RUNNING HEAD: neurocognitive training, tDCS and rumination

Transcranial electric stimulation and neurocognitive training in clinically depressed patients: A pilot study of the effects on rumination.

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Abstract

Rumination is a cognitive-affective thinking style that plays a key role in the onset and maintenance of depression. Recently, it was shown that clinically depressed patients who received a neurocognitive training - involving two weeks of repetitive cognitive control exercises that necessitate prefrontal engagement – are more able to control over ruminative negative thoughts than patients who only received treatment as usual. Transcranial Direct Current Stimulation (tDCS) is a biological technique that can directly modulate prefrontal excitability via the manipulation of neural membrane potentials. In this randomized double-blind trial, we investigated whether bifrontal tDCS (anode over the left/cathode over the right dorsolateral prefrontal cortex (DLPFC)) would enhance the influence of a neurocognitive training on depressive brooding, the maladaptive form of rumination. Major depressed patients were trained using a procedure based on the Paced Auditory Serial Addition Task (PASAT), a task that relies heavily on working memory and is found to engage the DLPFC. One group (n=19) completed the PASAT training together with active tDCS and another group (n=14) completed the same training together with sham (placebo) tDCS. In both groups, depressive brooding was reduced following the PASAT training. Moreover, we observed that improvement in working memory over the course of the training was associated with a greater reduction in depressive brooding post versus pre intervention. However, tDCS did not moderate this association between changes in working memory and changes in depressive brooding. Possible explanations for this absent moderation of tDCS, as well as avenues for future research to influence ruminative thinking in depression, are discussed.

1. Introduction

Rumination, recurrent uncontrollable thoughts united by a common theme (Martin & Tesser, 1996) such as the possible causes, meanings and implications of negative mood states (Nolen-Hoeksema & Morrow, 1991), is a crucial cognitive-affective thought process in depression. This meta-cognitive thinking style makes individuals vulnerable to depression by maintaining and exacerbating depressive symptoms, and even by predicting the likelihood of recurrent depressive episodes (for a review, see Nolen-Hoeksema et al., 2008). Ruminative thoughts are associated with cognitive mechanisms such as impaired disengagement from negative representations and updating in working memory (e.g., De Lissnyder, Koster, & De Raedt, 2012), and also to a neural dysregulation in frontocingulate and limbic circuits (for reviews, see Koster et al., 2011; Pizzagalli, 2011). More specifically, emotional stimuli activate the limbic circuit (Zald, 2003) which signals to the frontocingulate circuit to adjust the distribution of cognitive resources and, in turn, reduce the limbic activity (Hoplinger, Buonocore, & Magnun, 2000). However, this interplay between the neural activity related to emotional reactivity and cognitive control seems to be impaired in patients with major depression (Holmes & Pizzagalli, 2008), and appears to result in a maladaptive regulation of emotions (Davidson, Pizzagalli, Nitschke, & Putnam, 2002) and rumination (Koster et al., 2010). In sum, working memory processes (e.g. disengagement and updating of information) and the specific neurobiological functions associated with these processes have been proposed to be the mechanisms underlying the occurrence of ruminative thoughts and depression (for a review, see De Raedt & Koster, 2010).

In line with these process-oriented theoretical models in depression and rumination, non-pharmacological neurocognitive training procedures have been developed, during which

depressed patients are repeatedly exposed to cognitive tasks linked to the engagement of prefrontal activity. Siegle and co-workers (Siegle, Ghinassi, & Thase, 2007; Siegle et al., 2014) developed a Cognitive Control Training (CCT) during which participants are trained on two neurocognitive tasks. One task of the CCT, a low-load version of sustained-attention training exercises are used in which patients are asked to focus their attention on external stimuli (e.g., bird sounds) (attention training: Papageorgiou & Wells, 2000; Wells, 2000). This latter task is meant to enhance selective attention to stay on the task when automatic ruminative thoughts could occur. In the other task of the CCT, the Paced Auditory Serial Addition Task (PASAT, Gronwall, 1977), working memory is trained and -as the demands on working memory are high- this is associated with more emotional reactions (e.g., frustration, negative thoughts, small amount of negative affect). As a result, working memory is trained in an emotional task context, which suggests that both the frontocingulate and limbic circuits are activated. Clinically depressed patients who received daily sessions (for two weeks) of this latter CCT showed a greater decrease in rumination than patients who had only received treatment as usual (Siegle et al., 2007; 2014). Moreover, using functional magnetic resonance imaging (fMRI), patients demonstrated enhanced prefrontal activity during a digit sorting task and decreased amygdala activity during a personal relevance rating task after (as compared to before) the CCT (Siegle et al., 2007). So, the CCT in depressed patients influenced activation in neural correlates of the frontocingulate-limbic circuit, but also resulted in reduced rumination and depressive symptoms. Interestingly, as observed by Siegle et al. (2014), the CCT seemed to be most effective to reduce rumination when patients engaged in the working memory task by exerting cognitive resources at the start of the training (this was measured by pupillary responses to index task-related resource allocation). Furthermore, in a recent review, De Raedt, Vanderhasselt, & Baeken (2014)

