MASTER THESIS

Possible additive effects of combining rTMS with cognitive control training on mood and cognition in healthy subjects

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Abstract

Major depressive disorder (MDD) is a highly prevalent mental disorder and a leading cause of disability worldwide. Current treatments are not always effective, especially for treatment resistant depression (TRD). Repetitive transcranial magnetic stimulation (rTMS) on the dorsolateral prefrontal cortex (DLPFC) is an effective treatment for TRD by normalising depression related activity, but the effectiveness can be further improved. The mechanism of action is believed to be the modulation of cognitive control and HF-rTMS on the DLPFC improves cognitive control. Cognitive control training (CCT) is another effective treatment for depression by improving cognitive control which also targets the DLPFC. This randomised study investigates whether the combination of rTMS and CCT could have possible additive augmentation effects on mood and cognitive control in a healthy population. In a randomised order 17 participants received a single session of neuronavigated high-frequency rTMS with CCT, and a single session of neuronavigated high-frequency rTMS with a control task. After each intervention a negative mood was induced. We found no additive augmentation effects of the combination of rTMS and CCT on mood and cognitive control. Effects of the negative mood induction on mood and cognitive control were established, but no effects of rTMS and CCT were found to negate these induced negative mood affects. Overall, our results demonstrate that no additive augmentation effects were found by combining rTMS and CCT in a healthy population, even with the methodological improvement of the use of resting state-fMRI based neuronavigation with individualised targets. Combining rTMS with CCT as cognitive task has not shown any indication of augmentation effects for potential application in clinical practice to improve treatment efficacy. However, the personalisation of rTMS with personalised targets and resting state-fMRI based neuronavigation could be valuable for clinical implementation.

keywords

mood induction, rTMS, cognitive control training, resting state-fMRI based neuronavigation, augmentation

Introduction

MDD

Major Depressive Disorder (MDD) is a mental disorder characterised by anhedonia, a depressed mood, diminished interests, impaired cognitive functioning, and disturbance of sleep and appetite (*Diagnostic and Statistical Manual of Mental Disorders: DSM-V* 2013). These symptoms cause serious impairment in the ability to function, leading to a substantial loss of quality of life and increased mortality rates in depressed patients (Mrazek et al., 2014; Otte et al., 2016).

MDD is highly prevalent, one in six adults get MDD during their life and currently 280 million people worldwide suffer from this disorder (Otte et al., 2016; WHO, 2021). Besides the consequences for the patient, the societal and economic consequences are also substantial (Mrazek et al., 2014). In the US alone the economic- and healthcare costs of MDD were 326 billion dollars in 2020 (Greenberg et al., 2021). MDD is thus one of the leading causes of disability worldwide (WHO, 2021).

Primary therapies used to treat depression are pharmacological interventions and psychotherapy (Otte et al., 2016). However, these treatments are not always effective, 30% of patients do not fully remit even after several pharmacological and psychotherapy treatments (Berlim et al., 2014; Eaton et al., 2008; Otte et al., 2016; Rush et al., 2006). Only 33% of patients achieve remission when using medication as first and second treatment step, this declines to only 15% for the third and fourth step at which the depression is characterised as treatment resistant (Rush et al., 2006; Rush et al., 2009). More severe forms of depression such as treatment resistant depression are therefore difficult to treat and further development of effective therapies are necessary (Craighead & Dunlop, 2014; Otte et al., 2016).

rTMS

Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive brain stimulation technique with antidepressant properties (Rossi et al., 2009). A magnetic coil is placed against the scalp, through magnetic field pulses an electrical current is induced within the brain that depolarises the neurons (Hallett, 2007; Rossi et al., 2009). This has been shown to modulate the excitability of the cortex depending on the frequency of the stimulation, a high frequency (≥5 Hz) induces excitatory effects while a low frequency (≤5 Hz) induces inhibitory effects (Hallett, 2007; Rossi et al., 2009).

The most common target area of the stimulation thus far is the dorsolateral prefrontal cortex (DLPFC). The DLPFC is part of the frontoparietal control-/central executive network and has been defined as the functional basis of cognitive control (Kim et al., 2017; Miller, 2000; Ochsner & Gross, 2005). In depression, the DLPFC exhibits dysfunctional hypoactivity and thereby less top down influence on heightened limbic activity (George et al., 1994; Reid et al., 1998). The DLPFC has also

been identified in neuroimaging studies revealing altered functional connectivity and dysfunctional activity of the default mode network (DMN), central executive network (CEN), and salience network (SN) in MDD (Brakowski et al., 2017; Menon, 2011; Mulders et al., 2015). This depression related dysfunctional activity is proposedly normalised via indirect stimulation of these functional networks which are indirectly functionally and structurally connected to the DLPFC (Anderson et al., 2016). The restoration of the dysfunctional activity in these networks is believed to ameliorate the depressive symptoms, this could be achieved using rTMS (Anderson et al., 2016). Multiple studies show that repetitive stimulation of the DLPFC with HF-rTMS of 10 Hz for multiple sessions has antidepressant effects, this is used to treat MDD and treatment resistant depression (Berlim et al., 2013b; Berlim et al., 2014; Carpenter et al., 2012; Fitzgerald et al., 2003).

HF-rTMS is thus an effective treatment for MDD and treatment resistant depression, with response- and remission rates of about 40% and 20% (Berlim et al., 2013a; Berlim et al., 2014). The advantages of rTMS are that it is safe, non-invasive, and without severe side-effects (Berlim et al., 2013b; Berlim et al., 2014). This makes rTMS a good treatment option for treatment resistant depression (Berlim et al., 2013a, 2013b; Fitzgerald et al., 2003). However, the effectiveness of rTMS for treatment resistant depression can be further improved.

The proposed mechanism of action of rTMS is the modulation of cognitive control (Ochsner & Gross, 2005). Cognitive control refers to the cognitive processes involved in the selection and suppression of (in)appropriate thoughts, emotions and behaviours based on social context and task demands to implement goal-directed behaviour (Dixon, 2015; Miller & Cohen, 2001). Cognitive control is essential for emotional regulation and has been associated with affective disorders (Möbius et al., 2017; Pulopulos et al., 2020). The central executive network is also involved in executive control and attention, and is impaired in patients with MDD (Corlier et al., 2020; Siegle et al., 2014). Multiple studies show that stimulating the DLPFC with HF-rTMS improves cognitive control in both healthy and depressed populations (Corlier et al., 2020; Fitzgerald et al., 2006; Pulopulos et al., 2020).

CCT

The rTMS induced change in cognitive control can also be achieved via cognitive control training (CCT), this is another effective treatment in reducing depressive symptoms (Siegle et al., 2007; Siegle et al., 2014). CCT consists of repetitive tasks with a high working memory load that require cognitive control to perform, these tasks (e.g. n-back) are known to activate the DLPFC (Kim et al., 2017; Owen et al., 2005; Schweizer et al., 2013; Siegle et al., 2014). Siegle and colleagues hypothesise that repeatedly engaging the prefrontal cortex restores the imbalance between DLPFC hypoactivity and amygdala hyperactivity in MDD (Schweizer et al., 2013; Siegle et al., 2014). This is

believed to restore the impaired cognitive control and emotional regulation (Siegle et al., 2007; Siegle et al., 2014). Multiple studies further show that CCT increases the efficiency of the frontoparietal network (DLPFC and anterior cingulate cortex), and improves cognitive control (Kim et al., 2017; Schweizer et al., 2013).

State-dependent augmentation effects

The effects of non-invasive brain stimulation (NIBS) like rTMS are state-dependent, this means that the effect of the stimulation depends on the state of the targeted brain region (baseline neural activity) during the stimulation (Sathappan et al., 2019; Silvanto & Pascual-Leone, 2008). State-dependency is described as an interaction between the stimulation and the state of the stimulated network, this interaction can be used to augment the outcome of the stimulation and reduce variation in patient response. This state dependency can be controlled by functionally engaging the specific neural circuits involved, for instance by combining a cognitive task or therapy simultaneously with rTMS when both are targeting the same neural-network (Sathappan et al., 2019). Combining rTMS with cognitive tasks/therapies is highly feasible (Luber et al., 2008) and indeed several studies confirmed that response and remission in patients with MDD can be affected (Vedeniapin et al., 2010) (Neacsiu et al., 2018).

In addition, it is generally believed that the timing of the paired therapeutic intervention/cognitive task determines whether there is a priming- or engagement effect (Sathappan et al., 2019; Silvanto & Pascual-Leone, 2008). When the cognitive task is applied simultaneous with the stimulation, the involved networks are specifically engaged and this could facilitate synaptic plasticity beyond single stimulation with either rTMS or a cognitive tasks. When the intervention/cognitive task is performed before the stimulation, the target networks are being primed. The cortical excitability of the involved neuronal network is increased therefore making the networks more sensitive to the following stimulation. The neurostimulation may then enhance and facilitate task related learning processes (Sathappan et al., 2019). The feasibility of priming with rTMS in patients with treatment resistant depression has been illustrated before (Fitzgerald et al., 2008). In this study the target area of the stimulation was primed with preceding 6 Hz high-frequency rTMS, as a result the response rate to the following stimulation was enhanced.

Mood induction

There are several experimental ways to consistently induce a positive or negative mood, negative mood induction is often used to mimic a depressive state in experimental settings (Fitzgerald et al., 2011; Harrison et al., 2008; Möbius et al., 2018; Möbius et al., 2017). The resulting subjective mood changes of the negative mood induction were linked to changes in the functional activity of the resting state networks, thus reflecting the current brain state in these networks

(Harrison et al., 2008). Therefore mood induction is thought to be an important feature related to brain state-dependency, and could be used to modulate state of the resting state networks.

