Influencing Social-Emotional Actions: The Effect of Theta-Gamma Coupled tACS on Social-Emotional Actions and aPFC-M1 Functional Connectivity

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In our everyday life we are used to regulating our social-emotional behaviour, for example when you want to approach a fellow researcher at a conference for a possible collaboration. An important brain region involved in the implementation of social-emotional control is the anterior prefrontal cortex (aPFC). Previous research found that control over social-emotional behaviour is implemented by theta-band oscillations in the aPFC that are phase-locked to the power increase of gamma-band oscillations in the motor cortex. In this project we studied the effects of non-invasive brain stimulation on social-emotional behaviour using transcranial alternating current stimulation (tACS). We aimed to investigate (1) whether we can influence social-emotional actions by applying different types of theta-gamma coupled tACS and (2) how the functional connectivity patterns of the brain change as a consequence of the different stimulation conditions. In our tACS/functional magnetic resonance imaging (fMRI) study, 44 healthy participants performed the approach-avoidance task while receiving tACS stimulation (in-phase, anti-phase, or sham) in the magnetic resonance (MR) scanner. During the task, the participant used a joystick to either approach happy faces and avoid angry faces (affect-congruent condition) or avoid happy faces and approach angry faces (affect-incongruent condition). Error rates and reaction times were measured during the task, together with ongoing brain activity. We found reduced congruency effects for error rates but not for reaction times for in-phase stimulation as compared to anti-phase stimulation. Moreover, a stronger functional connectivity was found between aPFC (or lateral frontal pole) and primary motor cortex (M1) for in-phase compared to anti-phase stimulation. These findings show improvement in social-emotional control when theta-band oscillations of the aPFC are phase-coupled to the power increases of the gamma-band oscillations of the M1. This research has high clinical relevance as the findings suggest that theta-gamma coupled tACS could ultimately be used to develop possible new treatments for social, emotional, and behavioural disorders, such as social anxiety.

Keywords: social-emotional actions, control, anterior prefrontal cortex, lateral frontal pole, tACS, MRI

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Control over social-emotional behaviour plays an important role in our daily lives as is illustrated by our social interactions. Imagine a situation in which you are wandering around a conference and want to approach an interesting researcher to talk about their project or a possible collaboration. You probably have to exert some cognitive control to overcome your automatic "fear" of talking to this person, after which you approach them in order to achieve your goal. For some people this might come naturally. Others, for example, people who are more socially anxious, experience difficulties in overriding their automatic emotional responses in order to approach a person in this situation. Research has found that cortical oscillatory mechanisms support the control of human social–emotional actions through the coupling of slow theta- and fast gamma-band oscillations (Bramson, Jensen, Toni, & Roelofs, 2018). The most anterior section of the frontal cortex (aPFC) plays an important role in regulating social-emotional behaviour by orchestrating this theta-gamma band coupling. While research has been done on the role of the aPFC in overcoming automatic action tendencies and the neural mechanisms behind social-emotional control. However, limited research has been done on whether we can influence the oscillatory mechanisms underlying social-emotional control. Communication between neural networks and brain regions is influenced by coherence in oscillations between sender and receiver networks (Buzsáki & Wang, 2012; Womelsdorf et al., 2007). This type of neuronal coherence can also be observed between frequency bands and is known as cross-frequency coupling (Goodman et al., 2018; Varela, Lachaux, Rodriguez, & Martinerie, 2001). Previous research has found that the cross-frequency coupling between the phase of slow theta-band oscillations (4 – 8 Hz) and the amplitude of high gamma-band oscillations (30 – 100 Hz) underlies cognitive processes such as working memory (Engel, Fries, & Singer, 2001) and cognitive control (Cavanagh & Frank, 2014). This phenomenon is called theta-gamma coupling, which means that high-frequency gamma oscillations are modulated by low-frequency theta oscillations (Lisman & Jensen, 2013).

How does the function of theta- and gamma-band oscillations relate to theta-gamma coupling? Animal research has shown that theta oscillations play an important role in the communication between largely separated neural networks and that this is organized by a high level of coherence (Lisman & Jensen, 2013). Moreover, human research shows that frontal theta-band oscillations (4 – 8 Hz) are involved in control over motivational behaviour (Cavanagh & Frank, 2014; Cooper et al., 2015) while the synchronization of gamma-band oscillations (30 – 100 Hz) in the motor system is related to action preparation and movement selection (Donner, Siegel, Fries, & Engel, 2009; Schoffelen, Poort, Oostenveld, & Fries, 2011). These theta- and gamma-band oscillations are coupled during information encoding between different brain regions and suggest that complex cognitive functions, such as cognitive control, can be influenced by a mechanism based on inter-regional phase encoding (Voytek et al., 2015).

Social-emotional control defines our ability to override automatic action tendencies in order to control approach and avoidance behaviour. The lateral anterior prefrontal cortex (aPFC)—also known as lateral frontal pole (FPl; Neubert et al., 2014)—is involved in regulating social-emotional control implemented by theta-gamma band coupled oscillations (Bramson et al., 2019; Bramson et al., 2018). Strong inhibition of this region leads to an impairment in control over social-emotional actions (Volman, Roelofs, Koch, Verhagen, & Toni, 2011). The aPFC controls these social-emotional behaviours by upregulating regions that are involved in rule selection, such as the parietal cortex and premotor area, and downregulating regions involved in automatic emotion evaluation, such as the amygdala (Volman et al., 2011; 2013). Moreover, the aPFC shares strong anatomical and functional connections to the limbic system (Tamnes et al., 2009; Tyborowska, Volman, Smeekens, Toni, & Roelofs, 2016). Other regions that share functional connectivity with the aPFC, even though not anatomically linked, are the posterior parietal cortex (Neubert, Mars, Thomas, Sallet, & Rushworth, 2014), primary motor cortex (M1) (Bramson et al., 2018), and thalamus/pulvinar (Tyborowska et al., 2016). Linking this to theta-gamma coupling: theta-band oscillations in the prefrontal cortex and gamma-band oscillations in the primary motor system may be coupled via a mechanism in which aPFC neurons phase lock their spiking and gamma-band firing to theta-band rhythms (Ardid et al., 2015; Voytek et al., 2015). The theta-band rhythms create overlapping periods of excitability across the cerebral network involved in social-emotional regulation (Colgin, 2013; Lisman & Jensen, 2013), especially in the aPFC-M1 network. Therefore, the aPFC and the aPFC-M1 network probably play a crucial role in the control over social-emotional actions.

Previous research has found that transcranial alternating current stimulation (tACS) can externally influence phase-amplitude coupling of neural oscillations underlying complex cognitive processes. tACS is a non-invasive neuro-stimulation technique that uses a sinusoidal electrical current at a chosen frequency to directly interact with cortical rhythms (Antal & Paulus, 2013; Herrmann, Rach, Neuling, & Strüber, 2013). Adaptation of underlying brain processes can only occur when a person is already engaged in specific cognitive processes, such as memory retrieval or cognitive control, to synchronise the spike timing of neurons. As a consequence, tACS based on theta-gamma band coupled oscillations enhances communication between distant areas and consequently improves spatial working memory (Alekseichuk, Turi, de Lara, Antal, & Paulus, 2016) and value-based decision making (Polanía, Moisa, Opitz, Grueschow, & Ruff, 2015). Moreover, this technique can be used to revive working memory by synchronizing these rhythmic brain circuits (Reinhart & Nguyen, 2019). These findings show that theta-gamma band coupled tACS is able to improve cognitive processes and could possibly lead to long-term effects on cognition.

However, the possibilities of externally influencing existing neural rhythms underlying social-emotional control have not yet been investigated. Given that theta-gamma band coupling between the prefrontal cortex and primary motor area play an important role in regulating social-emotional behaviour, we think that theta-gamma coupled tACS can also be applied to influence the theta-gamma band coupled oscillatory mechanisms underlying this type of control. Non-invasive stimulation could possibly influence these mechanisms by synchronising the naturally occurring theta-gamma oscillations in these regions during social-emotional control.

In this study, we investigate whether we can improve social-emotional actions using theta-gamma band coupled tACS. Our first interest is the effect of theta-gamma coupled tACS stimulation on the control over social-emotional actions. This stimulation either synchronises (in-phase) or desynchronises (anti-phase) existing theta- and gamma-oscillations of the brain. We used the approach-avoidance task (AAT) in order to measure social-emotional control (Heuer, Rinck, & Becker, 2007). In the AAT, pictures of emotional faces are presented on a screen and the subject is told to either approach or avoid these faces by moving a joystick. Normally, people show the automatic response tendency to approach happy and avoid angry faces (affect-congruent) and have to exert control to override these automatic tendencies in order to approach angry and avoid happy faces (affect-incongruent). The AAT has extensively been proven to be a reliable task to investigate social emotional control in both healthy as well as clinical populations (Bramson et al., 2018; Roelofs, Elzinga, & Rotteveel, 2005; Roelofs, Minelli, Mars, Van Peer, & Toni, 2008; Volman et al., 2011; Volman et al., 2013). We expect that in-phase stimulation would lead to improved communication between the aPFC and primary motor areas while anti-phase stimulation would disrupt this communication. Therefore, we hypothesise that performance on the AAT will improve, reflected in reduced congruency effects, when theta-gamma coupled tACS is applied during in-phase stimulation as compared to anti-phase and sham (control) stimulation.