suggested that deficient prefrontal functioning in currently depressed patients might limit the effects of neurocognitive training. In other words, greater prefrontal engagement would augment the effects of neurocognitive training.

To directly enhance prefrontal excitability, transcranial Direct Current Stimulation (tDCS) can be used. This biological technique induces small changes (<1mV) in the membrane potential (Datta et al., 2009), acting in the frequency of spike timing and modifying net cortical excitability (Purpura & McMurtry, 1965), which can increase cortical perfusion and functional activity (Keeser et al., 2011). Anodal stimulation is found to increase cortical excitability, whereas cathodal stimulation is found to decrease excitability. Anodal tDCS of the prefrontal cortex causally enhances cognitive processes such as working memory (e.g., Fregni et al., 2005; for a review see Brunoni & Vanderhasselt, 2014) and conflict monitoring (Vanderhasselt et al., 2013a). Moreover, anodal tDCS of the prefrontal cortex has been found to reduce state rumination via a beneficial change in working memory processes (Vanderhasselt et al., 2013b) and also causally reduce other depressive symptoms (e.g., Brunoni et al., 2013a). Most important, tDCS doesn't require anesthesia and is well tolerated, which makes it a technique suitable to be combined with cognitive training (De Raedt et al., 2014). It has also been demonstrated that concurrent neurocognitive training enhances the antidepressant outcome of anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC) (Segrave, Arnold, Hoy, & Fitzgerald, 2014). These findings strengthen the idea that the results of neuromodulation are better when anodal tDCS is delivered to a cortical region that is functionally active during a cognitive task. We recently reported that depressive symptoms are reduced after two weeks of training using the PASAT (see above): concomitant neurocognitive training and anodal tDCS of left DLPFC (cathodal over the right DLPFC) had beneficial effects in reducing depressive

symptoms in older patients and those who perform better on the PASAT throughout the training (Brunoni et al., 2014). However, the effects of two weeks of concomitant prefrontal neuromodulation and PASAT training on rumination – a core vulnerability process in depression - have not been reported so far.

Hence, the present study was designed to train clinically depressed patients repeatedly on working memory processes that engage the prefrontal cortex while anodal tDCS or sham (placebo) neuromodulation of the left DLPFC was administered. The aim of this study was to investigate the specific effects on rumination. In the studies of Siegle and colleagues, as was described above, the PASAT training was combined with other attention training exercises (Papageorgiou & Wells, 2000). However, using two tasks makes it impossible to disentangle the specific contribution of each task. Given that the PASAT is specifically known to activate the left middle frontal gyrus (including the DLPFC) (Lazeron et al., 2003), we only used this latter computer-based program to train working memory. Importantly, ruminative thoughts are associated with impaired processes in working memory (e.g., De Lissnyder et al., 2012). We assessed rumination with the Ruminative Responses Scale (RRS; Treynor et al., 2003), which consists of two subscales. The depressive brooding subscale assesses the degree to which individuals passively focus on depressive symptoms, the reasons for their distress, and a passive comparison of one's current situation with some unachieved standards. The reflective pondering subscale assesses neutrally valenced pondering and is considered to be a more adaptive form of rumination. Depressive brooding, the maladaptive self-critical component of rumination, (Treynor et al., 2003) has been found to be specifically related to cognitive control impairments in working memory (De Lissnyder et al., 2010), and the activation in the DLPFC and the

posterior parts of the dorsal anterior cingulate cortex during cognitive control operations (Vanderhasselt et al., 2011; 2013).