Möbius et al. researched the interaction between rTMS and negative mood induction, revealing that rTMS induced a higher susceptibility in mood when a negative mood was induced immediately after rTMS (Möbius et al., 2017). This finding was interpreted as an enhancement of emotional provocation via rTMS and contradicted the theory that HF-rTMS over the DLPFC protects against negative mood induction. The study further suggested that the use of this of stimulation protocol in healthy young individuals could potentially heighten susceptibility to mood induction procedures in general both in the positive and negative direction thereby further augmenting experimental procedures

Neuronavigation

Another way to further optimise the efficacy of rTMS is to improve the localisation of the stimulation using neuronavigation in the correct placement of the TMS coil on the target (Fitzgerald, 2021). The use of neuronavigation to stimulate the DLPFC appears to enhance the response to rTMS treatment in depression (Fitzgerald et al., 2009). Traditionally a T1 anatomical MRI scan and a 3D reconstruction of the head are combined with MNI-coordinates of the DLPFC to ensure the precise position of the coil on the target during the stimulation (Lefaucheur, 2019; Pan et al., 2020; Schönfeldt-Lecuona et al., 2010). A more recent neuronavigation technique is resting-state fMRI-based neuronavigation, this technique allows for the individualisation of targets based on individual neuronal activity, and accurate placement of the rTMS stimulation (Fitzgerald, 2021).
To determine the individual target a connectivity analysis is performed on the resting-state data to identify the region within the DLPFC which is most negatively correlated (anticorrelated) with subgenual anterior cingulate cortex (sgACC) (Fitzgerald, 2021; Luo et al., 2021). This technique is based on the finding that the connectivity between the sgACC and DLPFC is correlated with the response to rTMS treatment, specifically the antidepressant effect of rTMS increased with the anticorrelation between the DLPFC and sgACC. Therefore stimulating the region of the DLPFC that is most anticorrelated with the sgACC is associated with an enhancement of the antidepressant effect of rTMS (Fitzgerald, 2021; Luo et al., 2021). This relationship between the connectivity and response to rTMS treatment is stronger when individual targets are determined instead of targets on group basis (Cash et al., 2019). Since using a group-level analysis to determine the stimulation target has the potential disadvantage of casting aside the interindividual differences in functional connectivity**.** Integrating these interindividual connectivity differences to determine personalised targets could potentially improve the personalisation of rTMS and help predict the treatment outcome on

individual basis (Cash et al., 2019; Weigand et al., 2018).

Current study

Both rTMS and CCT are effective treatments for depression that target the DLPFC. Currently during the clinical rTMS session, patients are not specifically engaged but passively receive the treatment. Thus there is room for them to perform a (cognitive control) task during the stimulation to potentially improve the stimulation effects as described above. To test this idea first a pilot study needs to be done in healthy participants before the study can be performed with subclinical samples or even patients.

Based on the previously explained concept of augmentation effects in state dependent networks, the aim of this pilot study is to stimulate the networks that are related to dysfunctional activity in depression with rTMS while functionally engaging this area using CCT. We aim to investigate whether this combination makes the DLPFC more receptive for the effects of the stimulation and could result in possible additive augmentation effects. These possible additive effects will be evaluated in a pre vs post design by measuring the effects of rTMS with CCT on mood, and the interference on cognitive control. To measure the effect on mood, a negative mood is induced immediately after the stimulation. In the control condition a control task will be performed instead of CCT during the rTMS.

Our hypothesis is based on the idea that the combination of rTMS and CCT could make the brain less susceptible to negative mood induction and improve cognitive control. Therefore the combination of rTMS and CCT is expected to result in a smaller decrease in mood after negative mood induction compared to the control condition. We further hypothesise that the combined treatment will also result in a smaller decrease in cognitive control in the experimental condition compared to control.

Our alternative hypothesis is based on the idea that the combination of rTMS and CCT could make the brain more susceptible to the following mood induction and negatively influence cognitive control. The combination of rTMS and CCT is then expected to result in a larger decrease in mood after negative mood induction compared to the control. We further hypothesise that that the combined treatment will result in a larger decrease in cognitive control compared to control.

Materials and Methods

Participants

Twenty healthy participants (14 females, age = 22,2 ± 2,4 years) aged between 18-65 with no current or prior mood disorders were recruited. The participants were screened for rTMS- and MRI-safety, and for the absence of depressive symptoms using Beck's Depression Inventory-II (BDI-II). Exclusion criteria were pregnancy, a history of brain surgery, cardiac pacemaker or intracardiac lines, implanted neurostimulator, cochlear implants, a history of severe neurological problems, epilepsy in the family, a history of mood disorders, severe physical illness, metal in cranium, and a BDI-II score of >13.

Study Design

This single blinded, randomised study consisted of 3 parts (day 1, day 2, day 3), which took place over 3 consecutive weeks. On day 1 screening and rsMRI was performed, on day 2 and 3 the participants received the experimental or control condition (Figure 1). In the experimental condition the participant received rTMS and CCT consisting of a progressive dual n-back task, see supplement 1 (Jaeggi et al., 2007; Jaeggi et al., 2008). The control condition consisted of rTMS combined with a single 1-back task (control task). The participants were randomised to determine the order of the conditions, either experimental – control or control – experimental.

Day 1: intake & resting state MRI. Participants signed the informed consent form and were screened based on the inclusion- and exclusion criteria. The participants were then randomised. After the screening a resting state fMRI scan was performed.

Days 2&3: rTMS & CCT. The second part took place 4 – 10 days after the first part and the third part 5-10 days after that. The procedure is the same for both days, only the task differed. They either performed the control task on day 2 and CCT on day 3, or the other way round, the order of which was randomized and counterbalanced.

First the participant filled in the rTMS safety and Positive and Negative Affect Schedule (PANAS) questionnaires (Watson et al., 1988). Following the questionnaires the participants performed the Stroop task (Stroop, 1935; Vanderhasselt et al., 2009).

Next, the motor threshold was determined, and the personalised DLPFC stimulation area was targeted using neuronavigation, see sections rTMS and neuronavigation. The participants then received a single session of high frequency rTMS. During stimulation the participant performed either the CCT- or control task. Immediately after stimulation a negative mood was induced (Fitzgerald et al., 2011; Möbius et al., 2017) and the Stroop and PANAS were conducted again. At the end of the

session the participant was shown a happy video to negate the effects of the negative mood induction (Möbius et al., 2018).

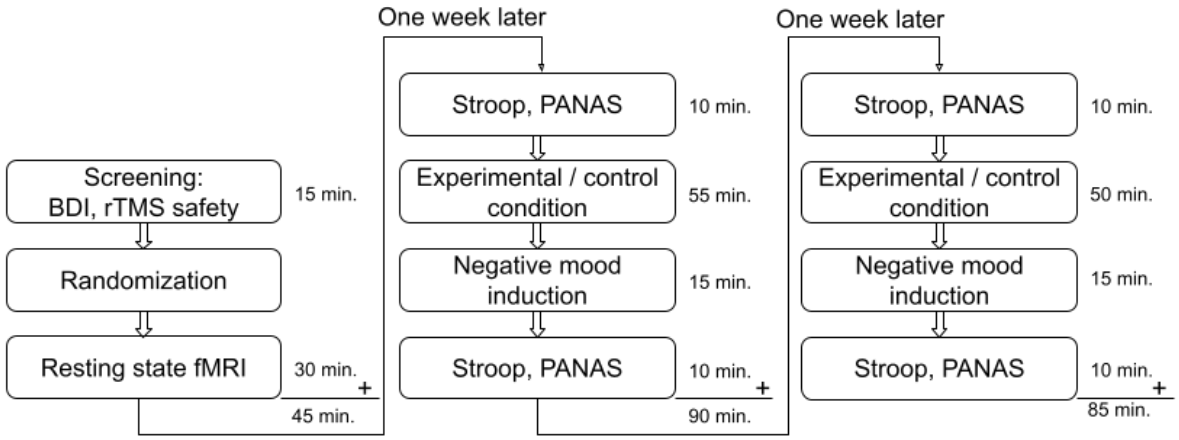

Figure 1. Overview study design.

Resting state fMRI acquisition and analysis

All subjects underwent a 8 minute resting state fMRI scan using a 3T MAGNETOM Skyra MR scanner (Siemens, AG, Healthcare Sector, Erlangen, Germany) and a product 32-channel head coil. The scan was acquired via single echo simultaneous multi slice (MB) EPI with the following parameters: TR/TE = 1000/35.2 ms, FA = 60° , FOV = 213 mm x 213 mm x 132 mm, slice number = 66, voxel size = 2.0 x 2.0 x 2.0 mm, mb = 6. The participants were instructed during the resting state scan to keep their eyes open and fixate on a white cross on a black screen, while trying to relax.

During the MRI session, a T1-weighted MRI scan was acquired in the sagittal orientation for anatomical reference and analysis. This was done using a MPRAGE sequence with the following parameters: TR/TI = 2300/1100/3 ms, FA = 8°, FOV 256 mm x 256 mm x 192 mm and a 1 mm isotropic resolution. Parallel imaging (iPAT = 2) was used to accelerate the acquisition. Participants were instructed to close their eyes.