Secondly, we are interested in the functional connectivity change when theta-gamma coupled tACS is applied to the aPFC and primary motor cortex (M1). One of the advantages of tACS is that you can use the technique in the magnetic resonance imaging (MRI) scanner, which allows you to look at haemodynamic responses and inter-regional functional connectivity while externally influencing underlying brain processes. We expect to find a stronger functional connectivity between aPFC and M1 during in-phase theta-gamma coupled stimulation as compared to anti-phase or sham stimulation. If our hypotheses prove to be correct, then this provides causal evidence for the contribution of theta-gamma coupling during social-emotional control. Moreover, the use of tACS in adapting social-emotional control could be highly relevant for clinical practice. Theta-gamma coupled tACS could provide possible treatments for people who have difficulties in controlling their automatic emotional action tendencies, for example, patients with social anxiety (Radke, Roelofs, & De Bruijn, 2013). The technique could be used as an addition to extinction therapy, where patients are exposed repeatedly to stressful cues and situations, thereby improving the effectiveness of the therapy and increasing the speed of recovery.

Method

Participants

Forty-four male subjects participated in the study after providing written informed consent for MR and transcranial current stimulation (tCS) according to the guidelines of the local ethics committee. All participants were right-handed, had corrected-to-normal vision and had no history of neurological or psychiatric illness. They received payment or course credits for their participation. Three participants were excluded due to technical difficulties. The participants took part in three sessions: one magnetic resonance spectroscopy (MRS) session (not further discussed in this manuscript) and two stimulation sessions (in which the subject performed the AAT).

Experimental task and procedure

The approach-avoidance task (AAT) was used as a measure to investigate social-emotional control in this study (Fig. 1) as used in several previous studies (Bramson et al., 2018; Volman et al., 2011). During the AAT, the participants were visually presented with happy and angry faces. The participants received written task instructions on the screen before each block. They either had to approach happy faces and avoid angry faces (affect-congruent) or avoid happy faces and approach angry faces (affect-incongruent). Participants had to respond to the congruent and incongruent conditions by either pulling the MRI-compatible joystick towards themselves (approach action) or pushing it away from themselves (avoidance action). The task rules changed each block. At the start of each trial a white fixation cross was presented on the screen for 1000 ms. After this, a face appeared on the screen for 100 ms and the participant had to respond by moving the joystick within 2000 ms after presentation of the stimulus. Responses were valid if they reached a 30% tilt of the joystick and if the participant responded within 2000 ms after the presentation of the stimulus. After responding, the participants had to bring back the joystick to the centre position. A warning message on the screen appeared if they did not bring the joystick back to the centre position or when they responded too late/missed a response. The inter-trial interval (ITI) was 2000 to 4000 ms. Reaction times (in ms) and error rates (percentage of correct trials) were measured. The participants performed the task in the MR scanner during two separate sessions. During the first session they did a practice run before the real task to get familiar with the task (this was left out during the second session). Each session consisted of 24 blocks with 12 trials. The block type of each first block was counterbalanced for each participant. The stimulation condition alternated at each block so that there was never a direct repetition of the same stimulation type in a row and the experiment included equal numbers of each block type (eight blocks per stimulation condition). The entire experiment included the total number of 576 trials (12 trials x 24 blocks x 2 sessions).

tACS procedure and conditions

Simultaneously with performing the AAT in the scanner, the participant received theta-band stimulation (6 Hz) over the aPFC and gamma-band stimulation (75 Hz) over the M1. An electrical current of 1 mA peak-to-peak was used during stimulation. The alternating current stimulation was administered using one transcranial electrical current stimulator for each site. Normally, tACS is applied by means of two single electrode patches that direct the electrical current between electrodes (Fig. 1). However, applying tACS to frontal areas in the classic montage could cause neurosensory effects (such as phosphenes), and does not allow for stimulation with two different frequencies on two different cortical locations, and thus cannot be used for localised theta-gamma band coupled stimulation (Bergmann, Karabanov, Hartwigsen, Thielscher, & Siebner, 2016).

Therefore, we used two sets of ring electrodes that consisted of a smaller inner circle and a larger outside ring, or a centre-ring montage. Each of the sets consisted of a small, circular, inner electrode (diameter 2 cm) and large, outer ring electrode (diameter 13 cm). According to Bergmann et al. (2016), this centre-ring montage set-up allowed for an effective focal stimulation of the area of interest and simultaneously reduced neurosensory side effects (such as phosphenes). For each block, the stimulation was either in-phase, anti-phase or sham (Fig. 2). For the in-phase condition, the power increases of the gamma-band oscillations

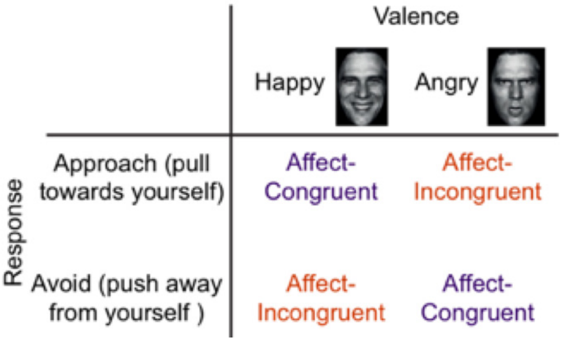

Figure 1. Schematic representation of the approach-avoidance task. In each block participants were presented with either affect-congruent conditions (approach-happy and avoid-angry faces) or affect-incongruent conditions (avoid-happy and approach-angry). Participants were instructed to respond accordingly by either pulling the joystick towards themselves or pushing it away from themselves. Reaction times and error rates were measured.

were phase-locked to the peaks of the theta-band oscillations. For the anti-phase condition, the power increases of the gamma-band oscillations were phase-locked to the troughs of the theta-band stimulation. These stimulation patterns were chosen to reflect the findings on increased theta-band power in aPFC and gamma-band power in premotor areas during control in the research of Bramson et al. (2018). For the sham condition, the stimulation was initiated in the first 10 seconds and then cancelled. Participants reported feeling no physical difference between the stimulation conditions. The stimulation blocks were randomly alternated.

Experimental procedure

The participants performed the approach-avoidance task (AAT) in the MR scanner while simultaneously receiving theta-gamma band tACS. Preparation included subject registration, preparation of the scalp sites and the application of the tACS electrodes. First, the Localite transcranial magnetic stimulation (TMS) Navigator was used for subject registration. Registration was done using a T1-weighted image of the subject that was acquired during a previous session and masks of the lateral frontal pole (FPl) and M1 that were specified for each individual subject. The FPl mask was obtained from Neubert et al. (2014) [MNI coordinates: 31 90 37] and the M1 mask from the MEG study by Bramson et al. (2018) [MNI coordinates: -28 -32 64]. We marked the target locations FPl and M1 on the scalp to indicate where the electrodes needed to be attached. Since all participants were right-handed and moved the joystick with their dominant hand, we used the M1 target location on the left hemisphere (contralateral to the right hand). Consequently, we stimulated the FPl on the right hemisphere due to the size of the electrodes and to prevent interference of the two electrode pairs. Regions under the electrodes were first thoroughly prepared with Nuprep skin preparation gel after which two sets of ring electrodes were attached to the scalp of the subject using conductive paste (Ten20, Weaver and Co., USA) to maximize contact with the scalp. The electrical impedance of the electrodes was measured after application to ensure that the impedance was lower than 10 kΩ.

The participants were instructed about the AAT and the stimulation was tested outside the scanner. The tACS electrodes were connected to the stimulation box when the participant was lying in the scanner. The participant performed the AAT while a multi-band six sequence (MB6) was used to obtain functional images during the task. When the participant finished the task, a MB6 inverse sequence was obtained. Saliva samples were collected before and after the scan to obtain current testosterone and cortisol levels. This was done to either control for or explain interpersonal variabilities in testosterone and cortisol levels on the participant's performance. A practice trial was included during the second session but not during the third session. After the third session, the participant filled in the State Trait Anxiety Inventory (STAI) questionnaire to measure anxiety in adults. The STAI questionnaire was used to look at interpersonal variabilities in trait anxiety symptoms, which could possibly influence the results.

