change of specific pathological mechanisms that are substantial for the maintenance of depressive symptoms. However, measurement of such mechanisms has not been exhausted by us. For example, given the causal influence of rumination on maintenance of MDD, the assessment of changes in dysfunctional ER strategies would have been interesting in this context and might have revealed differential tDCS effects on these. The assessment of specific underlying mechanisms of MDD might provide further insight into important factors for change due to tDCS or CCT in future studies.

Additionally, about 58% of our patients received concurrent psychotherapy and about 58% psychotropic medication that most likely influenced effects of tDCS and CCT. First, additional effects of tDCS might be obscured by effects of these interventions. In addition, neuroplastic effects targeted by tDCS could have been influenced and reduced by several psychoactive medications (Brunoni et al., 2013).

Furthermore, the combination of two interventions makes the interpretation of effects more difficult. Theoretically and as outlined in chapter 1.3.3., by a combination of tDCS and CCT a synergistic effect might be expected due to similar neural structures underlying both interventions (i.e., the dlPFC). However, an interesting thought about reduced effectiveness of combined tDCS and CCT comes from Vanderhasselt et al. (2015). Although the authors found a reduction of rumination over the course of a tDCS supported PASAT training, no additional effect of tDCS was found. They argued that increased levels of negative self-referential thoughts and negative affect, which are a critical mechanism of the PASAT training, might be reduced due to improved CC over emotions by increased tDCS driven dlPFC activity. Thus, in the present study, additional tDCS effects on MDD might have been counteracted by reduced efficacy of PASAT training in the two tDCS groups. Since we only

measured change of affect in the baseline and post session in which tDCS was not administered, we cannot make conclusions about the impact of tDCS on affect after PASAT performance which would be important to test this assumption.

5.5.2. Study I and III

Limitations of studies I and III particularly are specific features of the PASAT, which pose a challenge to the extraction of neural signatures. First, due to the adaptive ISI, the PASAT is highly time dynamic and even more importantly the ISI is variable, thus good performance goes along with shorter ISIs. In very good performers the ISI can reach durations as short as one second. Although EEG and ERPs are characterized by high temporal resolution, it is likely that differences in overlap of ERP components and very short ISIs depict a challenge that produces increases of noise in the data. Interestingly, due to increased difficulty the 2-back PASAT usually does not go along with such short ISIs, at least when it is performed for the first time. For this reason, measurements from study I might provide more informative ERPs than those from study III. Second, the PASAT is known to engage a variety of cognitive functions, partly but not all related to CC, like speed of information processing and capacity, working memory functions and different attentional processes (attention switching, sustained attention) (Tombaugh, 2006). Moreover, Tombaugh (2006, p. 66) states that "at the present time, any attempt to attribute scores to a single neuropsychological process is naïve". Although, most likely this variety of involved functions crucially contributes to the effectiveness of PASAT training for MDD, deriving neural signatures of specific cognitive functions is not possible, thus hampering the extraction of indicative biomarkers. Third, the number of negative feedback trials we could include into the analysis of study III was quite small, resulting in increased noise. Causal for this was the exclusion of trials that were not preceded by a response, since negative feedback trials without responses resulted from different causes (e.g., participants zoned out vs. did not know the answer) that reflect quite different underlying processes. Fourth, the simultaneous presentation of performance feedback and digits reflects conflicting processing of distracting, emotionally salient information opposed to task-relevant digits. Although, this represents a good illustration of CC processes to maintaining goal-directed behavior, the simultaneous presentation of visual and auditive stimuli might increase noise in the data.

Furthermore, since to our knowledge no other study so far examined neural signatures during PASAT performance, these were first explored in healthy participants in this doctoral research before the knowledge gathered in study I was used for study III. However, a direct comparison of neural signatures during PASAT performance of depressed patients and healthy subjects probably would have provided further insight into altered cognitive functions in MDD and could be subject of future studies. Additionally, about 58 % of participants in study III received psychotropic medication that might influenced neural reactions during PASAT performance.

Taken together, features like the adaptive ISI and the variety of cognitive functions that are engaged by the PASAT are most likely crucial factors contributing to the good properties of it as a CCT for depressive symptoms but make it at the same time difficult to use the PASAT to extract indicative biomarkers of CC functions that provide a tool to detect latent changes in CC and identify patients that particularly benefit from CCT and tDCS.

5.6. Summary and Conclusion

The goals of the current doctoral research were to examine the effects of a tDCS enhanced CCT on depressive symptomatology. Furthermore, I intended to contribute to the investigation of optimal stimulation intensity for the treatment of MDD and knowledge on neural signatures underlying the effective CCT task PASAT.

Taken together, the results of this doctoral research do not add evidence for the effectiveness of tDCS for the treatment of MDD. Modifications in treatment schedule or stimulation parameters, though, might improve efficacy. Moreover, the overall high improvement rates might partially be attributed to a beneficial effect of PASAT training on MDD, suggesting further research into PASAT training to ameliorate depressive symptoms. The medium effects sized, only trend-wise stronger reduction of MDD symptoms in the 1 but not 2mA vs. sham group might point towards two things: first, that tDCS enhancement of CCT may support the long-term change of mechanisms underlying MDD and second, that this change seems to be supported by low-intensity, 1mA but not high intensity 2mA tDCS. However, considering the non-significance of that result, it can only be seen as the basis that might inform further studies, needed to investigate long term changes of MDD and underlying mechanisms by low-intensity tDCS.

Neural signatures during PASAT performance in healthy subjects showed a significant differential reaction to positive than negative feedback that points towards increased neural and resource allocation in line with a negativity bias. Moreover, negative correlations of early ERPs after negative feedback and positive correlations of late ERPs after negative feedback with PASAT performance indicate stage dependent differences in processing of performance feedback in the PASAT. Whereas early strong neural reactions to negative feedback might indicate distraction by negative information, increased late neural reaction to negative feedback reflects resource allocation supporting maintenance of goal-oriented behavior. The investigation of ERPs during PASAT performance in MDD patients did not yield similar effects that could have served as neural signatures of PASAT performance to gain knowledge on the effectiveness of PASAT training for depressive symptoms. In line with studies showing attentional biased processing of emotional stimuli only for long presentation durations, differential neural reactions to negative vs. positive feedback was solely found for late processing stages. Additionally, no significant associations of ERPs and PASAT performance or MDD symptoms were found, thus limiting the explanatory power about neural mechanisms underlying PASAT performance in depressed patients.

Overall, by the examination of open research questions, the studies included in this doctoral MDD research contribute importantly to the investigation of tDCS and CCT for the treatment of MDD and additionally inform future research on optimizing protocols for effective brain stimulation treatment of depressive symptomatology.

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