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Report

# Anterior Prefrontal Cortex Inhibition Impairs Control over Social Emotional Actions

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## Summary

**When dealing with emotional situations, we often need to rapidly override automatic stimulus-response mappings and select an alternative course of action [1], for instance, when trying to manage, rather than avoid, another's aggressive behavior. The anterior prefrontal cortex (aPFC) has been linked to the control of these social emotional behaviors [2, 3]. We studied how this control is implemented by inhibiting the left aPFC with continuous theta burst stimulation (cTBS; [4]). The behavioral and cerebral consequences of this intervention were assessed with a task quantifying the control of social emotional actions and with concurrent measurements of brain perfusion. Inhibition of the aPFC led participants to commit more errors when they needed to select rule-driven responses overriding automatic action tendencies evoked by emotional faces. Concurrently, task-related perfusion decreased in bilateral aPFC and posterior parietal cortex and increased in amygdala and left fusiform face area. We infer that the aPFC controls social emotional behavior by upregulating regions involved in rule selection [5] and downregulating regions supporting the automatic evaluation of emotions [6]. These findings illustrate how exerting emotional control during social interactions requires the aPFC to coordinate rapid action selection processes, the detection of emotional conflicts, and the inhibition of emotionally-driven responses.**

## Results

Flexible behavioral control during emotional situations is crucial for effective social interactions, as illustrated by the consequences of altered emotional control in pathologies like social anxiety and psychopathy [7–9]. Previous work has associated emotional control with the detection of emotional conflict and the inhibition of emotionally driven responses [10–13]. Yet, conflict detection and response inhibition alone are unlikely to explain how we adaptively respond to an emotional situation [14]. Emotional control during social interactions might often require a generative component, namely the rapid selection of rule-based associations that override automatic emotional response tendencies [15, 16].

Here, we test the hypothesis that the anterior prefrontal cortex (aPFC) plays a causal role in emotional control. This hypothesis is grounded on the socially inappropriate behavior of patients with aPFC and orbital frontal cortex damage [17–19] and on recent findings linking lateral aspects of the aPFC with the voluntary control of social emotional responses [2, 20]. We propose that the aPFC supports emotional control by coordinating the automatic processing of emotional behavioral tendencies with the rapid selection of rule-based behaviors.

Continuous theta burst stimulation (cTBS; [4]) was used to noninvasively reduce neural activity of the left lateral aPFC (Figure 1C), a brain site previously involved in social emotional control [2]. We assessed whether disturbing this site would alter participants' ability to control their emotional responses. To isolate the cerebral mechanisms associated with this behavioral alteration, we measured regional cerebral blood flow (rCBF) over the whole brain with continuous arterial spin labeling (CASL; [21]). Control of social emotional behavior was quantified with a task requiring participants to approach or avoid visually presented emotional faces by pulling or pushing a joystick, respectively (approach-avoidance [AA] task, Figure 1A; [22, 23]). Given the automatic tendencies to avoid angry faces and approach happy faces during the AA task (affect-congruent responses; [23]), correct performance of affect-incongruent trials requires participants to exert control over those automatic response tendencies [2, 20], resulting in longer response latencies (Figure 1B).

The experiment was designed to assess two consequences of interfering with aPFC function. First, if the aPFC is necessary for implementing control over automatic emotional tendencies, then interfering with the aPFC should impair performance when emotional control is required. The results accordingly showed that, after cTBS over the aPFC, AA task performance resulted in disproportionally more errors during affect-incongruent trials than during affect-congruent trials (difference between task conditions during AA task after cTBS inhibition: $F(1,23) = 12.8$, $p = 0.002$; Figure 1D; see Supplemental Results available online for full repeated-measures analysis of variance). This impaired behavioral control was not present when the interference was designed to be functionally ineffective (control transcranial magnetic stimulation [TMS] sessions, Figures 1C and 1D) and when participants performed a control task involving the same stimuli and responses but with emotionally irrelevant rule reversals (gender evaluation task; all $Fs < 2.6$, see Supplemental Results and Table S1). Second, if the aPFC supports voluntary emotional control by coordinating the influence of automatic emotional tendencies with the selection of rule-based behaviors, then interfering with the aPFC should disturb activity in regions involved in those processes, when those processes are recruited. Accordingly, after cTBS over the left aPFC, performing the AA task increased rCBF in the left fusiform face area (FFA) and in the amygdala, regions known to support the automatic processing of visually presented faces [6]. Concurrently, the cortex underlying the cTBS intervention (extending to the contralateral right aPFC and the rostral anterior cingulate cortex) and the right posterior parietal cortex (PPC) showed robust decreases of rCBF during performance of the AA task (Figure 2; Table S2). These cerebral alterations occurred over and above generic interference effects evoked by applying repetitive TMS to the