Materials and apparatus

Structural and functional MR data was acquired

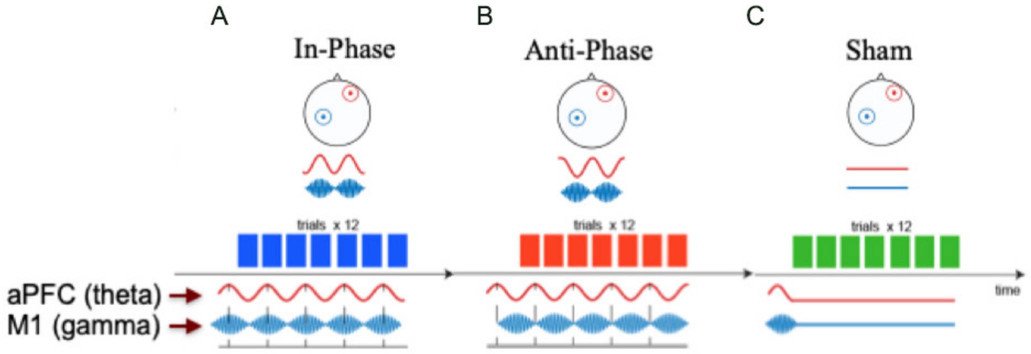

Figure 2. Theta-gamma band stimulation is applied to the primary motor cortex (blue circle) and anterior prefrontal cortex (red circle). A. In-phase stimulation in which the peaks of the slow theta (red) are phase locked to the peaks of the fast gamma (blue) oscillations (theta-gamma band coupling). B. Anti-phase condition in which peaks of the gamma waves are phase-amplitude locked to the troughs of the theta waves (no theta-gamma band coupling). C. Sham condition for which stimulation was only applied during the first 10 seconds and then cancelled.

on the institute 3 T MAGNETOM MRI scanner (Prisma and PrismaFit) (Siemens AG, Healthcare Sector, Erlangen, Germany) with a product 64-channel coil. The stimuli were projected to a screen located at the back of the scanner through an EIKI LC-XL100 beamer (resolution = 1024 x 768, refresh rate = 60 Hz). A mirror attached to the head coil was used to see the screen. The acquisition of functional scans was performed with a MB6 sequence (TR = 1000 ms, TE = 34 ms, flip angle = 60º, 104 x 104 x 68 FOV and 2 x 2 x 2 mm isotropic resolution). To correct for EPI artefacts, an inverse MB6 sequence was performed after the participant completed the main task (TR = 1000 ms, TE = 34 ms, flip angle = 60º, 104 x 104 x 68 FOV and 2 x 2 x 2 mm isotropic resolution). Structural T1 images were acquired in the sagittal orientation using a magnetisation prepared rapid gradient echo (MPRAGE) sequence (TR = 2300 ms, TI = 1100 ms, TE = 3 ms, flip angle = 8º). Parallel imaging (iPAT = 2) was used to accelerate the acquisition resulting in an acquisition time of 5 min and 21 sec.

Behavioural analysis

Reaction times (in ms) and error rates (percentage of correct trials) were used for the analysis of the behavioural data. Reaction times are defined as the time between stimulus presentation and displacement of the joystick. A displacement larger than 30% away from the centre in the sagittal plane was taken as a response. Trials with extremely short reaction times were removed (<150 ms). We also excluded trials for which the reaction times exceeded a threshold of 3 standard deviations above the mean reaction time of the subject per task condition (congruent and incongruent) separately. Reaction time analysis was only performed on correct responses.

Blocks with error rates above chance level were removed (>50% incorrect). Mean reaction times and error rates were calculated for each participant. Factors included stimulation condition (in-phase, anti-phase, sham), and congruency (approach-happy/ avoid-angry, avoid-happy/ approach-angry). We expected improved performance in participants on the AAT in the in-phase condition as compared to the anti-phase and sham condition. Therefore, we expected reduced congruency effects in error rates for the in-phase condition as compared to the anti-phase and sham condition. Previous research by Volman et al. (2011) only found increased congruency effects in error rate (or worse performance on the AAT) after inhibition of aPFC and no effects on reaction times. Therefore, we expected to find no differences in congruency effects for reaction time between stimulation conditions.

fMRI analyses: Pre-processing steps

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). The brain extraction tool (BET) of FSL was used in order to remove the neck and skull from the imaging data (Smith, 2002) and registration was performed using FNIRT and FLIRT (Andersson, Jenkinson, & Smith, 2007; Jenkinson, Bannister, Brady, & Smith, 2002). Pre-processing steps included motion correction (MCFLIRT), spatial filtering (spatial smoothing with 5mm FWHM Gaussian kernel) and global intensity normalization (Woolrich, Ripley, Brady, & Smith, 2001). The FSL topup tool was used to estimate and correct susceptibility induced distortions caused by distortions in opposite directions of the reversed phase-encoding sequences (Andersson, Skare, & Ashburner, 2003; Smith et al., 2004). Independent component analysis (ICA) in MELODIC was used to manually remove the components of the imaging data that do not reflect task effects, such as movement and cardiovascular responses (Beckmann & Smith, 2004).

fMRI analyses: Effective connectivity analysis (PPI)

The aim of the analysis was to investigate the effects of the different stimulation types on the functional connectivity between the FPl and the M1 during social-emotional actions. For this purpose, we used psychophysiological interactions (PPI) analysis. PPI analysis measures functional connectivity or, in other words, the statistical dependence between activity in between brain areas (O'Reilly, Woolrich, Behrens, Smith, & Johansen-Berg, 2012). This analysis investigates task-specific changes in the relationship between activity in different brain areas using fMRI data, and identifies voxels in which activity is more related to activity in a seed region of interest in a given psychological context (Friston et al., 1997; O'Reilly et al., 2012). More specifically, we tested for significant differences between the contrasts of parameter estimates (COPE) of FPl activity over M1 activity during the affect-incongruent versus the affect-congruent conditions of the AAT.

For this purpose, we created masks within the FPl as a seed region and a mask within M1 as volume of interest (VOI). The FPl, previously registered in the study of Neubert et al. (2014), was the targeted area during the stimulation and is involved in human social-emotional control. We created separate masks for the FPl of the right hemisphere (rFPI, stimulation site: direct stimulation) and left hemisphere (lFPl, (contralateral to the stimulation site: no direct stimulation) (Fig. 3). First, we selected a voxel within the rFPl that showed a maximum intensity for the contrast between affect-congruent versus affect-incongruent conditions (incongruent – congruent) and created a 5 mm mask surrounding this peak voxel (MNI coordinates rFPl: 33 87 29, radius = 5 mm, intensity = 3.64). Afterwards, we extracted the fMRI time series from the mask (representative time course of activity) in order to create the physiological regressor. The mask and physiological regressor of the lFPl were created by the same procedure (MNI coordinates lFPl: 55 89 29, radius = 5 mm, z-value = 3.48). For the volume of interest, we created a mask surrounding the peak voxel in M1 of the left hemisphere (MNI coordinates M1: -28 -32 64, z-value = 3.70).

FPl-M1 functional connectivity for congruency effects

PPI analysis was run in FEAT according to the guidelines of FSL and the research of O'Reilly (O'Reilly et al., 2012; Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004; Woolrich et al., 2001), for the FPl of the right hemisphere and left hemisphere separately. For the first level analysis, we looked in voxels within the FPl with increased functional connectivity to the M1 during the in-phase, anti-phase and sham stimulation condition.

Explanatory variables included the congruency effects of the stimulation conditions convolved with a haemodynamic response function (HRF) (3 psychological/task regressors: in-phase, anti-phase and sham stimulation)[1] and the time course of the right FPl seed region (physiological regressor). In addition, regressors were included for the co-variates of no interest, which included movement parameters (6 regressors: rotation and translation parameters in x/y/z direction), cerebrospinal fluid (CSF) noise, white matter noise and trials with missed responses. For the PPI, we tested the interaction between the seed region and the stimulation condition, or the interactions between the psychological and physiological regressors (in-phase congruency ~ rFPl, anti-phase congruency ~ rFPl, sham congruency ~ rFPl; z-threshold = 3.1). After the PPI, the average parameter estimates (congruency effect) were extracted from the M1 mask (MNI coordinates M1: 59 47 68) at the differences in functional connectivity between the right FPl and M1 during the in-phase, anti-phase and sham condition. Again, the same procedure was followed for the left FPl.

FPl-M1 functional connectivity for congruent versus incongruent trials

In order to investigate the PPI effects underlying

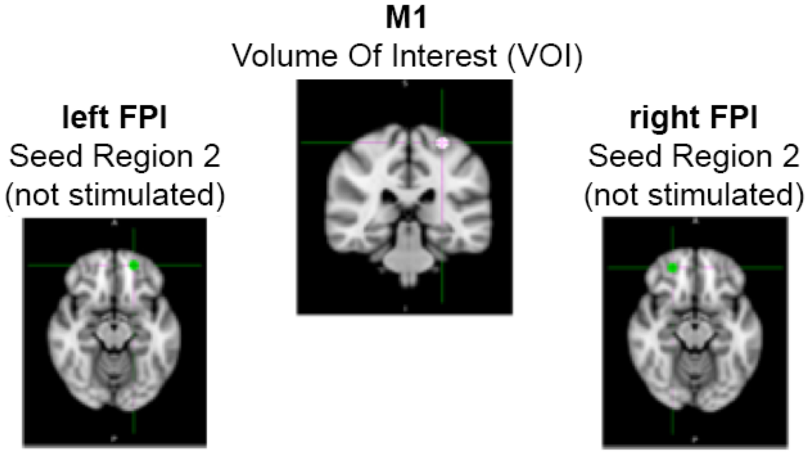

Figure 3. Seed regions and volume of interest (VOI) region of the PPI analysis. Interregional connectivity was investigated between the lateral frontal pole of the right hemisphere (green 5 mm mask at right FPl, seed region 1) and M1 (VOI, white 5 mm mask at primary motor cortex), and between the lateral frontal pole of the right hemisphere (green 5 mm mask at left FPl, seed region 2) and the M1. Right FPl and the M1 received tACS stimulation (stimulation side), whereas the left FPl did not receive local stimulation.