The acquired resting state scan was analysed by extracting the brain from the anatomical T1 images using the Brain Extraction Tool of FSL. The functional scans were first corrected for acquisition order with the scans acquired in the inverse order. The functional data was then pre-processed with FEAT (fMRI Expert Analysis Tool) version 6.00 of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Registration to high resolution and standard space images were carried out using FLIRT (Jenkinson et al., 2002; Jenkinson & Smith, 2001). The registration from high resolution structural to standard space was further refined using FNIRT nonlinear registration (Andersson J.L.R., 2007a, 2007b). The functional scans were linearly registered to the T1 anatomical scan and nonlinearly registered to Montreal Neurological Institute (MNI) 152 T1 standard brain template. Using FEAT the following pre-statistics processing was applied: motion correction using MCFLIRT

(Jenkinson et al., 2002); brain extraction using BET (Smith, 2002); spatial smoothing using a full-width half-maximum (FWHM) Gaussian kernel of 3 mm; grand mean intensity normalisation of the entire 4D dataset by a single multiplicative factor; high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=50.0 s). Afterwards a bandpass filter (0.01-0.1 Hz) was applied to the data.

Neuronavigation / Functional localiser

The personalised left DLPFC target for each participant was determined according to the methods as described by Fox et al. and Cash et al. (Cash et al., 2021; Fox et al., 2013). The acquired resting state scans were used for the functional localisation of our stimulation target. The target within the left DLPFC was determined by calculating the region with the most anticorrelated functional connectivity with the right subgeniculate Anterior Cingulate Cortex (sgACC).

Region of Interest (ROI) masks were created for two targets. The right sgACC mask (MNI 6,16,-10) was determined using a kernel sphere of 5 mm (Fox et al., 2013; Jing et al., 2020), whereas for the ROI mask for the left DLPFC (MNI -36,47,32) a kernel sphere of 25 mm was used (Tik et al., 2017). Both ROI masks were transformed to subject space. A ROI analysis was performed on the pre-processed fMRI data using the right sgACC mask. Afterwards the anticorrelation was calculated between the extracted eigen variants of the sgACC ROI and the pre-processed whole brain fMRI data of the subject. The resulting anticorrelation was mapped on the subjects' anatomical scan. Finally, the personalised left DLPFC mask was applied resulting in the strongest anticorrelation within this region. The target within the DLPFC was further translated in the neuronavigation system to a stimulation target on the skull for the positioning of the coil. This was done while keeping in mind that the rTMS coil must be placed at a 45 degree angle of the target within the DLPFC.

rTMS

Before stimulation the resting motor threshold was determined, which was defined as the minimal stimulation intensity that elicits a motor response (visually observed movement of finger/thumb) in ≥5 out 10 trials. rTMS was delivered using the Magstim rapid^2 with double 70mm air film coil. Parameters consisted of 2400 high frequency pulses (10 Hz) administered in 60 trains of 40 stimuli, each train had a duration of 4 seconds and was followed by an inter-train interval of 26 seconds. The total stimulation lasted for 25 minutes per session. The stimulation intensity during stimulation was set at 120% of the motor threshold. The coil was positioned at a 45 degree angle of the individualized left DLPFC target.

Tasks/questionnaires

CCT: In the experimental condition the participant performed a progressive dual n-back task (Jaeggi et al., 2007; Jaeggi et al., 2008). Participants were sequentially presented with both auditory and visual spatial stimuli that must be remembered. When the auditory and visual spatial stimuli were the same as n turns back (e.g. n=2), the participant must respond by pressing a key (supplement 2). The n-back level was altered based on their score (supplement 1). In the control condition the participants performed a single 1-back with only visual spatial stimuli and the level remaining at 1**.** Both tasks were presented in MATLAB R2020b using an adapted version of Layden's script (Layden, 2018). Further stimulus details can be found in supplements 1 and 2.

Stroop: The Stroop task was used to assess cognitive control (Stroop, 1935; Vanderhasselt et al., 2009). Participants were shown words which were the names of colours, the ink of the words itself were coloured as well. The participant must press a key corresponding to the correct ink colour while ignoring the word itself. They are instructed to respond as fast but also as correct as possible. The level of interference for congruent and incongruent trials is measured using the reaction time. Increased reaction time indicates a higher level of interference, which is often seen for incongruent trials. This task was adapted from Sivek (Sivek, 2016) for experimental use in MATLAB, see supplement 3.

PANAS: The PANAS (Positive and Negative Affect Schedule) was used to measure positive and negative affect and consists of twenty items (Watson et al., 1988). Ten items assess positive affect whilst the other ten assess negative affect.

Negative mood induction: To induce a negative mood a 7 minute clip from the movie 'Sophie's choice' was shown. This procedure has been used before by Fitzgerald, Mobius and Vissers to induce sadness in the viewer (Fitzgerald et al., 2011; Möbius et al., 2017; Vissers et al., 2010).

The participant was instructed to empathise with the main protagonist in order to effectively induce negative emotions.

A 4-minute clip of the movie Jungle Book was used to negate the effects of the negative mood induction before sending the participants home (Möbius et al., 2018).

Outcome measures

The primary outcome is the difference in positive and negative PANAS score from pre- to post-intervention, between the experimental and control condition. The secondary outcome is the difference in Stroop interference score pre- vs post intervention between the two conditions. The calculation of the interference score can be found in supplement 4.

Our hypothesis that the combination of rTMS and CCT is expected to result in a smaller decrease in mood after negative mood induction and less interference on cognitive control. In the outcome parameters this is defined as a smaller decrease in positive PANAS scores and smaller increase in negative PANAS scores in the experimental condition opposed to the control. And a larger decrease in Stroop interference score in the experimental condition compared to the control condition.

Our alternative hypothesis that the combination of rTMS and CCT is expected to result in a larger decrease in mood after negative mood induction and more interference on cognitive control. In the outcome parameters this is defined as larger decrease in positive PANAS scores and a larger increase in negative PANAS scores in the experimental condition opposed to the control. And an increase in Stroop interference score in the experimental condition compared to the control.

Data analysis

Based on a previous power calculation using G*power (Faul et al., 2007) with a previously found effect size of $d = 0.81$ on rTMS (Möbius et al., 2017), the sample size was estimated at $N = 15$. To compensate for drop-outs and potential overestimation of the effect 20 participants were included. Further details on the power calculation from the research protocol can be found in supplement 5.

All statistical analysis were performed using SPSS Statistics 25 (IBM Corp., Armonk NY, USA), the procedures were 2-tailed and $\alpha < .05$ was considered a statistically significant result. Data was analysed to check whether it was normally distributed, if the data was not normally distributed non-parametric tests were used.

An independent student's t-test was performed on age and chi^2 test was performed on the number of male and females in each condition order.

The difference between the pre and post PANAS scores were calculated per participant for each condition. A mixed design ANOVA was performed on the difference scores for both the positive and negative PANAS, with order as between-factor and condition (exp vs control) as the within factor.

The difference between the pre and post Stroop interference score was calculated per participant for each condition and analysed with a mixed design ANOVA, with the order as between-factor and the condition (exp vs control) as the within-factor.

Finally, a paired t-test was performed on the pre and post measurements for each outcome measure excluding condition or condition order. And the correlation was tested between the change in interference scores, and the change in positive and negative PANAS scores.

Results

Participants

Twenty participants were included in this study. One participant was considered a screening failure (BDI-II score >13), one participant was a no-show, and a third participant dropped-out during the 1st TMS session due to the stimulation being uncomfortable. The demographic characteristics of the 17 remaining participants are shown in table 1. There were no baseline differences in age and gender between the two groups (table 1).

Stroop scores of two participants had to be excluded because of invalidity, both from the control condition. An outlier on the negative PANAS scores was found in the experimental condition. Excluding this outlier normalized distribution of the data.

Table 1. Demographic characteristics of participants per condition order.

	Order 1 (*N*=9)	**Order 2 (*N*=8)**	**Total (*N*=17)**	***P*-value**
Female sex	8 (88.9%)	5 (62.5%)	13 (76.5%)	0.294
Age (years)	22.3 ± 2.6	22.1 ± 2.3	22.2 ± 2.4	0.864

Values represent mean ± SD or *N (%).* Order 1 = Experimental - Condition , order 2 = Condition – Experimental.

Effect on mood and cognitive control

The mean pre- and post-scores of the participants on the primary outcome measures are shown in table 2.

The results of the mixed design ANOVA for the PANAS and Stroop scores are shown in table 3. No significant effect of condition was found on the positive ($F(1,15)=0.229$, $p = .639$) and negative PANAS scores ($F(1,15)=0.055$, $p =.817$). No significant effect of the condition order was found for the positive ($F(1,15)= 0.260$, $p = .618$) and negative PANAS ($F(1,15)= 1.064$, $p = .323$). As a sensitivity analysis the ANOVA on positive PANAS scores was performed without the outlier, this revealed no change (supplement 6).

On the Stroop interference scores no significant effect of the condition ($F(1,13) =0.117$, $p = .738$) and the condition order ($F(1,13) = 0.002$, $p = .968$) were found.

Table 2. Mean pre and post scores on Stroop and PANAS per condition per order.