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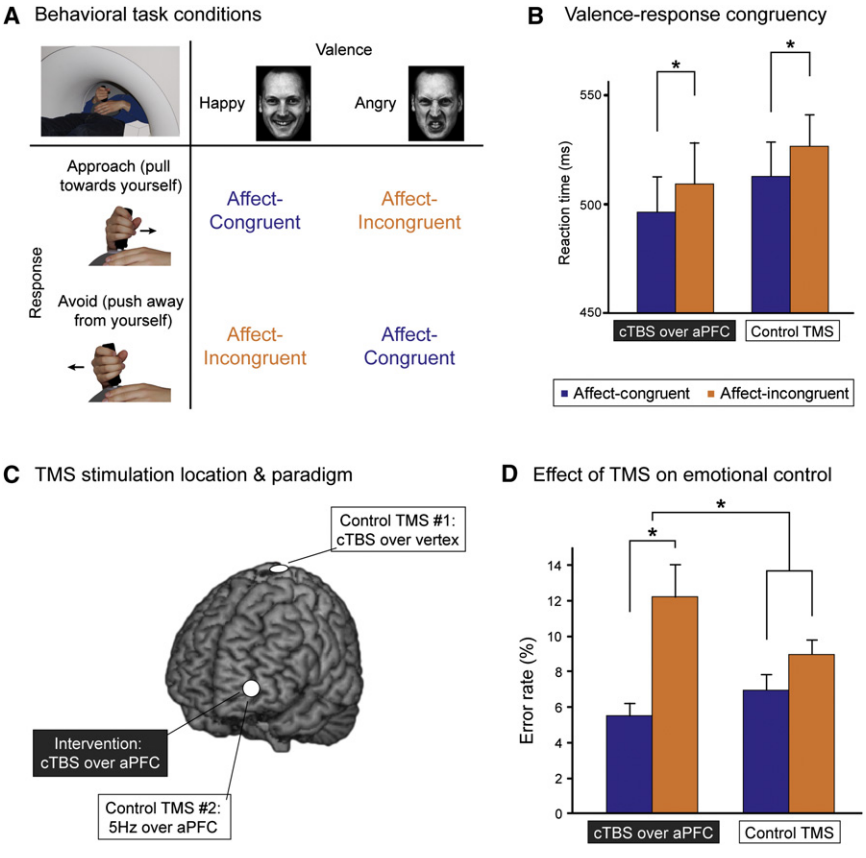


Figure 1. Experimental Procedures and Behavioral Results

(A) Conditions, stimuli, and responses of the tasks. Both the approach-avoidance and control task involved the presentation of either happy or angry faces and the performance of either approach or avoid responses. The combination of these emotion-response mappings resulted in affect-congruent (approach-happy, avoid-angry) and affect-incongruent (approach-angry, avoid-happy) conditions. During the approach-avoidance task, the participants had to select their response according to the perceived emotion of the face. During the control task, the response was based on an emotional-irrelevant feature, the perceived gender of the face. At the beginning of each block of 12 trials, the participants received instructions on whether to pull toward (approach) or push away (avoid) the joystick from themselves when seeing a face with a particular emotion or gender. Participants saw the faces and moved the joystick while lying in a MR scanner (top left corner of the table).