Based in prior research (Siegle et al., 2007; 2014), our hypotheses were that:

(1) working memory performance on the PASAT will be improved over the course and following of the training, with larger improvements in the tDCS condition (as compared to sham);

(2) depressive brooding reports will be reduced following the PASAT training, with larger effects in the tDCS condition (as compared to sham);

(3) the improvement in working memory will be related to the reduction in depressive brooding scores pre versus post training;

(4) the association between changes in working memory and changes in depressive brooding will be stronger in the tDCS condition as compared to the sham condition.

2. Methods

The study was approved by the Local and National Ethics Committee and is registered in clinicaltrials.gov (NCT01434836). All patients provided written informed consent. The trial was conducted in the University Hospital, University of São Paulo, Brazil and in the Mackenzie Presbyterian University, also situated in São Paulo, Brazil from September 2011 to May 2013. Participants were recruited in the context of a larger project investigating the clinical outcome and the effects other neurocognitive markers of this non-pharmacological anti-depressant

intervention[1]. In the present study, our primary outcome variable is depressive brooding, with depressive symptoms being a secondary outcome variable that would change more slowly (Siegle et al., 2014). The results of the neurocognitive training using the PASAT combined with active or sham tDCS on clinical outcome measures (Hamilton Depression Rating Score and the Beck Depression Inventory), including follow up moments at 4 and 6 weeks, are discussed in another paper (Brunoni et al., 2014).

2.1. Participants

Major depressed ambulatory patients were recruited from a local psychiatric clinic or were solicited through advertisements posted within the community. Prior to inclusion, board-certified psychiatrists (ARB and LV) administered the Portuguese-validated version of the Mini International Neuropsychiatric Inventory (MINI), a structured clinical interview to confirm an acute major depressive episode (Sheehan et al., 1998).[2]

The inclusion criteria for MDD were (a) current major depressive disorder, as assessed by the MINI with low suicide risk, and (b) a score greater than 21 on the Hamilton Depression Rating Score (HAM-D, Hamilton, 1960) both on the screening day and on the day of the first treatment session, and (c) aged between 18 and 65 years. Exclusion criteria were 1) other psychiatric disorders than MDD, except for anxiety disorders as comorbidity; 2) the intake of anti-psychotics, tricyclic anti-depressants and/or high-dose benzodiazepines (> 20 mg/day); 3) a history of neurological disorder, including epilepsy, head injury and loss of consciousness; 4) previous treatment with electroconvulsive therapy; 5) alcohol abuse during the past year; 6) a

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[1] Indices of the sympathetic nervous system were also measured, such as pupil size, cortisol and heart rate. Neural functioning was also assessed using an electroencephalogram. Behavioral measures -the Internal Shift Task and questionnaires- were collected before and after the treatment. These data will potentially be presented in other manuscripts on this dataset.

past or present substance dependence; 7) past or present experience of psychotic episodes; 8) less than 8 years of schooling, difficulties in performing arithmetic operations and/or learning disorders; 9) personality disorders; and finally 10) specific contraindications to tDCS, such as metallic plates in the head. All MDD participants had a stable anti-depressant medication during the time of testing (stable drug regimens for > 6 weeks), i.e. either based on Selective Serotonin Reuptake Inhibitors (SSRI) or Selective Noradrenalin Reuptake Inhibitors (SNRI). Benzodiazepine drugs were tolerated but tapered to a maximum of 20mg/d diazepam (or equivalent) according to previous findings suggesting that benzodiazepines could interfere in tDCS antidepressant mechanisms (Brunoni et al., 2013b).

The sample size was estimated based on previous findings from our group at the time of study design (Boggio et al., 2008), in which a 6-point difference in the HDRS scores between active vs. sham tDCS (*SD*=6) was observed. Therefore, with two-sided α=0.05 and β=0.2, we calculated that it would be necessary to enroll 32 patients to detect this 6-point difference between groups. Considering an attrition rate of 10-20%, we aimed to recruit 36 to 40 patients for this study.

Thirty-seven right-handed individuals meeting the DSM-IV criteria for MDD were included in this study. Participants were randomized to (1) PASATtraining with sham tDCS (n=17) and (2) PASAT training with active tDCS (n=20). Pre and post rumination data could only be obtained from 33 patients, leaving 14 patients in the training/sham tDCS group and 19 in the training/real tDCS group. Major demographic and clinical assessments for the two groups are listed in Table 1.

