

Emotion regulation before and after transcranial magnetic stimulation in obsessive compulsive disorder

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Background. Impaired emotion regulation may underlie exaggerated emotional reactivity in patients with obsessive compulsive disorder (OCD), yet instructed emotion regulation has never been studied in the disorder.

Method. This study aimed to assess the neural correlates of emotion processing and regulation in 43 medication-free OCD patients and 38 matched healthy controls, and additionally test if these can be modulated by stimulatory (patients) and inhibitory (controls) repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (dlPFC). Participants performed an emotion regulation task during functional magnetic resonance imaging before and after a single session of randomly assigned real or sham rTMS. Effect of group and rTMS were assessed on self-reported distress ratings and brain activity in frontal-limbic regions of interest.

Results. Patients had higher distress ratings than controls during emotion provocation, but similar rates of distress reduction after voluntary emotion regulation. OCD patients compared with controls showed altered amygdala responsiveness during symptom provocation and diminished left dlPFC activity and frontal-amygdala connectivity during emotion regulation. Real *v.* sham dlPFC stimulation differentially modulated frontal-amygdala connectivity during emotion regulation in OCD patients.

Conclusions. We propose that the increased emotional reactivity in OCD may be due to a deficit in emotion regulation caused by a failure of cognitive control exerted by the dorsal frontal cortex. Modulatory rTMS over the left dlPFC may influence automatic emotion regulation capabilities by influencing frontal-limbic connectivity.

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Introduction

Obsessive compulsive disorder (OCD) is a debilitating psychiatric disorder characterized by the presence of obsessions (repetitive intrusive thoughts) and/or compulsions (repetitive ritualistic behaviors; APA, 2013). When confronted with disease-relevant stimuli patients with OCD, compared with healthy individuals, experience higher anxiety levels (van den Heuvel *et al.* 2004; Schienle *et al.* 2005), greater attentional bias (van den Heuvel *et al.* 2005b; Moritz *et al.* 2009) and increased

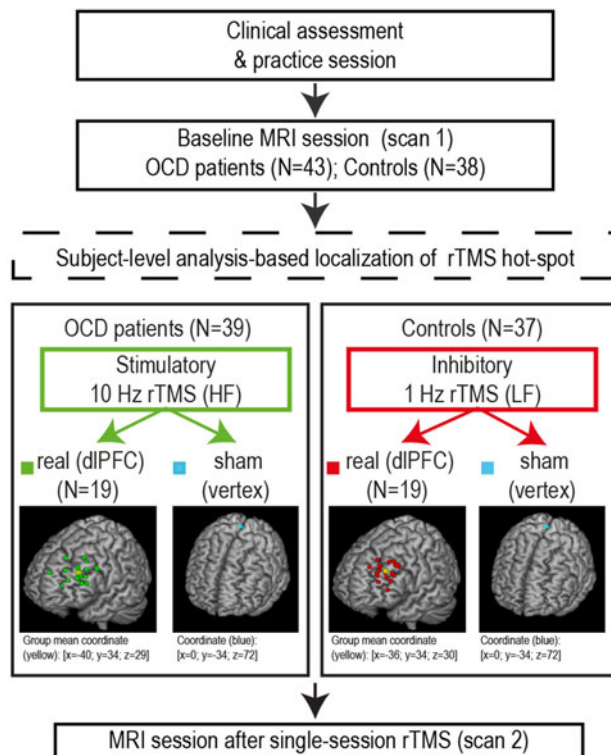
brain activity as measured by positron emission tomography and functional magnetic resonance imaging (fMRI) in ventral frontal and (para)limbic regions such as the rostral anterior cingulate cortex (rACC) and the amygdala (Rotge *et al.* 2008). Cognitive-behavior therapy (CBT) is the first-line treatment of choice for OCD (Franklin & Foa, 2011). In addition to exposure *in vivo* with response prevention, CBT for OCD also involves teaching patients emotion regulation strategies to help cognitively reframe, i.e. reappraise, negative symptom-eliciting situations as non-threatening. It has been hypothesized that the exaggerated emotional reactivity in OCD is related to emotion regulation impairments (Mataix-Cols & van den Heuvel, 2006).