		Order 1 (*N*=9)		**Order 2 (*N*=8)**		**Total (*N=17)***	
		pre	*post*	*pre*	*post*	*pre*	*post*
Exp	PANAS Positive	31.8 ± 6.5	25.4 ± 6.2	30.6 ± 7.6	24.6 ± 8.4	31.2 ± 6.9	25.1 ± 7.1
	PANAS Negative	13.6 ± 2.7	18.7 ± 6.8	12.6 ± 2.8	15.0 ± 2.8	13.1 ± 2.7	16.9 ± 5.5
	Stroop Interference	70.9 ± 8.3	66.9 ± 8.0	68.4 ± 16.4	65.3 ± 12.7	69.7 ± 12.4	66.2 ± 10.1
Control	PANAS Positive	30.4 ± 5.5	24.4 ± 7.6	32.4 ± 5.4	27.3 ± 8.0	31.4 ± 5.4	25.8 ± 7.7
	PANAS Negative	13.2 ± 3.8	18.1 ± 6.1	12.6 ± 1.8	15.8 ± 3.0	12.9 ± 2.9	17.0 ± 4.9
	Stroop Interference	73.3 ± 9.9	72.4 ± 12.8	69.9 ± 4.1	67.0 ± 6.4	71.7 ± 7.7	69.9 ± 10.3

Values represent mean ± SD. Order 1 = Experimental - Condition , order 2 = Condition – Experimental.

Table 3. Mixed ANOVA results outlier included

	Condition	**Order**
PANAS positive	0.639	0.618
PANAS negative	0.817	0.323
Stroop IC	0.738	0.968

Values represent *p*-values. IC = interference score.

Effect Negative Mood induction

Paired t-test was performed on pre and post measurements for each outcome measure independent of condition or condition order. For an overview of the results of the paired t-test in table form see supplement 7.

On average, Stroop interference scores were higher before negative mood induction (*M* = 70.697, *SD* = 10.320) than after (*M* = 67.911, *SD* = 10.234). This difference was significant and represented a medium-sized effect (2.786, 95% CI [0.271, 5.301]; *t*(31) = 2.259, *p* = .031; *r* = .376).

On average, positive PANAS scores were higher before negative mood induction (*M* = 31.29, *SD* = 6.093) than after (*M* = 25.41, *SD* = 7.262). This difference was significant and represented a large-sized effect (5.882, 95% CI [4.687, 7.078]; *t*(33) = 10.009, *p* = <001; *r* = .867).

On average, negative PANAS scores were lower before negative mood induction (*M* = 13.03, *SD* = 2.801) than after (*M* = 16.97, *SD* = 5.126). This difference was significant and represented a large-sized effect (-3.941, 95% CI [-5.680, -2.202], *t*(33) = -4.610, *p* = <001, *r* = .625).

Correlation interference cognitive control and mood affects

Two separate correlations were tested between the interference score and positive PANAS scores, and the interference scores and negative PANAS Scores.

There was no significant relationship between the change in positive PANAS scores and the change in interference scores on the Stroop (*r* = -.036*, p* = .844).

The change in negative PANAS scores was borderline significantly correlated with the change in interference scores on the Stroop (r = .320, p = .074).

Effects per condition

The change in outcome measures for each condition were plotted in figure 2. The positive PANAS scores decreased for both conditions. The negative PANAS scores increased for both conditions. The interference scores of the Stroop task generally decreased for both conditions, although an increase was observed for some participants in the control condition. But there was no larger difference between the conditions. Overall, no difference in scores between the conditions were observed.

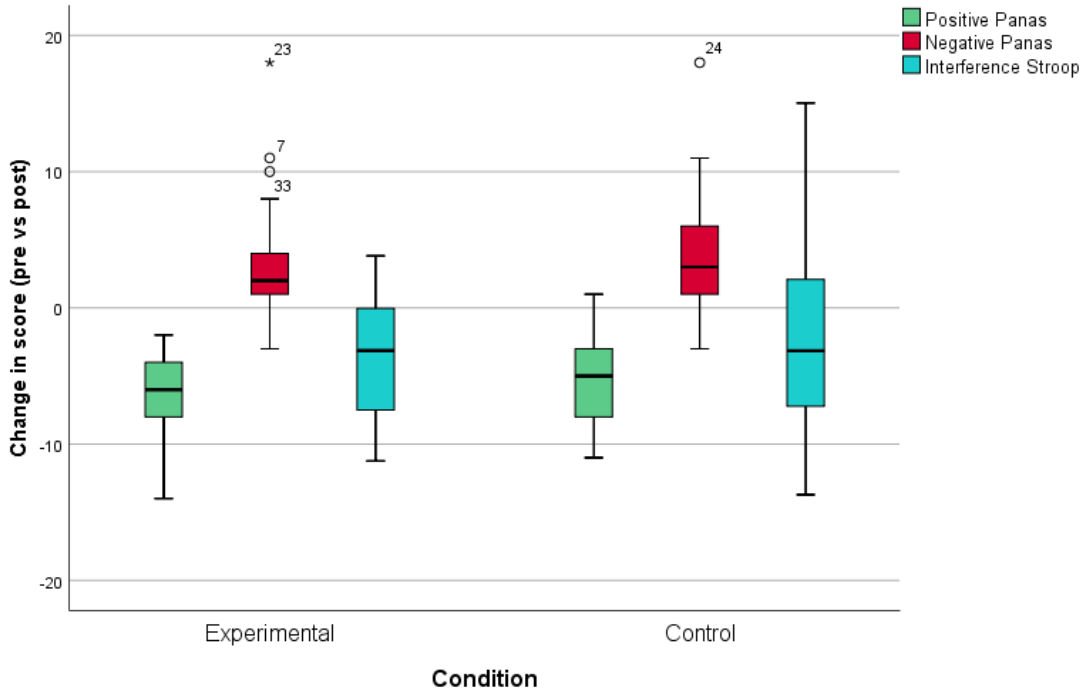

Figure 2. Mean change in outcome measure for each condition. The graph shows no difference in scores between the conditions for each outcome measure. The change in positive PANAS scores was negative for both conditions. The change in negative PANAS scores was positive for both conditions. The change in interference scores of the Stroop task was generally negative.

Effects per condition order

The change in outcome measures per condition order were plotted in figure 3. The change in scores for each outcome measure of the two condition orders were similar. A decrease was observed in positive PANAS scores, an increase in negative PANAS scores, and a general decrease in Stroop interference scores. However, only in order 1 some participants displayed an increase in interference scores on the Stroop. Overall, no effects of the condition order are observed on the scores of the outcome measures. Only the range in response seems to be larger for order 1.

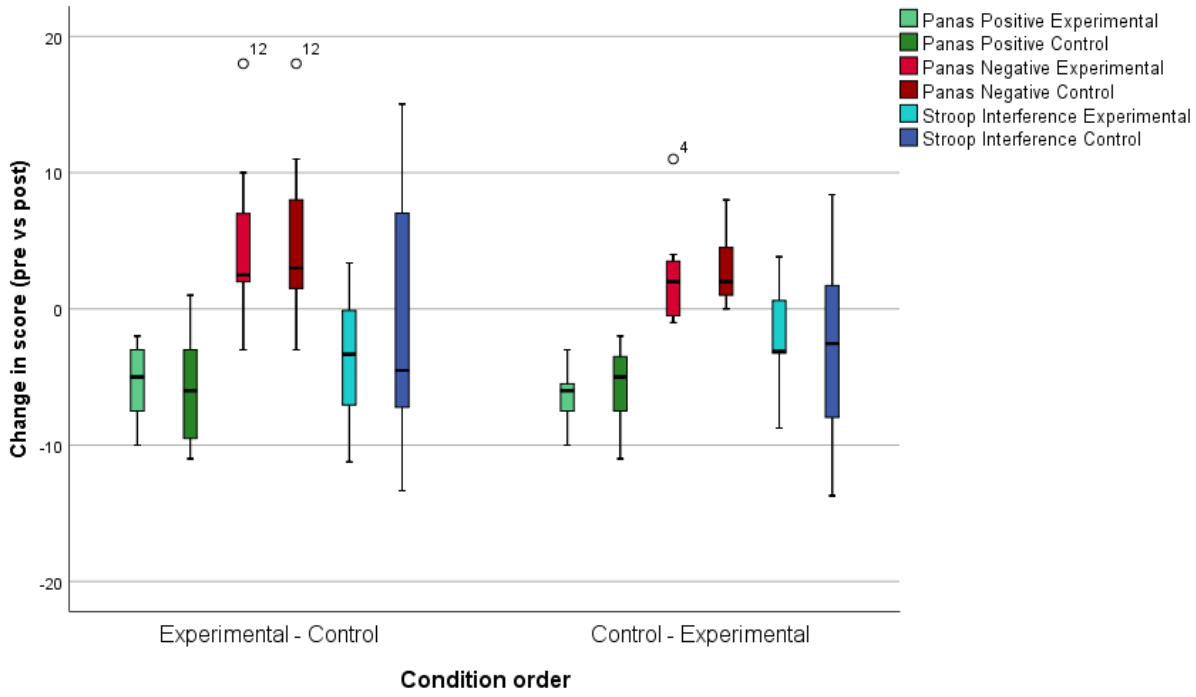

Figure 3. Mean change in outcome measures per condition order. Order 1 = Experimental - Condition , order 2 = Condition – Experimental. The graph shows that the change in score for each outcome parameter are similar for both condition orders. The range in response seems larger for the order 1.

Discussion

The purpose of our study was to investigate possible additive effects on mood and cognitive control by combining rTMS and CCT in healthy participants. Our study is a methodological extension on previous literature on augmentation effects in rTMS by integrating interindividual difference in functional connectivity using resting state-fMRI based neuronavigation. However, our findings did not support our hypothesis, since no significant effects of the intervention opposed to the control condition, or the condition order were found on mood and cognitive control.