2.2. Questionnaires

To examine the severity of the current MDD episode, the HAM-D was administered. The HAM-D is a semi-structured interview, evaluating the severity of depression. The interview consists of 21 items and explores depressed mood, vegetative (e.g., insomnia, fatigue, anorexia) and cognitive symptoms and comorbid anxiety disturbances.

Depressive symptoms were measured using the BDI-II (Beck et al., 1996). The BDI-II is a 21-question, multiple-choice, self-report inventory, examining the severity and the occurrence of cognitive, affective, somatic and vegetative symptoms of depression during the last two weeks. The BDI-II questionnaire has been found to have optimal internal reliability, with cronbach's alpha indexes of around .90 (Osman et al., 1997). Cronbach's alpha of the current BDI dataset was .77, which reflects good internal reliability of the items.

Rumination was assessed using the Ruminative Responses Scale (RRS; Treynor et al., 2003), which consists of items that are focused on the self, symptoms, or consequences of a depressed mood. A factor analysis of the RRS has identified a depressive brooding subscale (5 items). This subscale relates to a passive focus on one's problems, negative mood and their consequences. An example of an item is "think about a recent situation, wishing it had gone better". The RRS can also be used to assess a measure of reflective pondering (5 items), which is, compared to depressive brooding, a more adaptive form of rumination. The RRS is a reliable and valid measure of rumination with good psychometric properties (Cronbach alpha coefficient of .90 and the test-retest correlation around .67) (Treynor et al., 2003). The reliability score of the reflection (.72) and brooding (.77) subscale are somewhat lower, but given the fact that the subscales only consist of 5 items each, is acceptable (Treynor et al., 2003). Cronbach's alpha of the current RRS dataset was .81, which reflects very good reliability. The cronbach's alpha was

.74 and .51 for the subscales brooding and reflection, respectively. In this study, we focus on the brooding subscale, which shows to have good internal consistency among the subscale items.

2.3. Neurocognitive training

A variant of the Paced Auditory Serial Addition Task (PASAT, Gronwall, 1977) was employed for the neurocognitive training. For the present study, the numbers (1 to 9) were recorded in Portuguese and the software (developed by Greg Siegle's lab) presented digits out load in a random order to the participants. Patients listened to these serially presented digits and were asked to add each new digit to the digit that preceded it (i.e., sum of the last 2 digits), in order to select the correct response on the screen with a mouse click. Patients performed the PASAT in a quiet room and were sitting in a comfortable chair about 60 cm in front of the computer screen. As they were doing the task individually, no headphones were provided.

For this modified version of the PASAT, the speed of the presentation of the digits (and thus task difficulty) is adapted to participants' individual performance. The inter-stimulus interval (ISI) starts at 3000 ms and speeds up by 100 ms when participants get four consecutive items correct. Due to this gradual increase in difficulty, the task taps heavily on control processes in working memory to stay on the task. Participants were instructed to concentrate on the task, to get as many items correct and to resume the task as quickly as possible when they made an error. However, when four consecutive errors are made, the ISI slows down by 100 ms. Although the PASAT is known to induce frustration and negative self-referential thoughts (Siegle et al., 2007; 2014), the individually adapted speed keeps the task tolerable for depressed participants.

Participants completed three 5-min blocks per session, 5 sessions per week, for two weeks. During the first session, some practice trials were presented to make sure the patient understood the task. Over the course of the task, the ISI is adapted to the individual's

performance. For the PASAT, the median ISI for each patient/session is taken as the dependent variable of interest. In prior studies, the median ISI's per participants was averaged over all participants (e.g., Siegle et al., 2014). However, it is important to take into account the sequential adaptation (e.g., stability and variability of the change) in performance over each day of the training. Hence, regression coefficient analysis (RCA; Lorch & Myers, 1990) was used to regress the dependent variable (median ISI per session day) on the independent variable (ten days of training) individually for each participant, in order to extract the values of the slope. This method assumes a linear relationship between predictor and dependent variable for each participant, and avoids methodological problems when different observations (i.e., daily assessment of the working memory task) are not independent from each other.