Emotion regulation is thought to result from an intricate interplay between automatic bottom-up appraisals of a given stimulus in ventral emotion processing

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(a)



(b)

Task design with two instruction conditions:

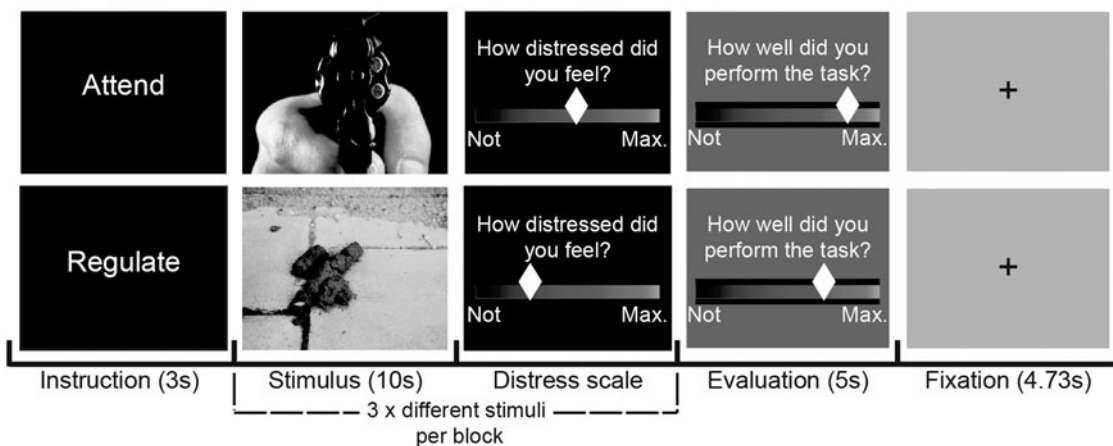


Fig. 1. (a) Design – study. Participants visited the VU University medical center on three occasions within the course of 1–4 weeks. During the first session participants underwent a psychiatric screening and practiced the emotion regulation task. During the second session participants had a first (baseline) functional magnetic resonance imaging (fMRI) scan session. During the third session participants received real or sham repetitive transcranial magnetic stimulation (rTMS) prior to a second fMRI scan session. The location of rTMS stimulation spots, i.e. individual dlPFC hot-spots and group mean coordinate (yellow) of OCD patients (left; green), controls (right; red), and the vertex coordinate (blue), are displayed at the bottom. Stimulation spots and all reported imaging results are overlain on the ch2better MNI template with MRICron (<http://www.mccauslandcenter.sc.edu/mricron/>), and all reported coordinates (x/y/z) are in Montreal Neurological Institute (MNI) space. HF, High-frequency (10 Hz); LF, low frequency (1 Hz). (b) Design - emotion regulation task. Participants viewed general fearful stimuli, neutral stimuli, and three OCD-related picture categories targeting contamination concerns (OCD wash), checking (OCD check) and ordering (OCD symmetry) under two possible instruction conditions. Participants attended to or regulated fear or OCD-related stimuli; attending to neutral stimuli was the baseline condition. Depicted are two blocks with the two possible task instructions. During the regulate condition participants were instructed to ‘reappraise [i.e. reinterpret] the stimulus such that it elicits less negative affect’. During the attend condition participants were instructed to ‘experience the stimulus naturally’. Fear and OCD-related pictures were presented both during attend and regulate; neutral only during