(B) Reaction times (mean ± standard error of the mean [SEM]) during performance of the approach-avoidance task following different transcranial magnetic stimulation (TMS) interventions. The participants took longer to respond to the presentation of a face during the affect-incongruent trials. This effect, as well as average reaction times, was matched across the different TMS interventions.

(C) Rendered brain indicating the two locations where TMS was applied (anterior prefrontal cortex [aPFC], vertex) and the three TMS sessions (continuous theta burst stimulation [cTBS] over aPFC [in dark gray]; cTBS over vertex [in white; control session 1]; 5 Hz stimulation over aPFC [in white; control session 2]).

(D) Error rate in percentage (mean ± SEM) during performance of the approach-avoidance task following the different TMS interventions. The participants made more errors during the affect-incongruent conditions after cTBS was applied to the aPFC than when the control stimulations were applied. See also Table S1.

aPFC or cTBS to a different brain region (control TMS sessions; see Figure 2). Furthermore, both behavioral and cerebral alterations occurred when participants were required to control their emotional actions (AA task), over and above performance during the gender evaluation task. Finally, matched reaction times (RTs) and overall performance across the TMS interventions exclude the possible influence of differences in general arousal between experimental sessions (also no session or session by congruency interaction effects on RTs, all Fs < 3).

## Discussion

In the present study, we measured the consequences of delivering cTBS over the left aPFC, and found that this region is necessary for the control of social emotional actions. Behaviorally, the cTBS intervention increased error rates only during trials requiring emotional control. Cerebrally, the cTBS intervention decreased neural activity in the aPFC region, both under the coil as well as in the controlateral homotopic area. Both behavioral and cerebral effects were conditional on the combination of aPFC inhibition and emotional control, as tested against functionally ineffective TMS interventions and a task involving the same stimuli and responses, but with emotionally irrelevant rule reversals. The behavioral effects indicate that inhibition of the aPFC reduces participants' ability to apply voluntary emotional control. The cerebral effects indicate that the cTBS-induced reduction of emotional control was associated with increased neural activity in the amygdala and FFA and reduced neural activity in the PPC. These spatially remote effects of left aPFC inhibition suggest that this prefrontal area implements emotional control by downregulating regions involved in the automatic evaluation of emotions [24, 25] and by upregulating regions supporting the rapid selection of a stimulus-response association based on an instructed rule [5, 26].

The reduced performance on affect-incongruent trials evoked by aPFC inhibition fits with the socially inappropriate behavior observed after large prefrontal lesions in humans [17–19] and selective lesions in macaques [27]. Here, we qualify those findings by describing how the aPFC controls behavioral tendencies triggered by emotions. During the AA task, as in many real-life circumstances, simple strategies limited to the suppression of emotional processing or to response inhibition are not viable options. In fact, when dealing with the affect-incongruent trials of the AA task, participants need to rapidly select an appropriate response by applying the required rule to emotional faces that are automatically associated with the opposite behavior. We show that this type of emotional control, based on overcoming automatic emotional tendencies with arbitrary rules, requires the aPFC, an area able to combine multiple sensorimotor associations into goal-directed hierarchical structures [28–30]. Accordingly, this study suggests that the aPFC solves this emotional control problem by coordinating neural processing in brain