2.4. Transcranial Direct Current Stimulation

tDCS was delivered by a battery-driven stimulator (Chattanooga Ionto Device; Chattanoga group) with two rubber electrodes placed in 5 x 5 cm saline-soaked rubber sponges. Electrodes were positioned over the F3 (anodal) and F4 (cathodal) areas according to the 10/20 EEG International System that corresponds to the regions over the left and right DLPFC, respectively. This montage simultaneously increases the left and decreases the right DLPFC activity (Ferrucci et al., 2009), which is an asymmetry that plays a crucial role in depression (Mayberg, 1997). For the real tDCS, a constant current of 2 mA intensity was applied for 30 minutes, whereas for the sham condition the device was turned off after 45 seconds[3] of real tDCS stimulation (with a 30-second ramp-in phase and 15-seconds ramp-out phase). This sham

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[3] Although there is no consensus regarding the optimal ramp-up time period, this step is used to provide a slow increase to the desired current in order to avoid unpleasant skin sensations (for a review, see Nitsche et al., 2008). As we used a 2mA current, we therefore applied a longer ramp-up period than used by Gandiga et al. 2006 (who used approximately 10 seconds ramp up/down period with 1mA) to more or less maintain the same speed of current increase.

procedure proved to be reliable for blinding purposes, being as reliable, for instance, to the use of placebo pill in pharmacological trials (Brunoni et al., 2013c). The experiment number randomly assigned to the participant defined the stimulation procedure (tDCS or sham) for that specific participant, which was applied by trained nurses. The nurses adopted the same procedure for both sham and active stimulation, and were trained to turn off the device outside of the patient eyesight.

2.5. Procedure

This study used a double-blind between subjects design. After study eligibility was assessed, participants were invited to start their daily training/neuromodulation sessions (5 sessions a week, for two weeks). In this study, an experimental group receiving PASAT training and anodal tDCS of the left DLPFC (cathodal right DLPFC) was compared to a control group receiving the same training and sham (placebo) stimulation. During each session, each patient received 30 minutes of active/sham tDCS. During the last 15 minutes of the stimulation, patients performed the PASAT. Participants were allowed 2 nonconsecutive missed visits; in such cases extra tDCS sessions were performed to complete the total number of sessions.

2.6. Statistical analysis

To investigate whether working memory was enhanced after as compared to before the PASAT training, with larger improvement in the tDCS condition (hypothesis #1), a mixed ANOVA with *Time* (first training session, last training session) as within subjects factor x *Stimulation* (tDCS, sham) as between subjects factor was performed, and the median ISI per session as dependent variables. Moreover, the slope of the improvement on working memory was compared between tDCS and sham neuromodulation conditions. To investigate the change in depressive brooding pre versus post treatment (hypothesis #2: depressive brooding will be

reduced following the training, with larger effects in the tDCS condition), a mixed ANOVA was performed with *Time* (pre, post) x, *Stimulation* (tDCS, sham), and the brooding scores as dependent variable.

To answer *hypothesis # 3* (improved working memory via the PASAT training is related to reduction in brooding scores pre versus post training) and *hypothesis # 4 (*the association between changes in working memory and changes in brooding will be stronger in the tDCS condition as compared to sham*)*, we performed an ANCOVA with *Stimulation* (tDCS, sham) as between subjects factor, *Slope of the change in working memory during the training* as a continuous factor, and the post minus pre brooding (delta) score as dependent variable. The interaction term between the covariate and the between subjects factor (slope*Stimulation) was inserted in the custom model (together with the two main effects of *Slope* and *Stimulation*). The more negative the value of the slope, the greater the improvement on the PASAT over the course of the training. The more negative the delta brooding score, the more brooding declined after the training. Significant effects of this ANCOVA were followed up by a Pearson correlation test.

Across analyses, significant ANOVA effects were followed-up using *t*-tests. Cohen's *d*-values are reported for *t*-test effect sizes: estimates of 0.1 are considered small, 0.3 medium, and 0.5 large (Cohen, 1988). Effect sizes for ANOVAs are reported in the form of partial eta squared (ηp^2), where 0.05, 0.1, and 0.2 correspond to small, medium, and large effects, respectively (Cohen, 1988). The significance level was set at an alpha level of 0.05.