[1] Design matrices for the congruency task regressors included the stimulus onset [tPict - start], the duration until response onset [RT] and the congruency condition [congruent = -1, incongruent = 1].

the findings of the VOI analysis above, we separated PPI analyses on the congruent and incongruent conditions for in-phase, anti-phase and sham stimulation. This was again done for the FPl in the left and right hemisphere separately. Task regressors included in-phase congruent, in-phase incongruent, anti-phase congruent, anti-phase incongruent, sham congruent, and sham incongruent[2], and physiological regressors in the left or right FPl. The average parameter estimates were again extracted from the M1 mask for these six factors.

Results

Behavioural outcomes

Average Reaction Times (RT) & Error Rates (ER)

Reaction times and error rates of individual subjects are presented in Figure 4. Mean group reaction times were longer for incongruent (M = 671 ms, SD = 133 ms) as compared to congruent conditions (M = 631 ms, SD = 108 ms) (t = -6.12, p < 0.001). In addition, participants had higher accuracy levels for congruent trials (M = 96.3%, SD = 2.9) as compared to the incongruent trials (M = 94.3%, SD = 4.2%) (t = 3.82, p < 0.001). These findings are in line with results of previous studies using the AAT (Bramson et al., 2018; Roelofs et al., 2008; Volman et al., 2011).

Error Rates

ER congruency effect

The congruency effect of error rates was calculated by subtracting the percentage of correct trials in the incongruent condition from the percentage of correct trials in the congruent condition[3] .

We compared the congruency effect of error rates for the in-phase (M = 1.43%, SD = 3.6%), anti-phase (M = 2.51%, SD = 3.2%) and sham (M = 2.21%, SD = 3.5%) stimulation condition (one-sided t-test). A significantly smaller congruency effect in error rates was found for the in-phase as compared to the anti-phase condition (t(40) = -1.71, p = 0.047) (Fig. 5), which indicates an improvement in performance. A trend in reduced congruency effect was also found

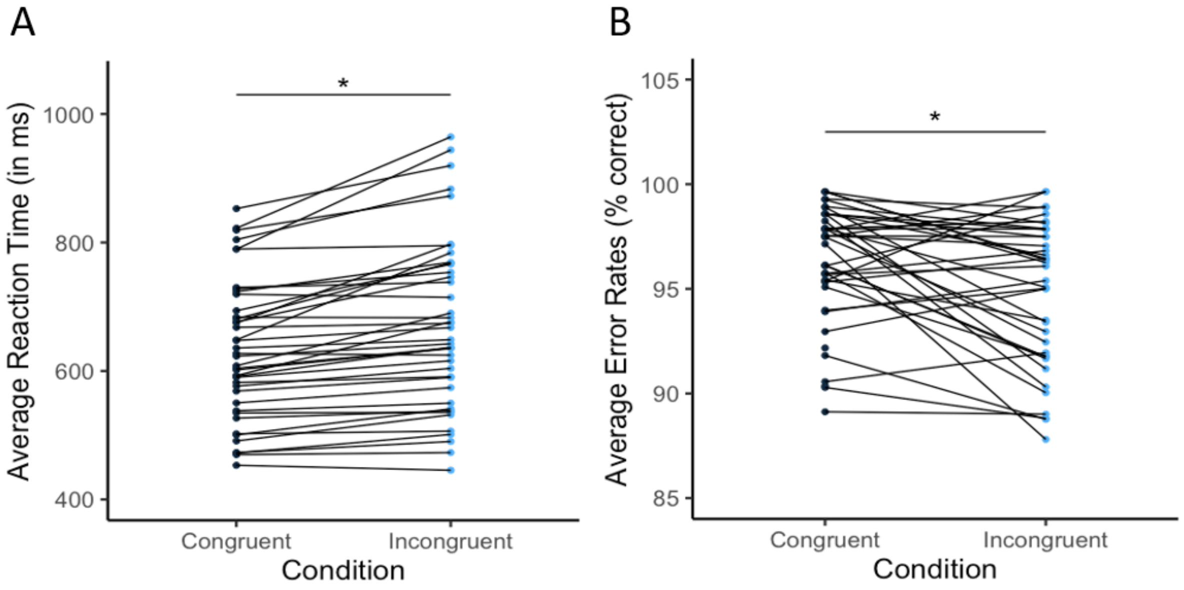

Figure 4. A. Average reaction times (in ms) per individual subject in congruent and incongruent conditions. Mean group reaction time is higher for incongruent conditions compared to congruent conditions, which indicates slower responses when a stimulus is affect-incongruent, and control needs to be applied by the participant. B. Average error rates (% correct) per individual subject in congruent and incongruent conditions. Mean error rates are higher for incongruent conditions as compared to congruent conditions, which indicates that subjects make more errors when control is needed to overcome automatic action tendencies.

[2] Design matrices for the congruent task regressors included the stimulus onset [tPict - start], the duration until response onset [RT] and the congruency condition [congruent = 1, incongruent = 0].
Design matrices for the incongruent task regressors included the stimulus onset [tPict - start], the duration until response onset [RT] and the congruency condition [congruent = 1, incongruent = 0].

when comparing the in-phase and sham condition (t(40) = -1.05, p = 0.15). No significant differences in congruency effect were found between the anti-phase and sham condition (t(40) = 0.5, p = 0.31). In line with our hypothesis, we found that theta-gamma tACS reduces the congruency effect and improves performance in the AAT when subjects receive in-phase stimulation while having to control their automatic responses (incongruent condition).

ER congruent versus incongruent

In order to investigate what underlies these congruency effects in error rates, we took the group mean from the percentage of correct responses of the congruent and incongruent trials. Figure 6 shows the congruent and incongruent group means compared for the three stimulation conditions. As seen in the figure, the congruency effects in each stimulation condition are explained by a smaller percentage of correct trials for the incongruent trials (in-phase: M = 95.1%, SD = 3.8%; anti-phase: M = 94.5%, SD = 3.8%; sham: M = 94.8%, SD = 4.1%) as compared to the congruent trials (in-phase: M = 96.6%, SD = 3.6%; anti-phase: M = 97.2%, SD = 2.6%; sham: M = 97.3%, SD = 2.3%). We observed the trend that more errors were made during the in-phase as compared to the anti-phase trials (t(40) = 1.28, p = 0.10). However, we found no significant difference between the other conditions (p > 0.20). We found no significant differences when comparing the congruent trials of the three stimulation conditions (for all comparisons, p > 0.40).

Reaction Times

RT congruency effect

The congruency effect of the reaction times is calculated by subtracting the mean reaction time (in ms) in the congruent conditions from the reaction time in the incongruent conditions[4] . We compared the congruency effect of reaction times for the in-phase (M = 43.8 ms, SD = 55.4 ms), anti-phase (M = 42.1 ms, SD = 41.1 ms), and sham (M = 48.4 ms, SD = 76.8 ms) stimulation condition (Fig. 5). No significant differences were found in the congruency effects of reaction times for the three stimulation conditions (in-phase vs anti-phase: t(40) = 0.21, p = 0.41; in-phase vs sham: t(40) = -0.50, p = 0.69; anti-phase vs sham: t(40) = -0.59, p = 0.28) (one-sided t-test).