regions such as the amygdala, and top-down stimulus appraisal by mostly frontal control regions such as dorsolateral prefrontal cortex (dlPFC) and the dorsomedial prefrontal cortex (dmPFC; medial frontal wall including the (pre)supplementary motor area (SMA) and dorsal ACC) (Phillips *et al.* 2003a; Ochsner & Gross, 2007). These frontal and cingulate areas are part of fronto-parietal cognitive-linguistic control networks implicated in effortful (i.e. explicitly applied) reappraisal by cognitively reframing the affective meaning of a negative stimulus in more neutral terms (Dosenbach *et al.* 2007; Ochsner & Gross, 2007). Dysfunctional interactions of the dorsal-ventral circuitries are hypothesized to be responsible for pathological emotional experiences in psychiatric patients (Phillips *et al.* 2003b). Studies in non-psychiatric participants indeed showed that cognitive reappraisal recruits the dlPFC and dmPFC, resulting in down-regulation of the amygdala (Ochsner *et al.* 2012). Impaired emotion regulation is found in anxiety (Goldin *et al.* 2009a; Hermann *et al.* 2009) and depression (Johnstone *et al.* 2007; Kanske *et al.* 2012). In OCD, structural and functional neuroimaging studies have shown deficits in brain areas associated with the ventral-dorsal circuitries (Menzies *et al.* 2008; de Wit *et al.* 2012, 2014). Some of these functional deficits have shown to normalize after symptom improvement (e.g. Huyser *et al.* 2010; Vriend *et al.* 2013). These findings suggest the hypothesis that failure in emotion regulation in OCD may be related to either a deficit in dorsal control functioning and/or hyperactivation in the ventral system. The neural correlates of instructed effortful emotion regulation in OCD, however, have never been studied.

With repetitive transcranial magnetic stimulation (rTMS) activity of the dorsal system (and therefore also cognitive control) may be modulated. rTMS is a non-invasive brain stimulation technique in which a patch of neural tissue is electrically stimulated by rapidly changing electromagnetic fields. A single session of rTMS changes neural functioning from minutes to hours after stimulation. Single-session high-frequency (HF) rTMS (>5 Hz) is thought to result in temporary excitation of a brain area, and low-frequency (LF) rTMS (≤ 1 Hz) in inhibition (Reithler *et al.* 2011). Single-session rTMS on frontal-parietal regions in combination with fMRI is used to probe brain function and has been shown to modulate behavior and brain activity during resting state, executive functioning and emotional tasks in healthy and clinical samples

(Harmer *et al.* 2001; Guse *et al.* 2010; van der Werf *et al.* 2010; van den Heuvel *et al.* 2013). A multi-modal imaging study combining rTMS with fMRI enables visualization of its effects on instructed emotion regulation and may herald future clinical studies combining rTMS with CBT in OCD.

The present study aimed to increase our understanding of the neural basis of OCD by probing emotional reactivity and regulation in medication-free adults with OCD and demographically matched healthy controls. Additionally, we wanted to visualize the effect of rTMS on emotion regulation. To this aim, we employed an emotion regulation paradigm with general fear and OCD-specific stimuli during fMRI scanning before and after a single session of rTMS on the left dlPFC using individual fMRI-based neuronavigation. We hypothesized that in OCD patients compared with controls, effortful emotion regulation would result in less effective anxiety reduction, associated with decreased recruitment of dorsal cognitive control areas. Further, we hypothesized that stimulatory HF rTMS *v.* sham would improve emotion regulation in patients, whereas inhibitory LF rTMS *v.* sham would temporarily impair it in controls.

Method

Study procedure

Overall, 43 OCD patients and 38 controls participated in the study (see Fig. 1a for study design, Table 1 for sample characteristics, and Supplementary Method S1.1 in the online data supplement for exclusions). Patients were recruited through outpatient clinics within The Netherlands OCD Association (Schuurmans *et al.* 2012), the Academic Anxiety Center Altrecht (Utrecht, the Netherlands) and online advertisements. Controls were recruited by local and online community advertisements.

We screened all participants for Axis-I psychiatric disorders with the Structural Clinical Interview for DSM-IV (First *et al.* 2002). OCD severity and symptom dimensions were assessed with the Yale-Brown Obsessive-Compulsive Scale (YBOCS; Goodman *et al.* 1989) and the Padua Inventory – Revised (Padua-IR; Van Oppen *et al.* 1995), respectively. Mood was assessed with the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979). The emotion regulation questionnaire (ERQ; Gross &

attend. For each block three pictures of a similar picture type were presented. After each picture participants rated their level of distress. After three pictures, participants were asked to evaluate how well they felt able to perform the task. Each block ended with a washout period (fixation). Each session 27 blocks (three blocks per condition) were presented with a total task duration of about 26 min.