3. Results

Patients in both groups (training/tDCS (n=19), training/sham (n=14)) did not differ significantly in gender, age, baseline depressive brooding, baseline depression scores, and

depression episode characteristics (all ps>.1). For the first hypothesis, an ANOVA with *Time* (pre, post) x *Stimulation* (tDCS, sham) yielded a main effect of *Time*, $F(1, 27)=97.05$, $p< .0001$. Post hoc analyses showed that the PASAT training enhanced working memory in both stimulation groups, as the median ISI during the first day was significantly higher as compared to the median ISI during the last day, ts>6.63, ps<.001. Cohen's d of both within subjects comparisons was ≥ 1, signifying a big difference (≥ 1 SD) between both means (pre-post). No other main or the interaction effect reached significance, Fs<2.37, ps>.14, indicating that this change in working memory performance was not different for the two stimulation groups. Interestingly, the slope of the improvement in performance on the PASAT was trend significantly different between both stimulation groups, $t(31)=2.00$, $p=.054$, with the slope being more negative in the sham as compared to the tDCS group. We refer to Table 1 and 2 for the means and statistics of these between group comparisons.

For the second hypothesis, the mixed ANOVA with *Time* x *Stimulation* yielded a significant effect of *Time*, $F(1, 31)=16.55$, $p<.001$, $\eta p^2 =.34$, demonstrating that brooding was significantly reduced post versus pre PASAT training (see table 2 for an overview of the brooding scores). No other main or interaction effects were observed, F's<1.67, ps>.2, ηp^2s<.05, indicating that this change in brooding was not different for the two stimulation groups.[4]

For the third hypothesis, the mixed ANCOVA with *Stimulation* as between subjects factor, *Slope* of the performance as covariate, and the delta brooding score as dependent variable yielded a main effect of *Slope*, $F(1, 32)=4.51$, $p<.05$, $\eta p^2=.15$. The Pearson correlation between

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[4] The same ANOVA analysis was performed for reflection scores, and yielded no main or interaction effects, Fs<.77, ps>.4.

slope and the delta score of brooding (post minus pre PASAT training) revealed a significant positive correlation, $r=.40$, $p=.02$, indicating that the greater the improvement in working memory over the course of the training, the larger the decrease in depressive brooding (hypothesis # 3, see Figure 1).

However, in contrast to hypothesis # 4, the factor *Stimulation* was not implied in any main or interaction effect of the mixed ANCOVA, Fs<.05; ps>.83, ηp^2s<.001, indicating that neuromodulation did not influence the relation between the slope of the performance during the PASAT training and brooding reports (see table 2 for an overview of the brooding scores and the slopes).

4. Discussion

In this randomized, double-blind clinical trial, we investigated (1) the effects of neurocognitive training using the PASAT combined with tDCS or sham neuromodulation on working memory performance; (2) the effects of this PASAT training combined with tDCS or sham neuromodulation on depressive brooding; (3) how training induced changes in working memory are associated with changes in depressive brooding; and (4) whether active tDCS would moderate this latter association between working memory and depressive brooding.

First, over all depressed patients, depressive brooding scores were reduced post as compared to before the PASAT training. This finding is in accordance with prior reports (Siegle et al. 2007; 2014) and confirms that an intensive training of working memory is associated with a reduction in maladaptive ruminative thoughts. As a theoretical mechanism to explain these results, it is proposed that training (e.g., enhancing) working memory by a task that elicits emotional reactions (e.g., due to the increasing task difficulty) increases the likelihood that depressed patients use this acquired cognitive ability to control recurrent negative thoughts (e.g.,

rumination) in daily life. Importantly, the current results go beyond the results of Siegle et al. (2007; 2014) as they show that the sequential improvement in working memory was associated with a reduction in depressive brooding after the training: the more that patients improved their working memory over the 10 days of the neurocognitive training using the PASAT (considering the daily change -slope- in performance), the greater the reduction in depressive brooding post versus pre intervention. Research has shown that activity in the left middle frontal gyrus (including the DLPFC) was increased during the PASAT as compared to a control task (Lazeron et al., 2003). Possibly, the more the DLPFC is engaged during the PASAT training to improve working memory, the greater the reduction in depressive brooding following the training. In other words, by enhancing prefrontal activity in an emotional task context, patients are more able to control over negative thoughts in daily life by disengaging from negative representations in working memory (e.g., De Lissnyder et al., 2012).