Effects on mood & cognitive control

We found no effects of rTMS combined with CCT opposed to rTMS with a cognitive control task on mood, and no effect of the order in which the conditions were presented. The observed effects on mood consisted of a decrease in positive mood affects and increase in negative mood affects. Our null findings on mood were in line with the findings of Bovy et al. and Möbius et al. that a single session of HF-rTMS over the left DLPFC is not sufficient to alter mood in healthy individuals (Bovy et al., 2019; Möbius et al., 2017)**.** This could be quite logical since the long lasting effects of rTMS in ameliorating mood and reducing depressive symptoms in patients are based on repeated sessions of stimulation (Berlim et al., 2013b; Berlim et al., 2014; Carpenter et al., 2012; Fitzgerald et al., 2003). Perhaps to reach stimulation effects on mood in healthy participants multiple rTMS sessions are needed, this could be tested in subsequent studies. Another explanation for the lack of effect on mood could be that the mood effect we were trying to detect was smaller than estimated in our power calculation. This could result in an overestimation of the effect and the sample size could have been too small.

Furthermore, we found no effects of rTMS combined with CCT opposed to rTMS with a cognitive control task on cognitive control, and no effect of the order in which the conditions were presented. The observed effects on cognitive control consisted of a general decrease in interference thus resulting in an improvement of cognitive control. A possible explanation for the null finding on cognitive control could be that a ceiling effect on cognitive control was reached in our participants. Our participant group consisted of young, healthy, and well-educated participants. All participants were between the age of 18 and 25, in this age group the participants generally have better cognitive control compared to later in life, since cognitive control declines with aging (Lövdén et al., 2020; Stern, 2012). Perhaps as a result cognitive control could not be further improved in this population by the combination of rTMS and CCT. The stimulation of the DLPFC, and indirectly the networks involved in cognitive control, while functionally engaging these networks with CCT could potentially have an augmentation effect in populations that have suboptimal cognitive control. For instance patient populations or older healthy populations with age decline in cognitive control.

A potential explanation for the observed improvement on cognitive control could be that there is a practice effect on the Stroop task, where performing the same task twice within a short period of time improves the performance. However, a decrease in cognitive control was observed for some participants in the control condition. This could have many causes such as lack of interest or exhaustion which we cannot establish using the current experimental design.

Since our null findings of rTMS with CCT on mood and cognitive control did not match our expectations, the effects of negative mood induction on these aspects were established. An effect of the negative mood induction was found on all outcome measures with a large effect on mood and a medium effect on cognitive control. The observed decrease in positive mood affects and increase in negative mood affects could thus be due to effects of the negative mood induction. However, since the effects of the separate interventions are not established we can only the mood induction had an effect. The conclusion that the observed mood effects is only due to the mood induction cannot be drawn.

We further inquired whether the observed change in interference on cognitive control was correlated with a change in positive or negative mood affects. No correlation was established between the change in interference and the positive mood affect. However, a trend towards a significant correlation was found between interference on cognitive control and the negative mood affect. This was a negative correlation, the reduction in interference resulting in an improvement of cognitive control was correlated with a more negative mood. However, correlation is not the same as causation. A potential explanation for the borderline significant correlation could be the combination of the practice effect on the Stroop resulting in the increase in performance on cognitive control, and the established effects of the negative mood induction on the negative mood**.** But to determine the cause of this correlation the effects of the rTMS, CCT and negative mood induction by itself need to be established with more active control conditions.

Another observed effect was a larger range in response on both mood affects and cognitive control in the experimental condition than the control condition in order 1. For these observed effects on interference and the response range we cannot distinguish whether the effects are caused by a practice effect or facilitated by rTMS due to the lack of control conditions of the single interventions. This could be further investigated in subsequent studies with separate control conditions for the independent manipulations.

Previous research on augmentation effects with rTMS

Similar studies on possible augmentation effects of combining in rTMS with negative mood induction and different cognitive tasks were previously done in our lab (Bovy et al., 2019; Möbius et al., 2017). Möbius et al. examined whether HF-rTMS stimulation on the DLPFC could protect against a

negative mood shift after emotional provocation. A similarity in design is the timing of rTMS before the negative mood induction for a potential priming effect to enhance the effects of the negative mood induction. The rTMS induced a higher susceptibility in mood when a negative mood was induced immediately after rTMS. Therefore it was suggested that the stimulation protocol of rTMS in a young healthy population could heighten susceptibility to mood induction procedures in general both in the positive and negative direction thereby further augmenting experimental procedures (Möbius et al., 2017). Our research follows this suggestion to stimulate a healthy population and evaluate the effects on mood using negative mood induction but goes further in depth by evaluating the effects on cognitive control.

Another study combined HF-rTMS on the left DLPFC with cognitive training to investigate possible augmentation effects of the combination of rTMS with attentional bias modification (ABM) (Bovy et al., 2019). A similarity in design is the concept to combine rTMS with a cognitive task to research potential additive augmentation effects based on the state dependency of these networks. A difference in design is the form of cognitive training that was used to for the functional engagement of the involved neural networks. ABM was used to modulate cognitive control through the modulation of attentional bias while our design uses cognitive control training. Another difference in design is the timing of the cognitive task, the rTMS was performed before the ABM for a priming effect to facilitate the learning effects of the ABM. Our design aimed to stimulate the depression related networks with rTMS while simultaneously functionally engaging these networks using CCT. Finally, there was a difference in the timing of the negative mood induction, Bovy performed the mood induction before rTMS for a possible priming effect on the rTMS. Our mood induction was performed after the combination of rTMS with CCT based on the design by Möbius. The study found no augmentation effect of the combination of rTMS with ABM on attentional bias, attentional control, and mood, similar to our null findings on mood and cognition.

We further expand on both studies by using individual resting state-fMRI activity to determine the best stimulation target within the left DLPFC for each participant, based on the anticorrelation to the sgACC. Thereby indirectly stimulating the ACC in the most optimal way. Furthermore, resting-state fMRI-based neuronavigation is used to ensure precise placement of the coil and accurate stimulation of the personalised targets. Thereby improving on this indicated limitation of both studies.

Despite these methodological improvements, we found no augmentation effects of the combination of rTMS and CCT on mood and cognitive control. Our findings showed no evidence for the proposed theory that the stimulation protocol of rTMS could induce a heightened susceptibility to mood induction procedures in a young, healthy population (Möbius et al., 2017). Our null findings on mood were in line with the null findings on mood of rTMS combined with ABM and in line with

literature stating that a single session of HF-rTMS over the left DLPFC may not be sufficient to alter mood in healthy individuals (Bovy et al., 2019; Möbius et al., 2017)**.** However, our null findings on mood were not in line with the mood effect by Möbius. A potential explanation for the difference in findings could be the difference in negative mood induction procedures. Even though the previous research and this study all used clips from Sophie's choice for the negative mood induction there were notable differences in the procedures (Bovy et al., 2019; Möbius et al., 2017). The procedures differed not only in timing of the negative mood induction as indicated before but also in duration. The mood induction before the rTMS and ABM lasted longer (total of 20 minute) than in our design, while the mood induction by Möbius consisted of multiple parts. The mood induction itself and a booster session afterwards of two short clips. Furthermore, the mood decline as a result of rTMS only became apparent after the negative mood booster at the end, no mood effect was initially found after the first negative mood induction (Möbius et al., 2017). Perhaps a single mood induction is not enough to interact with the effects of rTMS to induce a detectable effect on mood.

Another notable difference is the difference in participant population. Our study used a healthy population to investigate mood effects based on Möbius et al. This limits both studies since healthy participants have different functional connectivity in the depression related networks opposed to depressed patients (Möbius et al., 2017). The neural effects of the stimulation and the response to the combination of rTMS with CCT could be different in a patient population. The research on rTMS with ABM was conducted in a subclinical sample (BDI 9 -25), indicated as minimal to mild depressive symptoms (Bovy et al., 2019). This population would bear closer resemblance in altered functional connectivity to a patient population. However, no augmentation effects of the combination of rTMS and ABM training were found regardless of the different sample.

Our lack of augmentation effects of rTMS with CCT on mood and cognitive control were in line with the null findings of the combination of rTMS with ABM on mood and attentional bias in cognitive control (Bovy et al., 2019). A potential indicated reason was that a single session of rTMS was believed to be insufficient to induce differences in subtle cognitive processes like attentional bias and control, and mood. Practice effects on attentional control in all groups were also found, supporting our proposed practice effect on the Stroop as explanation for the observed improvement of cognitive control. These results seems to support our findings but to confirm the proposed theories of single session effects of rTMS being insufficient and practice effects on cognitive control, separate control conditions are needed to establish the effect of each manipulation separately.

Study limitations and strengths

The study has several limitations. First, since this study was a pilot study our study population consisted of young, healthy participants and not a subclinical or patient population. A subclinical or patient population might respond differently to the intervention due to the presence of depression related altered activity and functional connectivity. In these populations the alterations in activity and functional connectivity would impair cognitive control thus allowing the establishment of the effects of CCT without reaching the currently proposed ceiling effect. Furthermore, since this was not a clinical population, the comfort of the participants was kept in mind to prevent dropouts. Some participants experienced the stimulation at 120% of the motor threshold as painful or uncomfortable, to prevent dropouts the stimulation was then performed at 110% or 100% of the motor threshold.