Table 1. Demographic and clinical characteristics

	OCD patients (N = 43)		Controls (N = 38)		Statistical analysis	
	Mean	S.D.	Mean	S.D.	t (df = 79)	p value
Demographic data						
Age (years)	38.4	10.0	39.6	11.4	-0.517	0.606
Gender [men:women (% men)]	21:22	(49%)	18:20	(47%)	$\chi^2 = 0.017$	0.895
Handedness [right:left (% right)]	36:7	(84%)	34:4	(90%)	$\chi^2 = 0.569$	0.451
Educational level (years) ^a	5.9	1.9	5.9	2.0	796.5 ^b	0.845
Clinical data						
YBOCS score (points)	21.6	6.1	-	-	-	-
Padua-IR, total score (points)	53.4	25.0	9.0	8.3	54.5 ^b	<0.001
Padua-IR, washing score (points)	10.1	10.1	1.3	2.5	322.0 ^b	<0.001
Padua-IR, checking score (points)	13.2	6.9	1.9	2.6	126.0 ^b	<0.001
Padua-IR precision score (points)	5.8	4.6	0.8	1.1	245.5 ^b	<0.001
MADRS score (points)	11.2	8.1	0.8	1.4	102.0 ^b	<0.001
ERQ Reappraisal	4.1	1.3	4.9	1.1	508.0 ^b	0.003
ERQ Suppression	3.2	1.4	3.0	1.1	758.0 ^b	0.579
Current co-morbidity [Y:N (% yes)]	24:19	56%	-	-	-	-

^a Educational level was recorded in nine levels ranging from 1 (no finished education) to 9 (university training).

^b Mann-Whitney *U* test, *U* (df = 79).

χ^2 ; Chi-square test (df = 1); Padua-IR, Padua Inventory - Revised; MADRS, Montgomery-Åsberg Depression Rating Scale; ERQ, Emotion Regulation Questionnaire; YBOCS; Yale-Brown Obsessive Compulsive Symptom Severity Scale.

John, 2003; Koole & Jostmann, 2004) assessed to what extent participants used reappraisal and suppression as emotion modulating strategies in daily life. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971). All participants were aged between 18 and 65 years and all participants had (corrected to) normal vision.

Exclusion criteria were psychoactive medication use, current or past psychosis, major physical illness, a history of major neurological illness and MRI contra-indications. Patients were medication-free for at least 4 weeks. Patients had to have a primary diagnosis of OCD, but without predominant hoarding; psychiatric co-morbidity (including tic disorders) was not an exclusion criterion. Controls had no current DSM-IV Axis-I diagnosis.

The authors assert that all procedures contributing to this work comply with the ethical standards of the local medical ethical review board on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants provided written informed consent.

Sample characteristics

OCD patients and controls at baseline were well matched (Table 1). Patients compared with controls scored higher on OCD and depression measures and had lower ERQ-reappraisal but similar ERQ-

suppression scores. Twenty-four (56%) OCD patients met criteria for one or more current co-morbid Axis-I diagnosis (see Supplementary Method S1.1).

Randomization of patients and controls to the real and sham rTMS condition resulted in equal demographic, clinical and baseline task-performance measures (all $p > 0.1$; data not shown), apart from co-morbidity, which was significantly higher in patients in the real (79%) *v.* the sham (30%) rTMS group ($p = 0.004$). The mean interval between MRI sessions (11 days), between rTMS and MRI scanning (6 m 10 s), and the resting motor threshold (48%), did not differ significantly between the real and sham rTMS groups ($p > 0.05$).

Experimental task

Participants performed an OCD-specific emotion regulation task during fMRI scanning (see Fig. 1b and Supplementary Method S1.2 for additional details regarding task design and stimulus selection). Subjective distress ratings for each condition were used as behavioral outcome measures.