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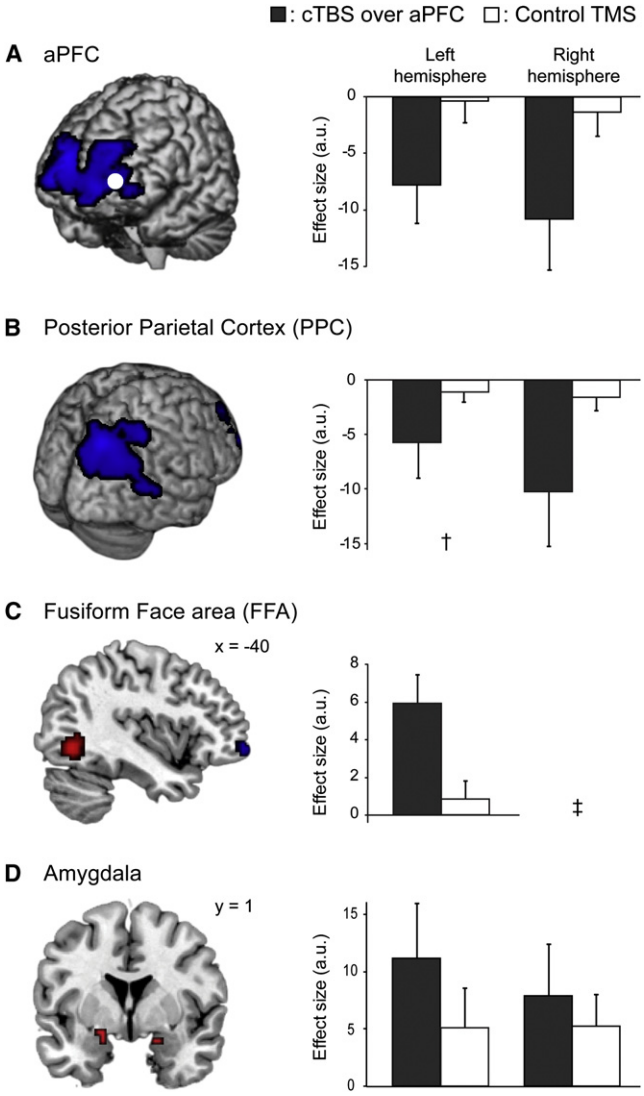


Figure 2. Functional Magnetic Resonance Imaging Results

Left column shows brain images indicating the localization of significantly decreased (blue) and increased (red) regional cerebral blood flow (rCBF) after cTBS over the aPFC, during performance of the approach-avoidance (AA) task (as compared to the control task). The stimulation location is indicated by a white circle in (A). Right column shows rCBF changes (mean ± SEM) during performance of the AA task (as compared to the control task) following cTBS over the aPFC (dark gray histograms) or control stimulations (white histograms), plotted separately for the left and the right hemisphere. cTBS over the left aPFC induced bilateral rCBF reductions in the anterior prefrontal cortex (A) and in the posterior parietal cortex (B), whereas the amygdala (D) and the left fusiform face area (C) showed increased rCBF. All $p < 0.05$ family-wise error corrected, except † ($p < 0.001$ [uncorrected], $t = 3.71$) and ‡ (no significant voxels). See also Table S2.

regions that deal with different types of sensorimotor associations. First, left aPFC inhibition leads to enhanced activity in the left FFA and in the amygdala during the AA task. These spatially remote effects of aPFC stimulation fit with the ability of the amygdala to trigger automatic behavioral tendencies in response to the presentation of emotional faces [24, 31], with the enhanced amygdala-FFA connectivity during processing of emotional face expressions [6, 32], and with the increased activity in both FFA and amygdala during the generation of automatic responses toward faces with negative emotional valence [33]. We suggest that the aPFC implements emotional control by downregulating activity in FFA and amygdala, reducing the gain of these automatic stimulus-response associations when they need to be replaced by rule-based behaviors [25, 31, 34]. An alternative possibility, namely that the increased FFA and amygdala activity is compensatory in nature, would not parsimoniously fit with the increased error rate on those trials requiring emotional control. Second, PPC activity decreased after aPFC inhibition. The PPC plays an important role during control processes involving rule selection, such as switching, competition, and updating of stimulus-response associations [5, 26, 35]. Inhibition of the aPFC could have reduced the efficacy of its direct projections to the PPC [36, 37], likely compromising the ability of the aPFC to bias the PPC away from the automatic stimulus-response association in order to complete the rule-driven response when required [38]. Other portions of the distributed parieto-frontal circuit involved in the maintenance and updating of arbitrary stimulus-response associations [39, 40] were not equally influenced by the aPFC as the PPC, possibly a reflection of less robust monosynaptic connectivity with the aPFC [37].