RT congruent versus incongruent

When looking at the congruent and incongruent conditions separately, no significant differences in reaction times were found between stimulation conditions of the congruent trials (in-phase: M = 647 ms, SD = 116 ms, anti-phase: M = 641 ms, SD

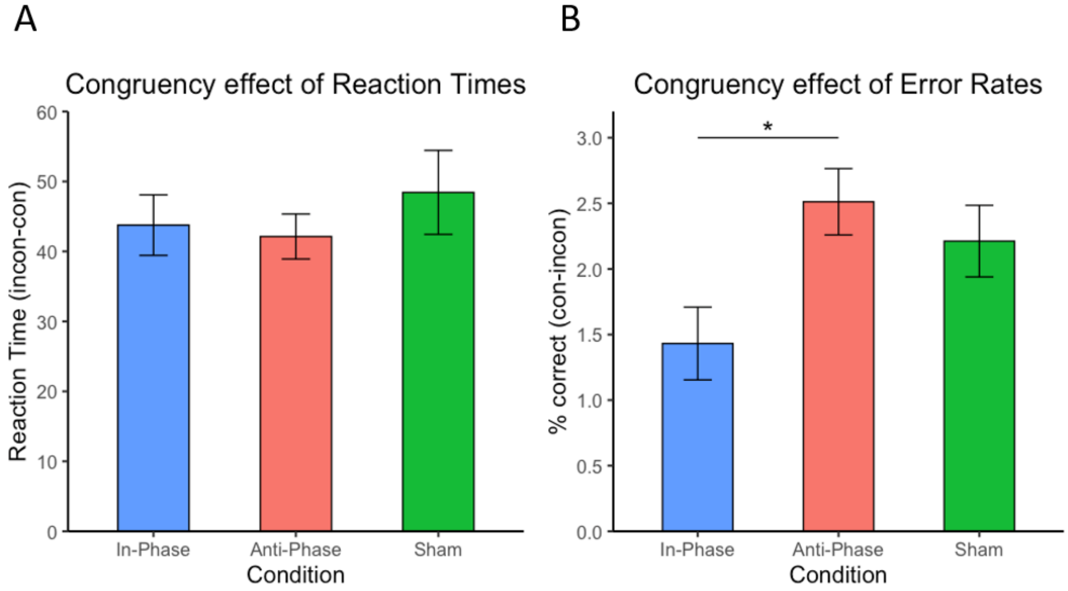

Figure 5. A. Congruency effect on reaction times. No significant differences were found when comparing the congruency effects of reaction times. **B.** Congruency effects on error rates. Reduced congruency effects (improved social-emotional control) was found during in-phase stimulation as compared to anti-phase and sham stimulation. A trend was seen in increased congruency effects for anti-phase compared to sham stimulation.

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3 Congruency effect Error Rates = % correct congruent trials - % correct incongruent trials

= 105 ms, sham: M = 638 ms, SD = 106 ms) (p > 0.10 for all comparisons) or incongruent trials (in-phase: M = 690 ms, SD = 143 ms, anti-phase: M = 684 ms, SD = 127 ms, sham: M = 688 ms, SD = 139 ms) (p > 0.10 for all comparisons) (Fig. 6). Within the stimulation conditions, no significant differences were found between the congruent and incongruent conditions of the in-phase, anti-phase or sham condition (p> 0.10 for all comparisons).

These findings show that theta-gamma band stimulation does not result in differences in congruency effect in reaction times for the in-phase condition as compared to the anti-phase and sham condition, thus does not affect the response time of subjects during the task.

Neuroimaging outcomes

Functional connectivity between M1 and rFPl

The goal of our PPI is to identify task-specific changes in the relationship between the FPl and M1 (or functional connectivity) during the different stimulation conditions (O'Reilly et al., 2012). The task effect underlying the PPI is the congruency effect (incongruent – congruent trials). We found a negative task-specific change in functional connectivity between the right FPl (seed region) and the M1 (VOI) for in-phase stimulation (M = -6.5, SD = 2.6) and sham stimulation (M = -2.1, SD = 2.6) (Fig. 7B). These findings indicate that for in-phase and sham stimulation there is a stronger relationship (or stronger functional connectivity) between right FPl and M1 in congruency effect. This relation is in the negative direction, which means that there is a negative relation between the difference in FPl activation for congruent and incongruent trials on the one hand and the difference in M1 activation between the congruent and incongruent trials on the other hand (incongruent-congruent difference scores are negatively correlated). Or, in other words, more positive congruency effects in the FPl are linked to more negative congruency effects in the M1. In contrast, we found that for the anti-phase stimulation (M = 0.8, SD = 1.2) there is a positive change in functional connectivity between the right FPl and M1. When comparing stimulation conditions, we find significantly stronger functional connectivity change for in-phase stimulation compared to anti-phase stimulation (t(40) = -2.1, p = 0.04). No significant differences are found between in-phase and sham stimulation (t(40) = -1.2, p = 0.22), and between anti-phase and sham stimulation (t(40) = 0.7, p = 0.43). These results indicate that when a subject receives in-phase stimulation there is a stronger functional connectivity change between the FPl and M1 for the congruency effect as compared to anti-phase and sham stimulation.

Functional connectivity between M1 and lFPl

Likewise, for the left FPl, we found a negative task-specific change in functional connectivity between the left FPl and the M1 for in-phase stimulation (M = -6.0, SD = 1.9) and sham stimulation (M = -2.6, SD = 2.1) while positive effects were seen for anti-phase stimulation (M = 3.1, SD = 2.5)(Fig. 7A).

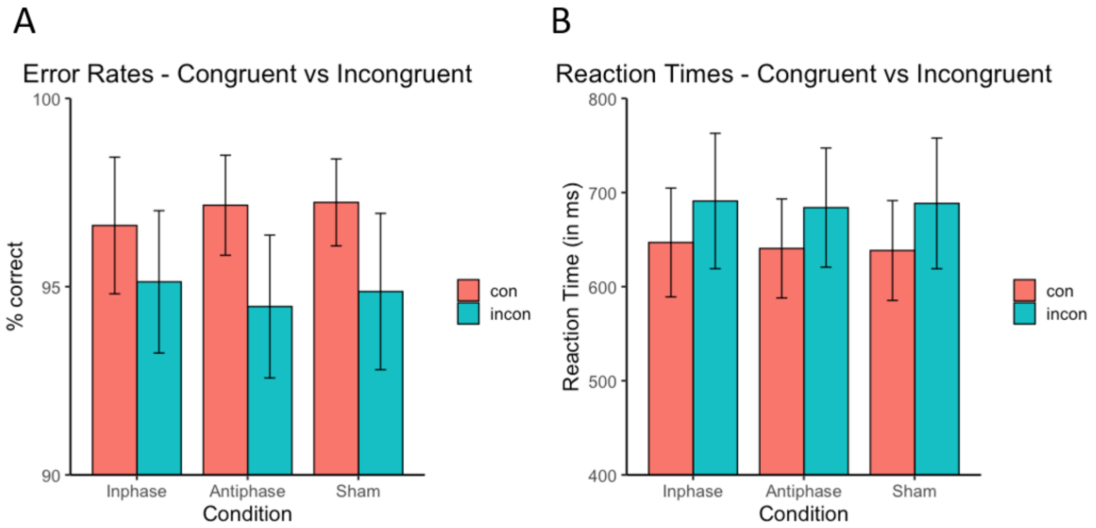

Figure 6. A. Error rates for congruent versus incongruent trials. **B.** Reaction times for in-phase, anti-phase and sham stimulation.

4 Congruency effect Reaction Time = mean reaction time incongruent trials - mean reaction time congruent trials

Significant differences were found for in-phase as compared to anti-phase stimulation (t(40) = -2.7, p = 0.01, SD = 22) and for anti-phase compared to sham stimulation (t(40) = 2.2, p = 0.03, SD = 16.9). The effect differences were not significant between in-phase and sham stimulation (t(40) = -1.1, p = 0.26, SD = 18.8). These results replicate the findings found in the right FPl, thereby showing that the effects are transferable to the contralateral hemisphere.

PPI congruent versus incongruent

These findings are supported by the PPI effects between FPl and M1 for congruent and incongruent conditions (Fig. 9). In-phase stimulation shows more positive effects for congruent (lFPl: M = 7.8, SD = 26 ; rFPl: M = 9.3, SD = 26) compared to incongruent trials (lFPl: M = -3.9, SD = 14, rFPl: M = -3.2, SD = 18). These findings are widely interpretable but could support the earlier finding that there is a larger task-related difference in functional connectivity (or stronger functional connectivity) between FPl and M1 for congruent trials as compared to incongruent trials.

Surprisingly, large negative PPI effects in the sham condition are found for the incongruent condition (lFPl: M = -5.8, SD = 15; rFPl: M = -7.2, SD = 21) as compared to the congruent condition (lFPl: M = -3.0, SD = 26 ; rFPl: M = -3.2, SD = 34). Smaller differences are found for the anti-phase condition between congruent trials (lFPl: M = -2.9, SD = 20; rFPl: M = 1.0, SD = 25) and incongruent trials (lFPl: M = 2.8, SD = 24 ; rFPl: M = 3.2, SD = 28). Similar PPI effects are found for both the right as well as the left FPL.