Statistical analysis

Group differences in demographics, clinical measures and task-related measures between patients and controls overall, and real rTMS and sham rTMS subsamples

were analyzed with SPSS v. 15 (SPSS Inc., USA). Since the distress rating data did not meet parametric assumptions, planned repeated-measures analyses of variance (ANOVAs) could not be performed. We therefore analyzed the data with non-parametric tests. Results were considered significant at $p < 0.05$ after Bonferroni correction for the number of comparisons per investigated effect; trends were set at $0.05 < p < 0.10$.

To assess *emotion provocation at baseline* we computed mean distress ratings collapsed over instruction [fear distress rating = (fear attend + fear regulate)/2; OCD distress rating = (OCD attend + OCD regulate)/2]. The fear, OCD and the neutral distress ratings were entered in a Friedman's ANOVA per group to assess within-group effects of picture type. This ANOVA was followed up by Wilcoxon signed-rank tests comparing fear distress *v.* neutral and OCD distress *v.* neutral within groups (Bonferroni correction $p < 0.05/2$). Mann-Whitney tests compared the mean fear, mean OCD and neutral distress ratings between the groups to assess differences in emotion provocation (Bonferroni correction $p < 0.05/3$).

To assess *emotion regulation at baseline* we computed the mean score for the attend and regulate instructions over all conditions [attend = (fear attend + OCD attend)/2; regulate = (fear regulate + OCD regulate)/2]. To assess within-group instruction effects, these overall attend and regulate scores (main effect; $p < 0.05$), as well as, the attend and regulate distress ratings per picture type (fear, OCD; $p < 0.05/2$) were compared with Wilcoxon signed-rank tests. We computed fear difference and OCD difference scores as a measure of emotion regulation (fear difference = fear attend - fear regulate; OCD difference = OCD attend - OCD regulate). These difference scores were compared between the groups with Mann-Whitney tests ($p < 0.05/2$).

In the exact same manner we analyzed emotion regulation task performance after rTMS (performance during scan 2) between the groups of real (10 Hz) and sham (10 Hz) OCD patients and between real (1 Hz) and sham (1 Hz) controls, respectively. Additionally, given our fixed-order repeated-measures design, we compared distress ratings of scans 1 and 2 within groups with Wilcoxon signed-rank tests ($p < 0.05/4$), and we calculated change scores between distress ratings of scan 1 and those of scan 2 and compared them between the groups with Mann-Whitney tests ($p < 0.05/4$).

Spearman's rho was used to assess correlations between clinical variables (YBOCS, MADRS, ERQ) and reappraisal performance (the difference between attend minus regulate distress ratings) in patients.

fMRI analyses

Functional gradient echo-planar and structural T1-weighted imaging was performed on a GE Signa

HDxt 3.0-T MRI scanner (General Electric, USA). See Supplementary Method S1.3.1 for imaging acquisition parameters and preprocessing steps. To probe the blood-oxygen-level dependent (BOLD) response related to emotion processing and regulation during scans 1 and 2, different subject-level and group-level analyses were performed (see also Supplementary Method S1.3.2). In all first-level analyses nine regressors of interest contained the onsets of the pictures [neutral attend, fear attend/regulate, OCD (wash/check/symmetry) attend/regulate]. Regressors of no interest comprised the rating scales and instruction periods (boxcars, duration = 5 s and 3 s) and the participants' movement parameters. Fixation periods remained unmodeled as a low-level implicit baseline. A high-pass filter (128 s cut-off period) was used to remove noise associated with low-frequency confounds. All second-level group comparisons were masked by relevant within-group effects at $p < 0.05$ uncorrected. Since in this study we were interested in what is common to all OCD patients and since most patients appeared to have mixed symptoms, OCD-related contrasts were averaged over all OCD stimuli.