## Methodological Considerations

It might be argued that the cerebral effects of cTBS reported here lack anatomical specificity. First, they are spatially distributed over a large circuit. In fact, this finding illustrates the importance of quantifying the effects of cTBS manipulations beyond the targeted area, extending previous observations on the functional relevance of spatially remote TMS effects [41, 42]. Second, we applied cTBS only to the left aPFC. Yet, the cerebral effects of cTBS clearly illustrate that the intervention inhibited aPFC in both hemispheres during performance of the AA task, in line with previous functional magnetic resonance imaging findings [2]. Third, the cTBS effects might have been further qualified by using additional (excitatory) TMS control conditions over aPFC. Unfortunately, pilot studies revealed that participants could not easily tolerate other TMS protocols (such as intermittent TBS; [4]) at the aPFC site.

## Conclusion

Inhibition of the left lateral aPFC disturbs the control of social emotional actions, such that participants follow their automatic emotional tendencies even when the situation would require them to override those stimulus-response mappings with rule-driven behavior. After aPFC inhibition, brain areas important for automatic emotional processing increased their activity, whereas areas implicated in rule selection showed a decreased activity. These findings indicate that aPFC alterations impair the coordination between emotional processing and rule-driven behavior. This altered coordination might form a crucial element for understanding social psychopathologies, like social anxiety, psychopathy, and conduct disorder, known to display dysfunctional prefrontal activity [9, 43]. It remains to be seen how aPFC inhibition disturbs the temporal dynamics of the distributed circuits supporting emotional control.

### Experimental Procedures

#### Participants

Forty-one males were screened for participating in the experiment. The analyses reported in this study are based on 24 participants that fit the inclusion criteria (see TMS procedure) and completed the four experimental sessions. The participants were right-handed (Edinburgh Handedness Inventory [44] >45), young (age: 18–25 years), and had normal or

corrected-to-normal vision and no history of psychiatric or neurological illness. After providing a written informed consent according to the guidelines of the local ethics committee (Commissie Mensgebonden Onderzoek region Arnhem-Nijmegen, The Netherlands), they were prescreened for contraindications of TMS and informed on the experimental procedures. All participants received payment or course credits for their contribution.

### Experimental Design

The experiment consisted of four sessions. During session 1, participants were familiarized with the experiment. They were trained in the AA and control task while a structural magnetic resonance image (sMRI) of their brain was acquired (15 min). The sMRI scan was followed by a resting-state functional MRI scan (9 min, not included in this report). After leaving the scanner, they completed a series of questionnaires (10 min). Hereafter, the participants were brought to the TMS lab, where resting and active motor thresholds (rMT and aMT, respectively) were determined [45], and a frameless stereotactic system (BrainSight, Rogue Research Inc.) was calibrated, linking each participant's anatomical scan and TMS stimulus locations (aPFC [2] and vertex) to his location in the TMS lab. rMT and aMT were used to calibrate the TMS stimulator output value for the subsequent TMS protocols. Furthermore, each participant received a sample of the cTBS protocol used in the following sessions for 10 s on the vertex at 100% and on the aPFC at 10% and 100% of the determined stimulator output. Session 1 occurred at least 1 week before session 2.

During sessions 2, 3, and 4, participants received the three TMS protocols used in this study (Figure 1C), in a counterbalanced order. Each session was separated by at least 1 week (maximum 2 weeks) and occurred at the same time of the day (±1 hr) for each participant. During each of these three sessions, the participants completed an informed consent form and several collateral measures were acquired (e.g., mood questionnaires). Using the calibrated frameless stereotactic system, the TMS coil was positioned over the relevant brain location (either aPFC or vertex). After delivery of the TMS protocol (40 s), the participants stared at a white wall for 1 min and then walked to the MR scanner (25 m away). Tasks performance and MR acquisition started ±8 min after onset of the TMS protocol, lasting for 25 min. The two tasks used in this study were administered in between-subjects counterbalanced order. Details on the task, MRI and TMS procedures, and the analyses can be found in the Supplemental Experimental Procedures.

### Supplemental Information

Supplemental Information includes two tables, Supplemental Results, and Supplemental Experimental Procedures and can be found with this article online at doi:10.1016/j.cub.2011.08.050.

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