Whole-brain effects

A post hoc whole-brain PPI analysis was performed to investigate the functional connectivity between the aPFC and other regions in the brain comparing the in-phase and anti-phase stimulation conditions. For this purpose, we used the right FPl (stimulation site) as seed region and looked at whole-brain effects in the contrast between in-phase and anti-phase stimulation. Cluster-corrected results show clusters with increased activity in the right FPl (max intensity = 4.18, voxels = 1143, p < 0.0001, MNI coordinates = 36 79 41), cingulate gyrus (intensity = 3.71, voxels = 811, p < 0.0001, MNI coordinates = 45 40 46), right thalamus (max intensity = 3.7, voxels

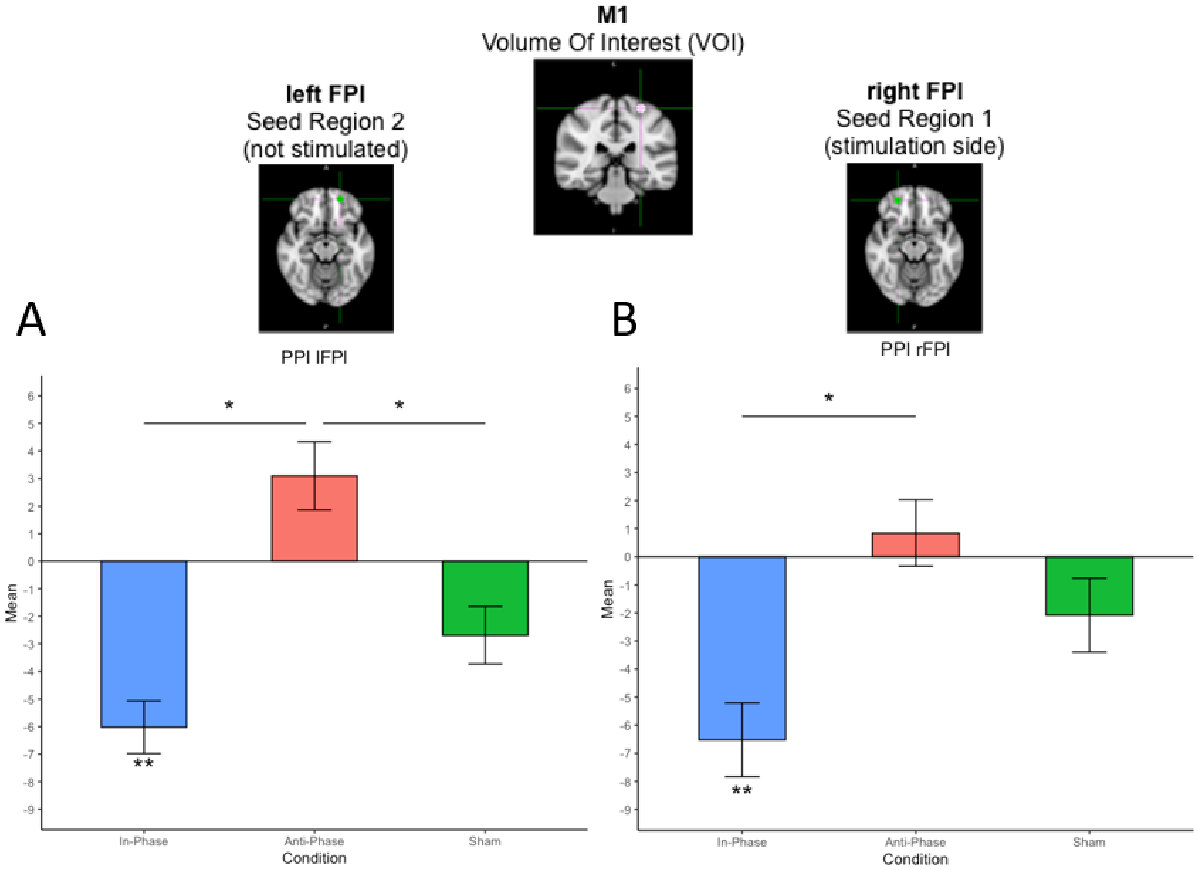

Figure 7. PPI effects. A. Left lateral frontal pole B. Right lateral frontal pole. Larger (negative) functional connectivity changes were found for in-phase as compared to anti-phase and sham stimulation.

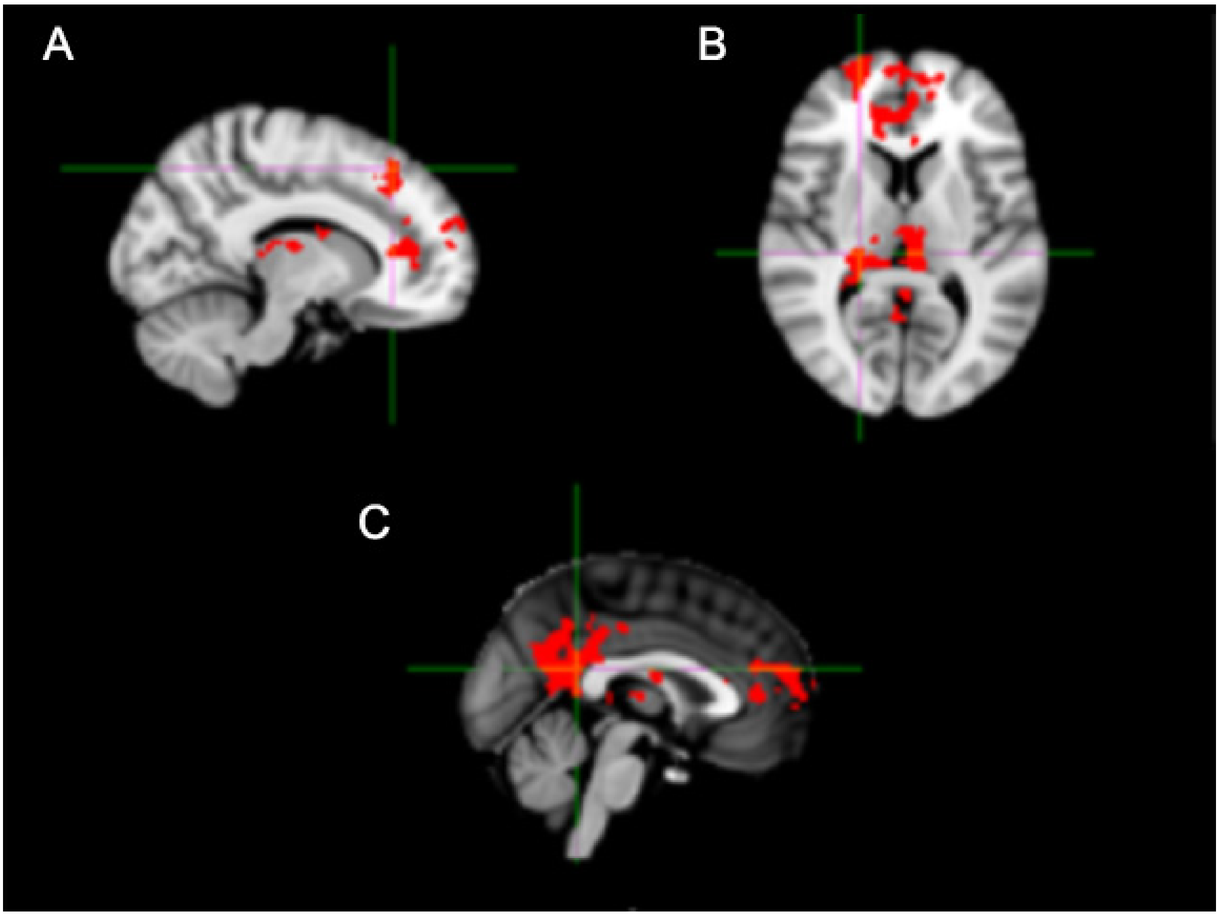

Figure 8. PPI cluster-corrected results for in-phase versus anti-phase stimulation. These individual images show clusters **A.** superior frontal gyrus and FPl **B.** Thalamus and pulvinar **C.** cingulate gyrus.

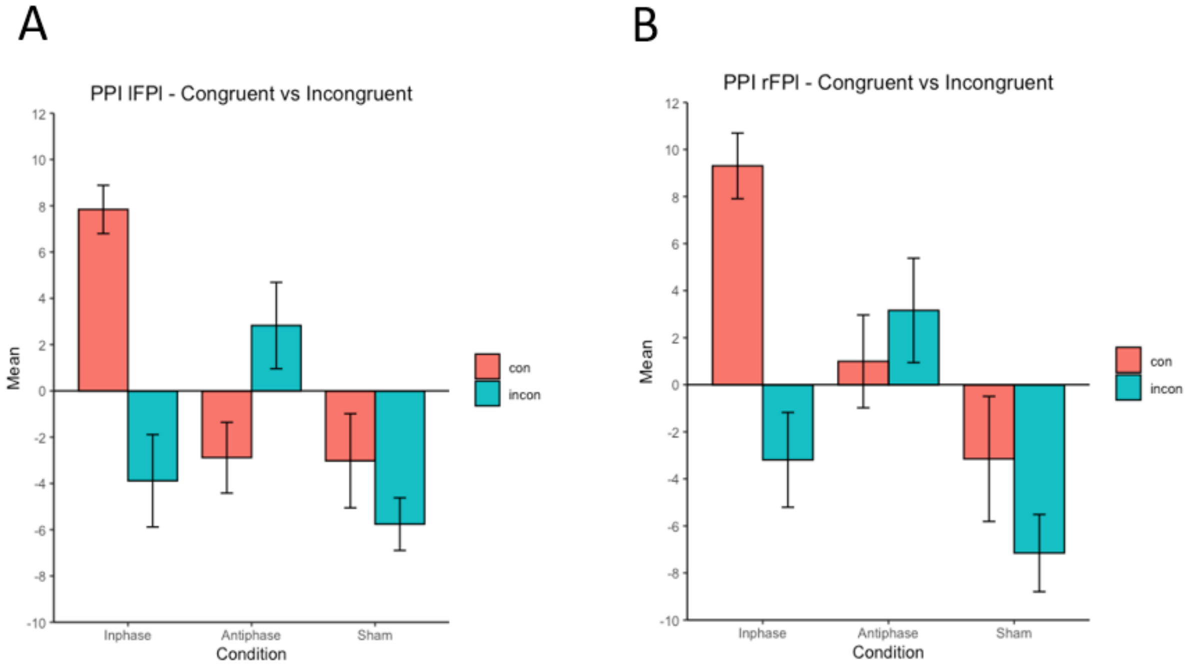

Figure 9. PPI effects for congruent and incongruent conditions separately. **A.** PPI effects for the left FPl **B.** PPI effects for the right FPl for congruent and incongruent trials. A larger functional connectivity was found the in-phase congruent as compared to incongruent trials. For the other stimulation conditions, larger effects were found for incongruent compared to congruent trials.