In Analysis 1 we assessed *emotion provocation at baseline*. To accurately model the fast limbic response associated with emotion processing and account for possible differences in hemodynamic response function (HRF) shape between brain regions and study groups (Larson *et al.* 2006; Caseras *et al.* 2010; Waugh *et al.* 2010), conditions at the participant level were entered as delta functions and convolved with both the canonical HRF and its time and dispersion derivatives. Contrast images containing parameter estimates for comparisons of interest were subsequently entered into a second-level mixed ANOVA with group [OCD patients ($N = 43$); controls ($N = 38$)] as between-participant factors and picture type (fear > neutral; OCD-related > neutral), and HRF regressor (3) as within-participant factors to assess effects of group and group \times picture type interactions.

In Analysis 2 we assessed *emotion regulation at baseline*. Since reappraisal is characterized by an early recruitment of control areas (Goldin *et al.* 2008, 2009a, b, Hermann *et al.* 2009; Lang *et al.* 2012), the 10 s stimuli were split in an early (1st 5 s) and late (6–10 s) boxcar per condition. These boxcars were convolved with the canonical HRF. At the participant level, regulation was thus contrasted with attend per picture type (fear regulate > attend; OCD-related regulate > attend) for the early time bin only. We assessed main effect of task over all subjects ($N = 81$) in a mixed ANOVA with group (patients, controls) and picture type (fear regulate > attend; OCD-related regulate > attend). Since regulation of OCD-related stimuli seemed behaviorally relevant for patients only, group

comparisons were subsequently performed per picture type (fear regulate > attend; OCD-related regulate > attend) using two-sample *t* tests. Analyses of covariance were performed between reappraisal performance (the difference between attend and regulate distress ratings) and YBOCS severity score (patients only) on regulation-related BOLD response at baseline (contrasts: fear or OCD-related regulate > attend).

Analysis 3 probed the effects of real *v.* sham rTMS on emotion regulation within OCD patients [real (10 Hz): $N=19$; sham (10 Hz): $N=20$] and controls [real (1 Hz): $N=19$; sham (1 Hz): $N=18$]. Because of our fixed-order repeated-measures design our rTMS analysis was two-fold. Two-sample *t* tests were performed between the real and sham rTMS groups on day 2 for the BOLD response related to the general process of picture appraisal regardless of instruction conditions (condition-independent contrast: all pictures > fixation) and for emotion regulation contrasts: (fear regulate > attend; OCD-related regulate > attend). Additionally, group \times session effects were assessed, by comparing the sham rTMS and real rTMS groups on subject-level *change* contrasts over sessions (all pictures > fixation, day 1 > 2; fear or OCD-related regulate > attend, day 1 > 2).

Imaging results were considered significant when controlled for type I errors after small-volume family-wise error (FWE) correction (Worsley *et al.* 1996) with a 10 mm-radius sphere in *a priori* regions of interest (ROIs) concerning the ventral-dorsal emotion regulation circuitry (i.e. amygdala, rACC, dlPFC and dmPFC as assessed with the WFU Pick atlas; Maldjian *et al.* 2003) Bonferroni-corrected for the number of ROIs ($p_{FWE-SVC} < 0.0125$) after image-thresholding at $p < 0.001$ uncorrected. Whole-brain voxel-wise FWE-corrected results are reported as well. Given that this is the first report of emotion regulation in OCD and the exploratory nature of our TMS experiment (Volman *et al.* 2011), additional results are reported for exploratory purposes at $p < 0.001$ uncorrected (Lieberman & Cunningham, 2009) and a minimum cluster-extent (k_c) of 3 voxels as well.

To specifically test for regulation-related changes in frontal-amygdala connectivity between the groups (Goldin *et al.* 2013) we performed a *post-hoc* general psycho-physiological interaction (gPPI) (McLaren *et al.* 2012), using the left dmPFC as a seed region (sphere with 10 mm radius around coordinate of main effect: $x/y/z = -9/8/64$; chosen since it was recruited during emotion regulation in both groups) and the bilateral amygdala as ROI. With gPPI all relevant task conditions and interactions can be modeled simultaneously, resulting in better model fit compared with traditional PPI (McLaren *et al.* 2012). At baseline dmPFC connectivity on the fear regulate > attend

contrast was compared in a second-level *t* test in SPM. To assess how rTMS affected dmPFC-amygdala connectivity, we used the MarsBar toolbox (<http://marsbar.sourceforge.net>) to extract mean beta values in bilateral amygdala (see Supplementary Results S2.2) on scans 1 and 2 in the real and sham rTMS groups and performed a repeated-measures ANOVA in SPSS with rTMS group as between-subject factor, session as within-subject factor, and the change in fear attend distress ratings over sessions as a covariate.