However, no evidence could be found for our hypothesis that neuromodulation of the DLPFC would have a supplementary effect on the reduction in rumination. In other words, concomitant neuromodulation did not reveal any added value on the effects of the PASAT training on depressive brooding, nor did it influence the relation between working memory and depressive brooding. This finding could be due to multiple reasons. In the current study, anodal stimulation of the left DLPFC was combined with cathodal stimulation of the right DLPFC, producing a respective left-sided increase and right-sided decrease in cortical excitability. This bifrontal electrode montage is frequently used in treatment of clinically depressed patients (see Brunoni et al., 2013a,b; 2014) aiming to augment (hypo)activity in the left hemisphere, as well as to restore the well known imbalance between both hemispheres in depression (Phillips et al., 2003). In fact, anodal tDCS over the left DLPFC is ubiquitously used in depression trials,

whereas the cathode position varies between the right DLPFC, right supraorbital area and extra-cephalic positions (as reviewed by Moffa, Valiengo, Shiozawa, & Brunoni, 2014). For cognitive functioning, a review of the literature showed that most tDCS studies with a focus on working memory have placed the anodal electrode over a frontal scalp location (mostly F3), and the cathode over the controlateral supraorbital cortex (for a meta-analysis, see Brunoni & Vanderhasselt, 2014). Nevertheless, prior studies in major depressed patients have shown beneficial changes in working memory using a bifrontal electrode montage applying 2 mA (e.g., Oliveira et al., 2014). Recently, an extracephalic reference electrode has also been used to influence cognitive processes in depression and healthy subjects (Wolkenstein & Plewnia, 2013; Clarke, Browning, Hammond, Notebaert & MacLeod, in press). However, this wider interelectrode distance has been found to reduce the intensity of the stimulation under the anodal electrode (Moliadze, Antal, & Paulus, 2010), and has also been associated with no clear differences between the effects of active and sham tDCS (Martin et al., 2013). All together, the research domain of combining neuromodulation with cognitive training is flourishing extremely fast, but more research is needed to explore and consider the impact of alternative and/or less investigated tDCS montages on cognition and behavior.

Another possible explanation for why tDCS did not moderate the relation between working memory and rumination can be found at the level of negative self-referential thoughts. The neurocognitive training using the PASAT puts high continuous cognitive demands on working memory and is known to inherently induce reactive frustration and distracting (emotional) thoughts regarding one's cognitive ability and the consequences of task performance (Siegle et al., 2007; 2014). A possible mechanism of the PASAT training is that it increases working memory despite distracting negative thoughts in which patients engage during the task

(Siegle et al., 2007; 2014), and which - in turn - trains and prepares MDD patients to control ruminative negative thoughts in daily life. Because tDCS is known to increase working memory performance via the causal enhancement of DLPFC neural excitability, distracting (emotional) thoughts regarding one's cognitive ability might have been reduced, preventing patients to learn to deal with negative (ruminative) thoughts. This means that the extra benefit of tDCS above sham might have been reduced by this phenomenon. In other words, tDCS could have antagonized the effects of PASAT training as both interventions were administered concomitantly. Nevertheless, future research is warranted to replicate our findings in a larger population of severely depressed patients. Moreover, future research could use an offline stimulation protocol, by performing the PASAT training first followed by a neuromodulation session (with different electrode set-ups). This way, the PASAT training can still induce frustration and associated negative self-referential thoughts, which can, in turn, be reduced by increasing executive control using PASAT training and neuromodulation. Moreover, even though the current results are indicative for an important role of DLPFC activation underlying the change in depressive brooding, future research should examine the underlying change in neural functionality and connectivity by means of fMRI measurements.

Along with suggestions for future research, a couple of limitations of this study should be discussed. First, because no placebo training of working memory was used, it is not clear whether the antidepressant effects of the neurocognitive intervention using the PASAT are specific for the training of working memory or whether the same effects might be obtained when patients are trained on another task. Second, even though the number of participants was based on power analysis, the sample size is rather small and groups were not well balanced. Third, because the PASAT training is an add-on intervention to the treatment as usual, the use of

specific psychotropic medication (low doses of benzodiazepines, SSRI and SNRI) was allowed. The possible influence of medication on the present results could not be eliminated, and further research is needed to explore this possible bias.

In sum, the current study provides evidence for the role of neurocognitive training using the PASAT on depressive brooding, and adds to the literature by showing that the more cognitive resources are employed during the training, the more depressive brooding is reduced post treatment. However, concomitant tDCS during the training did not increase this association between working memory improvement and depressive brooding. Future research using alternative electrode montages and designs should be performed to investigate the role of neuromodulation on neural and cognitive mechanisms underlying working memory and depressive brooding.