= 650, $p < 0.001$, MNI coordinates = 34 50 40) and superior frontal gyrus (max intensity = 4.3, voxels = 379, $p < 0.01$, MNI coordinates = 39 79 61) (Fig. 8). High intensity values were found in the right FPl (-3.67), left FPl (-2.91), pulvinar in left thalamus (-3.23), precuneus (part of the parietal lobule of the brain) (-3.0) and the cingulate gyrus (-3.5).

Correlation neuroimaging data and behavioural data

The relation between behavioural performance and functional connectivity for the three stimulation conditions is represented in Figure 10. For the right FPl, a significant positive correlation between congruency effect in reaction times and PPI score for the anti-phase condition was found ($r = 0.3752$, $p = 0.0156$). For the left FPl, a significant negative correlation between congruency effect in error rates and PPI score was found for the sham condition ($r = -0.3371$, $p = 0.0312$). No significant correlations were found for Reaction Time x PPI or Error Rate x PPI in the other stimulation conditions for either the lFPl or the rFPl. These results show that there is limited to no interaction between performance and functional connectivity.

Discussion

Influence of theta-gamma coupled tACS on social-emotional actions

Our findings show that theta-gamma band coupled tACS influences social-emotional control and functional aPFC-M1 connectivity. Firstly, in-phase stimulation leads to improvement in overriding automatic emotional action tendencies when one is engaged in social-emotional control, compared to anti-phase stimulation. This confirms our hypothesis and shows that we can improve social-emotional behaviour when coupling theta- and gamma-oscillations between the aPFC and M1. This finding is supported by a stronger functional

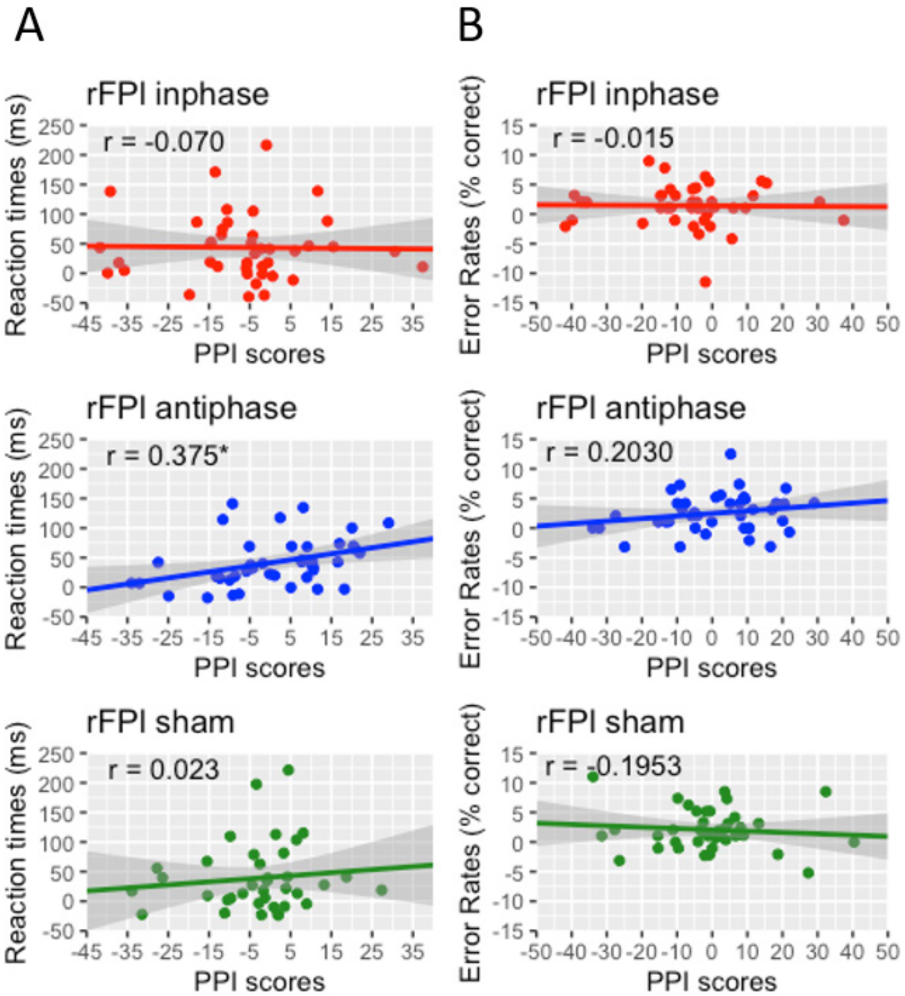

Figure 10. A. interaction between PPI scores of right FPl and congruency effect of reaction times **B.** PPI scores of right FPl and congruency effect of error rates.

connectivity between the lateral frontal pole and the primary motor cortex for in-phase as compared to the other stimulation conditions. Even though no interaction was found between behavioural performance and functional connectivity, these results may suggest that in-phase theta-gamma band stimulation improves social emotional control and strengthens the interregional connectivity in regions involved in social-emotional control.

Effect of theta-gamma band coupled tACS stimulation on approach/ avoidance behaviour

In line with our hypothesis, subjects show improved control over social-emotional actions (reduced congruency effect) when stimulated in-phase as compared to anti-phase and sham stimulation. This improvement is specifically relevant for incongruent conditions, where control is needed to overcome automatic emotional action tendencies when avoiding happy faces and approaching angry faces. We applied theta-band tACS to the aPFC and gamma-band tACS to the M1 to influence theta-gamma coupling between the two brain regions. During the in-phase stimulation, the power increases of the M1 gamma-band stimulation are phase-locked to the peaks of the aPFC theta-band stimulation. In contrast, during anti-phase stimulation, these gamma-band power increases are phase-locked to the troughs of the aPFC theta-band stimulation. Our behavioural findings suggest that we can use in-phase theta-gamma coupled tACS to influence underlying cognitive processes related to social-emotional control. However, anti-phase tACS did not lead to significant impairments of social-emotional control, suggesting that desynchronising these oscillatory patterns does not lead to major disruptions in communication between the aPFC and M1.

Our finding that in-phase theta-gamma coupled stimulation enhances control supports the theory that social-emotional control exerted by the aPFC may be implemented by theta-gamma coupled oscillations. This is consistent with previous work by Bramson et al. (2018) which found stronger pre-movement gamma-band oscillations of premotor areas[5] during affect-incongruent trials compared to affect-congruent trials. Power increases of M1 gamma-band oscillations were phase locked to the peaks of aPFC theta-band oscillations, suggesting that these gamma-band power increases during control could be guided by long-range communication between the aPFC and M1. Our research suggests that these oscillatory effects can be replicated by externally influencing the spike-timing of theta- and gamma-oscillations in these regions during social-emotional control. The spike-timing depends on the relative timing of pre- and postsynaptic action potentials (spike-timing dependent plasticity; (Song, Miller, & Abbott, 2000)). This means that the magnitude of change in synaptic strength between pre- and postsynaptic neurons is based on the timing of neuronal spikes. When the presynaptic spike reaches the postsynaptic neuron before the latter fires, then the synapse gets potentiated. When the presynaptic spike reached the postsynaptic neuron after it fires, the synapse gets depressed. When applying in-phase stimulation the presynaptic spike would be externally influenced by the tACS before the postsynaptic neuron fires after which the synapse would be potentiated. As a consequence, this potentiation would lead to an enhanced communication between aPFC and M1, thereby improving the ability of the aPFC to implement social-emotional control.