Another limitation was the difference in personalised targets. The creation of the individualised stimulation targets based on the resting state activity was dependent on how well the participant was able to relax during the resting state scan. If the participant was able to relax well this resulted in better resting state activity for the connectivity analysis. As a result the determination of the best personalised target was easier compared to a participant who was not able to relax properly. In that case it was harder to determine the best personalised target but it remained feasible. Despite this limitation this technique is also feasible and used in clinical populations (Cash et al., 2021; Fox et al., 2013). Finally, there were no sham conditions as active controls to evaluate the effects of each the interventions, rTMS, mood induction, and CCT separately on our results. Therefore we are unable to establish whether our findings are caused by the effects of a single intervention. The effects of the negative mood induction could also influence interference on cognitive control but we cannot establish this. And to perform the control task a baseline measure of cognitive control is needed, thus baseline measures on the Stroop and PANAS must be performed.

Nonetheless, the study is a methodological improvement on previous research by using resting state-fMRI based neuronavigation to improve the efficacy of rTMS by ensuring the stimulation is precisely located on our target and remains on our target during the session. Another improvement is the creation of personalised stimulation targets based on the individual resting state-fMRI activity. Thus allowing for the integration of interindividual differences in functional connectivity in the connectivity analysis instead of discarding the differences using a group analysis. This integration could contribute to the personalisation of rTMS and optimise the effects of the stimulation.

Future directions

Future research on augmentation effects should continue to implement resting state-fMRI based neuronavigation for the creation of personalised targets. However, the study design can be improved in a larger sample size. First, a cognitive task must be found that does interact with rTMS. Second, the effect of negative mood induction by itself must be established before including sham conditions of rTMS and the cognitive task. The separate effects of the different interventions can be established and used to further corroborate the cause the results of the combination of interventions. The study could be further optimised by using a different population either a subclinical population or an open pilot patient study, with depression related altered activity and functional connectivity. The participant may respond differently to the interventions. Furthermore, the effects of multiple rTMS sessions could be evaluated to verify the proposed theory of single session rTMS not being sufficient in a healthy population.

Conclusion

Overall, no effects of single session rTMS and CCT were found on mood and cognitive control in a healthy sample. A systematic effect of the negative mood induction was found potentially resulting in a decrease in positive mood affects and increase in negative mood affect but no effects of rTMS and CCT were found to negate these negative mood effects. We found no protective- or susceptibility inducing effects of our intervention on mood and cognitive control contrary to our predictions. Furthermore, no evidence was found for augmentation effects of the combination of rTMS with CCT even though resting state-fMRI based neuronavigation was used as methodological improvement on previous literature. However, the personalisation of rTMS with personalised targets and resting state-fMRI based neuronavigation could be valuable for clinical implementation.

References

Anderson, R. J., Hoy, K. E., Daskalakis, Z. J., & Fitzgerald, P. B. (2016). Repetitive transcranial magnetic stimulation for treatment resistant depression: Re-establishing connections. *Clin Neurophysiol*, *127*(11), 3394-3405. https://doi.org/10.1016/j.clinph.2016.08.015

Andersson J.L.R., J. M. a. S. S. M. (2007a). Non-linear optimisation. *FMRIB technical report TR07JA1*.

Andersson J.L.R., J. M. a. S. S. M. (2007b). Non-linear registration, aka Spatial normalisation. *FMRIB technical report TR07JA2*.

Berlim, M. T., Van den Eynde, F., & Daskalakis, Z. J. (2013a). High-frequency repetitive transcranial magnetic stimulation accelerates and enhances the clinical response to antidepressants in major depression: a meta-analysis of randomized, double-blind, and sham-controlled trials. *J Clin Psychiatry*, *74*(2), e122-129. https://doi.org/10.4088/JCP.12r07996

Berlim, M. T., Van den Eynde, F., & Daskalakis, Z. J. (2013b). A systematic review and meta-analysis on the efficacy and acceptability of bilateral repetitive transcranial magnetic stimulation (rTMS) for treating major depression. *Psychol Med*, *43*(11), 2245-2254. https://doi.org/10.1017/s0033291712002802

Berlim, M. T., van den Eynde, F., Tovar-Perdomo, S., & Daskalakis, Z. J. (2014). Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. *Psychol Med*, *44*(2), 225-239. https://doi.org/10.1017/s0033291713000512

Bovy, L., Möbius, M., Dresler, M., Fernández, G., Sanfey, A., Becker, E., & Tendolkar, I. (2019). Combining attentional bias modification with dorsolateral prefrontal rTMS does not attenuate maladaptive attentional processing. *Sci Rep*, *9*(1), 1168. https://doi.org/10.1038/s41598-018-37308-w

Brakowski, J., Spinelli, S., Dörig, N., Bosch, O. G., Manoliu, A., Holtforth, M. G., & Seifritz, E. (2017). Resting state brain network function in major depression - Depression symptomatology, antidepressant treatment effects, future research. *J Psychiatr Res*, *92*, 147-159. https://doi.org/10.1016/j.jpsychires.2017.04.007

Calkins, A. W., Deveney, C. M., Weitzman, M. L., Hearon, B. A., Siegle, G. J., & Otto, M. W. (2011). The effects of prior cognitive control task exposure on responses to emotional tasks in healthy participants. *Behav Cogn Psychother*, *39*(2), 205-220. https://doi.org/10.1017/s1352465810000652

Carpenter, L. L., Janicak, P. G., Aaronson, S. T., Boyadjis, T., Brock, D. G., Cook, I. A., Dunner, D. L., Lanocha, K., Solvason, H. B., & Demitrack, M. A. (2012). Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. *Depress Anxiety*, *29*(7), 587-596. https://doi.org/10.1002/da.21969

Cash, R. F. H., Cocchi, L., Lv, J., Fitzgerald, P. B., & Zalesky, A. (2021). Functional Magnetic Resonance Imaging-Guided Personalization of Transcranial Magnetic Stimulation Treatment for Depression. *JAMA Psychiatry*, *78*(3), 337-339. https://doi.org/10.1001/jamapsychiatry.2020.3794

Cash, R. F. H., Zalesky, A., Thomson, R. H., Tian, Y., Cocchi, L., & Fitzgerald, P. B. (2019). Subgenual Functional Connectivity Predicts Antidepressant Treatment Response to Transcranial Magnetic Stimulation: Independent Validation and Evaluation of Personalization. *Biol Psychiatry*, *86*(2), e5-e7. https://doi.org/10.1016/j.biopsych.2018.12.002

Corlier, J., Burnette, E., Wilson, A. C., Lou, J. J., Landeros, A., Minzenberg, M. J., & Leuchter, A. F. (2020). Effect of repetitive transcranial magnetic stimulation (rTMS) treatment of major depressive disorder (MDD) on cognitive control. *J Affect Disord*, *265*, 272-277. https://doi.org/10.1016/j.jad.2020.01.068

Craighead, W. E., & Dunlop, B. W. (2014). Combination psychotherapy and antidepressant medication treatment for depression: for whom, when, and how. *Annu Rev Psychol*, *65*, 267-300. https://doi.org/10.1146/annurev.psych.121208.131653

Diagnostic and Statistical Manual of Mental Disorders: DSM-V (2013). American Psychiatric Association.

Dixon, M. L. (2015). Cognitive control, emotional value, and the lateral prefrontal cortex. *Front Psychol*, *6*, 758. https://doi.org/10.3389/fpsyg.2015.00758

Eaton, W. W., Shao, H., Nestadt, G., Lee, H. B., Bienvenu, O. J., & Zandi, P. (2008). Population-based study of first onset and chronicity in major depressive disorder. *Arch Gen Psychiatry*, *65*(5), 513-520. https://doi.org/10.1001/archpsyc.65.5.513

Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*, *39*(2), 175-191. https://doi.org/10.3758/bf03193146

Fitzgerald, D. A., Arnold, J. F., Becker, E. S., Speckens, A. E., Rinck, M., Rijpkema, M., Fernández, G., & Tendolkar, I. (2011). How mood challenges emotional memory formation: an fMRI investigation. *Neuroimage*, *56*(3), 1783-1790. https://doi.org/10.1016/j.neuroimage.2011.02.061

Fitzgerald, P. B. (2021). Targeting repetitive transcranial magnetic stimulation in depression: do we really know what we are stimulating and how best to do it? *Brain Stimul*, *14*(3), 730-736. https://doi.org/10.1016/j.brs.2021.04.018

Fitzgerald, P. B., Brown, T. L., Marston, N. A., Daskalakis, Z. J., De Castella, A., & Kulkarni, J. (2003). Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry*, *60*(10), 1002-1008. https://doi.org/10.1001/archpsyc.60.9.1002

Fitzgerald, P. B., Hoy, K., McQueen, S., Herring, S., Segrave, R., Been, G., Kulkarni, J., & Daskalakis, Z. J. (2008). Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol*, *28*(1), 52-58. https://doi.org/10.1097/jcp.0b013e3181603f7c

Fitzgerald, P. B., Hoy, K., McQueen, S., Maller, J. J., Herring, S., Segrave, R., Bailey, M., Been, G., Kulkarni, J., & Daskalakis, Z. J. (2009). A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. *Neuropsychopharmacology*, *34*(5), 1255-1262. https://doi.org/10.1038/npp.2008.233

Fitzgerald, P. B., Oxley, T. J., Laird, A. R., Kulkarni, J., Egan, G. F., & Daskalakis, Z. J. (2006). An analysis of functional neuroimaging studies of dorsolateral prefrontal cortical activity in depression. *Psychiatry Res*, *148*(1), 33-45. https://doi.org/10.1016/j.pscychresns.2006.04.006