Acknowledgments

Figure

Figure 1: Scatterplot of the association between the slope of the improvement in working memory during the neurocognitive training using the PASAT (y-axis) and the change in depressive brooding (RRS delta score, post minus pre intervention) (x-axis).

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Table 1. Demographical and clinical data.

	training /sham tDCS (n=14)		training/active tDCS (n=19)		Statistics	
	M	*SD*	*M*	*SD*	*t*	*p*
Age	41	11.54	46.26	10.67	1.35	.19
% Female	79%		68%		0.63	.53
Number of depressive episodes	.79	1.42	.58	.90	1.64	.15
Age of onset depression (in years)	23,71	12.06	30.06	11.99	1.44	.16
Duration present episode (in months)	10	9.63	31.31	8.17	1.52	.14

Table 2. Mean and standard deviation (SD) of questionnaire data and performance on the PASAT for both treatment groups, before and after the neurocognitive training using the PASAT.

	training/sham tDCS (n=14)	training/active tDCS (n=19)	*p*
HDRS			
pre	27,42 *(6.09)*	25,78 *(5.92)*	.44
post	19,23 *(10.08)*	19,63 *(10.05)*	.91
RRS-total score			
pre	66 *(8.44)*	59,89 *(11.19)*	.1
post	58,57 *(13.25)*	62,21 *(14.00)*	.45
RRS-Depressive brooding			
pre	16.71 *(1.90)*	15.32 *(2.98)*	.14
post	14.00 *(3.35)*	13.21 *(3.19)*	.50
RRS-Reflective pondering			
pre	11.93 *(2.53)*	11.37 *(3.04)*	.57
post	11.64 *(2.06)*	11.84 *(3.37)*	.1
BDI			
pre	35 *(7.19)*	30,83 *(7.43)*	.14
post	22,92 *(13.79)*	21,41 *(11.74)*	.75
PASAT			
pre (median ISI)	4169 *(713)*	4028 *(878)*	.64
post (median ISI)	2720 *(798)*	3094 *(1003)*	.32
Slope	-112 *(46)*	-76 *(55)*	.05

Figure 1: Scatterplot of the association between the slope of the improvement in working memory during the neurocognitive training using the PASAT (y-axis) and the change in depressive brooding pre versus post intervention (RRS delta score) (x-axis). The Pearson correlation between slope and the delta score of brooding (post minus pre PASAT training) revealed a significant positive correlation, r=.40, p=.02, indicating that the greater the improvement in working memory over the course of the training, the larger the decrease in depressive brooding
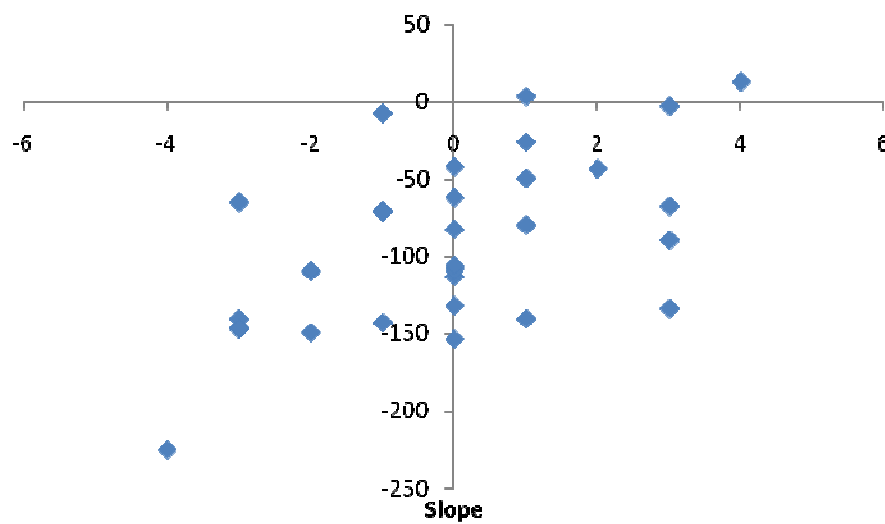
Note: the value of Cook's distance (.054) is smaller than .12 (in this case, 4/33 = .12), suggesting no outliers.