We expected that the participants would show an increase in congruency effect for the anti-phase condition as compared to the sham condition, which indicates that participants get worse in controlling their actions. While a trend was seen in this direction, no significant changes in congruency effect were found in the anti-phase and sham conditions for both reaction times as well as error rates. We speculate that during anti-phase coupling, the stimulation would influence the cortical oscillations such that the power increases of the gamma-band oscillations would phase-lock to the troughs of the theta-band oscillations of the aPFC. The inhibitory effects of theta-band oscillations would make it unlikely that presynaptic activity in aPFC drives postsynaptic spikes in the M1. Consequently, neural coherence and information transfer between the aPFC and the sensorimotor cortex would be impaired. This could lead to limited communication between the aPFC and distant regions as well as disrupted action preparation and selection by the premotor areas.

Looking at influencing social-emotional control specifically, our findings are in line with research by Volman et al. (2011), who found disruption of social-emotional control when the aPFC was inhibited using continuous theta-burst stimulation. They also only found differences in behavioural effects in error rates and not in reaction times. This

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[5] contralateral to the responding hand

implies that non-invasive stimulation affects one's ability to override automatic emotional tendencies but does not affect the time to respond to affect-incongruent trials.

In a broader perspective, our findings are in support of previous studies using a multi-electrode tACS set-up to influence complex cognitive processes. Previous research showed that the precision of value-based choice in humans can be manipulated by (de-)synchronising phase-coupling between parietal and frontal regions (Polanía et al., 2015). When tACS was used to disrupt fronto-parietal coherence, participants made less accurate choices between value-based food choices without affecting closely matched perceptual decisions. Other research found cognitive improvement on the revival of working memory (Reinhart & Nguyen, 2019). They applied customised electrical stimulation based on theta-gamma coupling to individual network dynamics in older adults. The revival effects lasted for 50 minutes, which may suggest that this technique can assist in long term improvements for cognitive processes. These studies applied tACS in a circle-ring set-up similar to our study. Our research gives further support to that hypothesis that tACS could influence coupling or decoupling of behaviourally relevant neural oscillations between distant cortical areas, and even has the possibility of long-term changes in cognitive processes.

Functional connectivity change during theta-gamma coupled tACS

Congruency effect

We investigated the effect of the different stimulation conditions by looking at the change in functional connectivity between the aPFC and the M1 during social-emotional actions. We found stronger aPFC-M1 connectivity after applying in-phase stimulation as compared to anti-phase and sham stimulation. These connectivity estimates are highly similar in contralateral aPFC-M1, indicating that this is not an artefact of potential distortion due to the electrode or electrical currents applied over the right aPFC. Therefore, the task-specific increase in the relationship between the aPFC and M1 (a PPI effect) is suggestive of an increased information flow between these regions. Together with the behavioural results, these findings suggest that the communication between these areas is improved by externally synchronising theta-gamma coupling resulting in improvement in social-emotional control.

More specifically, we found stronger functional connectivity effects for in-phase stimulation as compared to the anti-phase and sham conditions. This negative relation could suggest that more positive congruency effects in the FPl (larger difference in activity between congruent and incongruent trials) are linked to more negative congruency effects in the M1 (smaller difference in activity between congruent and incongruent trials). We suggest that this effect could be explained by the inhibitory nature of theta-band oscillations that would lead to stronger inhibitory effects implemented by the aPFC on other brain regions.

Congruent versus incongruent

We found surprising results in functional FPl-M1 connectivity when separating congruent and incongruent conditions. When applying sham stimulation, we found stronger task-related functional FPl-M1 connectivity changes for incongruent as compared to congruent conditions. This is what we expected, as we hypothesised that during affect-incongruent trials the aPFC/FPl has to exert more control in order to overcome automatic action tendencies. There would be a stronger functional connectivity to establish this and an increase in information flow between the FPl and M1. For anti-phase stimulation, larger PPI effects are also found for incongruent as compared to congruent trials but in the positive direction, which could indicate that more negative effects in the FPl are linked to more positive effects in the M1. This is surprising, as we would rather expect weaker functional connectivity between the aPFC and M1 that is related to impaired control. Both sham and stimulation show larger functional connectivity changes when control needs to be exerted during approach and avoidance actions (incongruent) compared to when less control is needed (congruent).

In line with the reasoning above, we therefore expected that during in-phase stimulation the FPl-M1 functional connectivity would be even stronger, matching the increased information transfer related to the improved behavioural performance we found. However, instead we found the opposite results, namely a stronger change in task-related activity for the congruent condition as compared to the incongruent condition. One speculation could be that, during congruent conditions, the aPFC does not need to be involved in that many control-regulating processes and therefore there would not be a lot of change in this low neural activity baseline. Stimulation would then increase neural activity even more from this low baseline as compared to when the aPFC is already engaged in increased neural firing during control. However, further research into this matter is needed as we were not able to directly measure this baseline of neuronal activity. We can only speculate about the processes underlying these functional connectivity effects.

Interpretational issues

This study only focussed on the connectivity between aPFC and the motor cortex in social-emotional control. However, the connections between the aPFC and other regions should be taken into account when looking at influencing social-emotional control. We found no functional connectivity between the aPFC and the M1 during the whole-brain analysis but did find functional connectivity with the thalamus/pulvinar, cingulate gyrus/precuneus and superior frontal gyrus. Prefrontal-pulvinar functional connectivity was also found in the study by Tyborowska and colleagues (2016) as an alternative pathway for effective emotional control to the prefrontal-amygdalar connection. Functional connectivity between the aPFC and precuneus (part of the parietal lobule of the brain) can be explained by its role in emotion and social cognition. Moreover, this area shows connections with the dorsalmost nuclei of the thalamus (lateral pulvinar, amongst others; (Cavanna & Trimble, 2006), and lower task related deactivation is found for people with social anxiety as compared to healthy controls (Gentili et al., 2009). The mechanisms underlying social-emotional control are very complicated and are far more extensive than the interaction between prefrontal and sensorimotor areas.

Control over social-emotional actions by the aPFC or the FPl is likely mediated by the amygdala (Bramson et al., 2019). Impairment of prefrontal-amygdala connectivity, for example in social anxiety, is related to problems in social-emotional regulation (Gold et al., 2016; Radke et al., 2013). Previous research has shown that the aPFC inhibits the amygdala, which is involved in automatic emotion evaluation, and upregulates areas involved in action selection during social-emotional control (Volman et al., 2011; Volman et al., 2013). Therefore, we suggest that in-phase theta-gamma coupled stimulation could lead to a larger suppression of the aPFC over the amygdala and an enhanced communication between the aPFC and the M1. This mechanism could explain why participants become better at inhibiting the automatic emotional tendencies and improve in exerting social-emotional control.

Subsequently, we only found small improvements in behavioural performance when applying in-phase theta-gamma coupled stimulation as compared to the other stimulation types. Generally, healthy participants are already quite good at inhibiting their automatic emotional tendencies and exerting social-emotional control, so we did not expect to find very large improvements. Theta-gamma coupled tACS as an intervention strategy could therefore be more effective for people who experience problems in exerting social-emotional control. These people would benefit more from in-phase stimulation to improve the communication between prefrontal and motor areas, possibly mediated by a larger suppression of the amygdalar response, resulting in greater improvement in correctly inhibiting their automatic emotional tendencies.

Our hypothesis was based on the idea that theta-gamma band stimulation leads to the synchronisation of the neuronal activity of the targeted areas. However, another possibility is that the reported effects are caused by transcutaneous stimulation of peripheral nerves (Asamoah, Khatoun, & Mc Laughlin, 2019). It could be that tACS stimulation itself does not entrain neural activity but that the rhythmic activity from peripheral nerves entrains cortical neurons. We argue against this notion as our circle-ring set-up sends electrical currents between the inner and outer electrode instead of between two distant locations. This allows the current to flow over the superficial layer of the cortex. More importantly, the frontal and motor areas are stimulated in two different frequencies that are either in-phase or anti-phase. Behavioural and functional connectivity differences as a consequence of these stimulation types show that the effects are not just due to peripheral nerve stimulation but due to transcranial stimulation.

Conclusion

Taken together, our findings show that control over social-emotional actions can be influenced by theta-gamma band coupled tACS. When applying theta-band stimulation to the aPFC that is phase-locked to the power increase of gamma-band stimulation to the M1, participants showed improvements in overriding their automatic emotional action tendencies. Moreover, in-phase theta-gamma coupled stimulation was linked to stronger FPl-M1 functional connectivity. This suggests that in-phase stimulation can be used as a technique to facilitate communication between these areas. We speculate that the mechanism underlying the improvement in social-emotional control would be an enhancement in theta-gamma coupling caused by externally synchronising theta- and gamma-band oscillations. This research has a high clinical relevance, as the technique could be used in treatment of patients who have difficulties regulating their social-emotional behaviour, such as in social anxiety. tACS influences naturally occurring oscillations and only leads to synchronisation of neuronal activity when one already engages in related cognitive processes, such as control. Therefore, the technique could be used as an addition to extinction therapy, where people are exposed repeatedly to stressful cues and situations, thereby improving the effect of the therapy and increase speed of recovery. This technique could provide promising possibilities for treatment of disorders that are related to social-emotional control.

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