Fox, M. D., Liu, H., & Pascual-Leone, A. (2013). Identification of reproducible individualized targets for treatment of depression with TMS based on intrinsic connectivity. *Neuroimage*, *66*, 151-160. https://doi.org/10.1016/j.neuroimage.2012.10.082

George, M. S., Ketter, T. A., & Post, R. M. (1994). Prefrontal cortex dysfunction in clinical depression. *Depression*, *2*(2), 59-72. https://doi.org/https://doi.org/10.1002/depr.3050020202

Greenberg, P. E., Fournier, A. A., Sisitsky, T., Simes, M., Berman, R., Koenigsberg, S. H., & Kessler, R. C. (2021). The Economic Burden of Adults with Major Depressive Disorder in the United States (2010 and 2018). *Pharmacoeconomics*, *39*(6), 653-665. https://doi.org/10.1007/s40273-021-01019-4

Hallett, M. (2007). Transcranial magnetic stimulation: a primer. *Neuron*, *55*(2), 187-199. https://doi.org/10.1016/j.neuron.2007.06.026

Harrison, B. J., Pujol, J., Ortiz, H., Fornito, A., Pantelis, C., & Yücel, M. (2008). Modulation of brain resting-state networks by sad mood induction. *PLoS One*, *3*(3), e1794. https://doi.org/10.1371/journal.pone.0001794

Jaeggi, S. M., Buschkuehl, M., Etienne, A., Ozdoba, C., Perrig, W. J., & Nirkko, A. C. (2007). On how high performers keep cool brains in situations of cognitive overload. *Cogn Affect Behav Neurosci*, *7*(2), 75-89. https://doi.org/10.3758/cabn.7.2.75

Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. *Proc Natl Acad Sci U S A*, *105*(19), 6829-6833. https://doi.org/10.1073/pnas.0801268105

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*, *17*(2), 825-841. https://doi.org/10.1016/s1053-8119(02)91132-8

Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Med Image Anal*, *5*(2), 143-156. https://doi.org/10.1016/s1361-8415(01)00036-6

Jing, Y., Zhao, N., Deng, X. P., Feng, Z. J., Huang, G. F., Meng, M., Zang, Y. F., & Wang, J. (2020). Pregenual or subgenual anterior cingulate cortex as potential effective region for brain stimulation of depression. *Brain Behav*, *10*(4), e01591. https://doi.org/10.1002/brb3.1591

Kim, H., Chey, J., & Lee, S. (2017). Effects of multicomponent training of cognitive control on cognitive function and brain activation in older adults. *Neurosci Res*, *124*, 8-15. https://doi.org/10.1016/j.neures.2017.05.004

Layden, E. A. (2018). *N-Back for Matlab*. In Psychology, The University of Chicago. https://doi.org/10.12751/g-node.f87128

Lefaucheur, J. P. (2019). Transcranial magnetic stimulation. *Handb Clin Neurol*, *160*, 559-580. https://doi.org/10.1016/b978-0-444-64032-1.00037-0

Lövdén, M., Fratiglioni, L., Glymour, M. M., Lindenberger, U., & Tucker-Drob, E. M. (2020). Education and Cognitive Functioning Across the Life Span. *Psychol Sci Public Interest*, *21*(1), 6-41. https://doi.org/10.1177/1529100620920576

Luber, B., Stanford, A. D., Bulow, P., Nguyen, T., Rakitin, B. C., Habeck, C., Basner, R., Stern, Y., & Lisanby, S. H. (2008). Remediation of sleep-deprivation-induced working memory impairment with fMRI-guided transcranial magnetic stimulation. *Cereb Cortex*, *18*(9), 2077-2085. https://doi.org/10.1093/cercor/bhm231

Luo, X., Hu, Y., Wang, R., Zhang, M., Zhong, X., & Zhang, B. (2021). Individualized rTMS Treatment for Depression using an fMRI-based Targeting Method. *J Vis Exp*(174). https://doi.org/10.3791/62687

Menon, V. (2011). Large-scale brain networks and psychopathology: a unifying triple network model. *Trends Cogn Sci*, *15*(10), 483-506. https://doi.org/10.1016/j.tics.2011.08.003

Miller, E. K. (2000). The prefrontal cortex and cognitive control. *Nat Rev Neurosci*, *1*(1), 59-65. https://doi.org/10.1038/35036228

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annu Rev Neurosci*, *24*, 167-202. https://doi.org/10.1146/annurev.neuro.24.1.167

Möbius, M., Ferrari, G. R. A., van den Bergh, R., Becker, E. S., & Rinck, M. (2018). Eye-Tracking Based Attention Bias Modification (ET-ABM) Facilitates Disengagement from Negative Stimuli in Dysphoric Individuals. *Cognit Ther Res*, *42*(4), 408-420. https://doi.org/10.1007/s10608-018-9889-6

Möbius, M., Lacomblé, L., Meyer, T., Schutter, D., Gielkens, T., Becker, E. S., Tendolkar, I., & van Eijndhoven, P. (2017). Repetitive transcranial magnetic stimulation modulates the impact of a negative mood induction. *Soc Cogn Affect Neurosci*, *12*(4), 526-533. https://doi.org/10.1093/scan/nsw180

Mrazek, D. A., Hornberger, J. C., Altar, C. A., & Degtiar, I. (2014). A review of the clinical, economic, and societal burden of treatment-resistant depression: 1996-2013. *Psychiatr Serv*, *65*(8), 977-987. https://doi.org/10.1176/appi.ps.201300059

Mulders, P. C., van Eijndhoven, P. F., Schene, A. H., Beckmann, C. F., & Tendolkar, I. (2015). Resting-state functional connectivity in major depressive disorder: A review. *Neurosci Biobehav Rev*, *56*, 330-344. https://doi.org/10.1016/j.neubiorev.2015.07.014

Neacsiu, A. D., Luber, B. M., Davis, S. W., Bernhardt, E., Strauman, T. J., & Lisanby, S. H. (2018). On the Concurrent Use of Self-System Therapy and Functional Magnetic Resonance Imaging-Guided Transcranial Magnetic Stimulation as Treatment for Depression. *J ect*, *34*(4), 266-273. https://doi.org/10.1097/yct.0000000000000545

Ochsner, K. N., & Gross, J. J. (2005). The cognitive control of emotion. *Trends Cogn Sci*, *9*(5), 242-249. https://doi.org/10.1016/j.tics.2005.03.010

Otte, C., Gold, S. M., Penninx, B. W., Pariante, C. M., Etkin, A., Fava, M., Mohr, D. C., & Schatzberg, A. F. (2016). Major depressive disorder. *Nat Rev Dis Primers*, *2*, 16065. https://doi.org/10.1038/nrdp.2016.65

Owen, A. M., McMillan, K. M., Laird, A. R., & Bullmore, E. (2005). N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp*, *25*(1), 46-59. https://doi.org/10.1002/hbm.20131

Pan, F., Shen, Z., Jiao, J., Chen, J., Li, S., Lu, J., Duan, J., Wei, N., Shang, D., Hu, S., Xu, Y., & Huang, M. (2020). Neuronavigation-Guided rTMS for the Treatment of Depressive Patients With Suicidal Ideation: A Double-Blind, Randomized, Sham-Controlled Trial. *Clin Pharmacol Ther*, *108*(4), 826-832. https://doi.org/10.1002/cpt.1858

Pulopulos, M., Allaert, J., Vanderhasselt, M. A., Sanchez-Lopez, A., De Witte, S., Baeken, C., & De Raedt, R. (2020). Effects of HF-rTMS over the left and right DLPFC on proactive and reactive cognitive control. *Soc Cogn Affect Neurosci*. https://doi.org/10.1093/scan/nsaa082

Reid, P. D., Shajahan, P. M., Glabus, M. F., & Ebmeier, K. P. (1998). Transcranial magnetic stimulation in depression. *Br J Psychiatry*, *173*, 449-452. https://doi.org/10.1192/bjp.173.6.449

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*, *120*(12), 2008-2039. https://doi.org/10.1016/j.clinph.2009.08.016

Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Stewart, J. W., Warden, D., Niederehe, G., Thase, M. E., Lavori, P. W., Lebowitz, B. D., McGrath, P. J., Rosenbaum, J. F., Sackeim, H. A., Kupfer, D. J., Luther, J., & Fava, M. (2006). Acute and longer-term outcomes in depressed

outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry*, *163*(11), 1905-1917. https://doi.org/10.1176/ajp.2006.163.11.1905

Rush, A. J., Warden, D., Wisniewski, S. R., Fava, M., Trivedi, M. H., Gaynes, B. N., & Nierenberg, A. A. (2009). STAR*D: revising conventional wisdom. *CNS Drugs*, *23*(8), 627-647. https://doi.org/10.2165/00023210-200923080-00001

Sathappan, A. V., Luber, B. M., & Lisanby, S. H. (2019). The Dynamic Duo: Combining noninvasive brain stimulation with cognitive interventions. *Prog Neuropsychopharmacol Biol Psychiatry*, *89*, 347-360. https://doi.org/10.1016/j.pnpbp.2018.10.006

Schönfeldt-Lecuona, C., Lefaucheur, J. P., Cardenas-Morales, L., Wolf, R. C., Kammer, T., & Herwig, U. (2010). The value of neuronavigated rTMS for the treatment of depression. *Neurophysiol Clin*, *40*(1), 37-43. https://doi.org/10.1016/j.neucli.2009.06.004

Schweizer, S., Grahn, J., Hampshire, A., Mobbs, D., & Dalgleish, T. (2013). Training the emotional brain: improving affective control through emotional working memory training. *J Neurosci*, *33*(12), 5301-5311. https://doi.org/10.1523/jneurosci.2593-12.2013

Siegle, G. J., Ghinassi, F., & Thase, M. E. (2007). Neurobehavioral therapies in the 21st century: Summary of an emerging field and an extended example of cognitive control training for depression. *Cognitive therapy and research*, *31*(2), 235-262.

Siegle, G. J., Price, R. B., Jones, N. P., Ghinassi, F., Painter, T., & Thase, M. E. (2014). You gotta work at it: Pupillary indices of task focus are prognostic for response to a neurocognitive intervention for rumination in depression. *Clinical Psychological Science*, *2*(4), 455-471.

Silvanto, J., & Pascual-Leone, A. (2008). State-dependency of transcranial magnetic stimulation. *Brain Topogr*, *21*(1), 1-10. https://doi.org/10.1007/s10548-008-0067-0

Sivek, R. (2016). *Stroop test for Matlab*. In https://github.com/nanowizard/stroopeffect

Smith, S. M. (2002). Fast robust automated brain extraction. *Hum Brain Mapp*, *17*(3), 143-155. https://doi.org/10.1002/hbm.10062

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol*, *11*(11), 1006-1012. https://doi.org/10.1016/s1474-4422(12)70191-6

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. . *Journal of Experimental Psychology*, *18(6)*, 643–662. https://doi.org/10.1037/h0054651

Tik, M., Hoffmann, A., Sladky, R., Tomova, L., Hummer, A., Navarro de Lara, L., Bukowski, H., Pripfl, J., Biswal, B., Lamm, C., & Windischberger, C. (2017). Towards understanding rTMS mechanism of action: Stimulation of the DLPFC causes network-specific increase in functional connectivity. *Neuroimage*, *162*, 289-296. https://doi.org/10.1016/j.neuroimage.2017.09.022

Vanderhasselt, M. A., De Raedt, R., & Baeken, C. (2009). Dorsolateral prefrontal cortex and Stroop performance: tackling the lateralization. *Psychon Bull Rev*, *16*(3), 609-612. https://doi.org/10.3758/pbr.16.3.609

Vedeniapin, A., Cheng, L., & George, M. S. (2010). Feasibility of simultaneous cognitive behavioral therapy and left prefrontal rTMS for treatment resistant depression. *Brain Stimul*, *3*(4), 207-210. https://doi.org/10.1016/j.brs.2010.03.005

Vissers, C. T., Virgillito, D., Fitzgerald, D. A., Speckens, A. E., Tendolkar, I., van Oostrom, I., & Chwilla, D. J. (2010). The influence of mood on the processing of syntactic anomalies: evidence from P600. *Neuropsychologia*, *48*(12), 3521-3531. https://doi.org/10.1016/j.neuropsychologia.2010.08.001

Watson, D., Clark, L. A., & Tellegen, A. (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol*, *54*(6), 1063-1070. https://doi.org/10.1037//0022-3514.54.6.1063

Weigand, A., Horn, A., Caballero, R., Cooke, D., Stern, A. P., Taylor, S. F., Press, D., Pascual-Leone, A., & Fox, M. D. (2018). Prospective Validation That Subgenual Connectivity Predicts Antidepressant Efficacy of Transcranial Magnetic Stimulation Sites. *Biol Psychiatry*, *84*(1), 28-37. https://doi.org/10.1016/j.biopsych.2017.10.028

WHO. (2021). *Depression*. Retrieved 30-03 from https://www.who.int/news-room/fact-sheets/detail/depression

Supplementary material

Supplement 1: Task details

Cognitive Control Training. For the experimental condition a progressive dual n-back task as described by (Jaeggi et al., 2007; Jaeggi et al., 2008) was used as cognitive control training. Visual spatial and auditory stimuli were presented sequentially to the participant, the participant had to remember the location of stimuli and auditory sounds. The participant was supposed to respond when either the location or sound is the same as n-turns back, starting at n=2. If the participant scored ≥0.9 the level of the dual n-back was increased, to for instance n=3. If the score of the participant was ≤0.9 the n-back level was lowered. One block consisted of 20+n trials, each trial had a duration of 3000 ms. The visual spatial stimuli consisted of blue squares projected on a computer screen at 9 different location. The auditory stimuli consisted of eight consonants presented through a speaker. For experimental use in MATLAB the dual n-back task by Layden was used (Layden, 2018). In the control condition a single n-back task was used. In this version the participants were only presented visual spatial stimuli and the n-back level was set at 1. This task was not progressive, the participant received no score at the end of the block, and the level remained at 1. This task was presented in MATLAB using an adapted version of Layden's script (Layden, 2018).

Supplement 2: Visual representation of dual 2-back

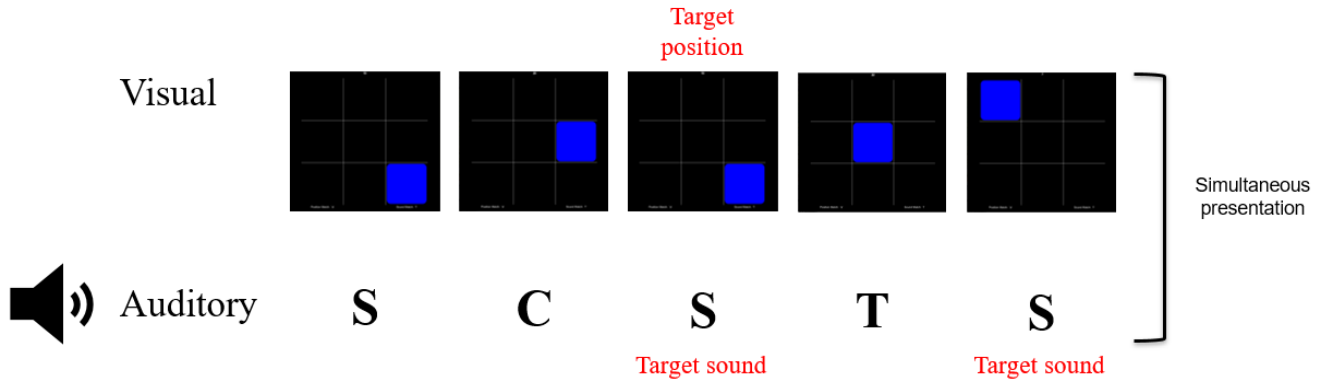

Figure 4. Visual representation of CCT training using a progressive dual 2-back task.

Supplement 3: Adapted Stroop task

Figure 5. Experimental presentation of the adapted Stroop task in MATLAB. (A) Congruent Stroop. (B) Incongruent Stroop

Supplement 4: Interference Score STROOP

This interference score was calculated using the following formula;

Interference score = total score + ((2 mean reaction time per word) * number of uncorrected errors)*

Total score = overall time for reading

Mean time per word = overall time for reading divided by the number of times

Number of uncorrected errors = the number of error not spontaneously corrected.

Supplement 5: Sample size calculation

In this study a total of 20 participants were included. This number is based on a power calculation based on previous studies on similar subjects. A study performed by our group investigated the effect of rTMS on NMI and found an effect size of d = 0.81 (Mobius et al., 2017). When doing a sample size calculation using G*power (Faul et al., 2007), this resulted in a sample size estimation of N = 15. See table 4 for the input and output parameters. Another study assessed the effect of CCT on NMI, and reported an effect size of d = 0.89 (Calkins et al., 2011). Using this effect size, the sample size calculation resulted in N = 12 (input and output parameters can be found in table 4).

We need to include at least 15 participants in the experiment. To compensate for drop-outs and for a potential overestimation of the effect, we will aim to include 20 participants in the experiment.

Table 4. Summary of input and output parameters of sample size calculation using G*power.

		Effect size *d* = 0.81	**Effect size *d* = 0.89**
Input parameters	Test	ANOVA, repeated measures, within factors	ANOVA, repeated measures, within factors
	Effect size *f*	0.405 (Cohen's *d* = 0.81, converted to *f* = 0.405)	0.445 (Cohen's *d* = 0.89, converted to *f* = 0.445)
	Alpha error probability	0.05	0.05
	Power	0.80	0.80
	Number of groups	1	1
	Number of measurements	2	2
	Correlation among repeated measures	0.5	0.5
	Nonspheriticy correction	1	1
Output parameters	Noncentrality parameter	9.84	9.51
	Critical F	4.60	4.84
	Numerator df	1	1
	Denominator df	14	11
	Total sample size	15	12
	Actual power	0.83	0.80

Supplement 6: Mixed ANOVA results on outcome parameters (outlier excluded)

Table 5. Mixed ANOVA results outlier excluded

	Within subject	Between subject
PANAS positive	0.464	0.862
PANAS negative	0.832	0.001*
Stroop interference	0.944	0.023*

* indicates a statistically significant result.

Supplement 7: Paired t-test results effect negative mood induction on outcome parameters

Table 6. Effect negative mood induction on outcome parameters

	Pre NMI scores	*Post NMI scores*	*p-value*	*r (effect size)*
PANAS positive	31.29 ± 6.093	25.41 ± 7.262	<001*	.867
PANAS negative	13.03 ± 2.801	16.97 ± 5.126	<001*	.625
Stroop interference	70.697 ± 10.320	67.911 ± 10.234	.031*	.376

NMI = negative mood induction. Values represent mean ± SD. * indicates a statistically significant result.