TMS protocol

Offline rTMS was applied using a hand-held statically cooled figure-of-eight TMS coil (Medtronic MagOption) under guided real-time neuronavigation (Visor v. 1.0, Eemagine GmbH, Germany). Participants were randomly assigned to the real (dlPFC) or sham (vertex) rTMS condition. Coordinates for stimulation in the active condition were based on a participant-specific functionally derived hot-spot (Sack *et al.* 2009; see Fig. 1a and Supplementary Method S1.4 for hot-spot definition and localizations). In the active (dlPFC) condition, patients ('therapy model') received 10 Hz rTMS over left dlPFC at 110% of resting motor threshold during 20 min in 30 10-s trains with a 30-s inter-train-interval (Conca *et al.* 2002), which resulted in 3000 pulses in total. Controls ('virtual lesion model') in the active dlPFC condition received 1 Hz rTMS for 20 min (Rossi *et al.* 2009; Siebner *et al.* 2009), resulting in 1200 pulses in total. In the sham condition, the protocol was similar to the active condition of patients (10 Hz) and controls (1 Hz), respectively, except that the coil localization was ~ 2 cm behind the vertex. Participants were naive to rTMS and blind to stimulation condition.

Results

Emotion regulation task performance in OCD

At baseline (see Fig. 2a; Supplementary Table S1), distress ratings in patients compared with controls were higher for fear ($U = 417$, $p < 0.001$) and OCD stimuli ($U = 236$, $p < 0.001$), but not neutral stimuli ($p > 0.1$). There was a significant within-group effect of picture type [OCD: $F_r(2,40) = 68.0$, $p < 0.001$; controls: $F_r(2,35) = 50.4$, $p < 0.001$], due to fear stimuli (OCD: $Z = -5.6$, $p < 0.001$; controls: $Z = -4.5$, $p < 0.001$) and OCD stimuli (OCD: $Z = -5.5$, $p < 0.001$; controls: $Z = -3.5$, $p < 0.001$) being rated significantly more distressing than neutral stimuli.

When comparing the fear and OCD difference scores, the groups did not differ in fear regulation ($p > 0.1$), but patients compared with controls had a significantly larger regulation effect on OCD-related stimuli ($U = 545$, $p < 0.01$). There was a main effect of

instruction collapsed over picture types in both groups with distress ratings being higher in the attend *v.* the regulate condition (OCD: $Z = -3.6$, $p < 0.001$; in controls this was at trend-level: $Z = -1.9$, $p = 0.06$). In patients the instruction effect was significant in both the fear and OCD-related stimuli (both $p < 0.005$), whereas in controls it was present in fear ($p = 0.057$; trend) but not OCD-related ($p > 0.3$) stimuli.

In patients, YBOCS, but not MADRS, score correlated with ERQ reappraisal [YBOCS: $r_s(df = 41) = -0.50$, $p = 0.001$; MADRS: $r_s(df = 41) = -0.23$, $p = 0.13$]. YBOCS and MADRS scores did not significantly correlate with fear or OCD-related reappraisal success (difference scores) or with ERQ-suppression scores [$r_s(df = 41) < 0.23$, $p > 0.14$].

Neural correlates of emotion regulation in OCD

During emotion provocation (main effect of group) and especially during processing of disease-relevant stimuli (group \times picture type interaction) OCD patients compared with controls showed an increased amplitude and/or altered timing of the BOLD response in the right amygdala ($x/y/z = 27/-4/-17$, $Z = 3.9$, $k_e = 21$, $p_{FWE-SVC} = 0.004$) and occipital cortex at the uncorrected level (Supplementary Fig. S1, panels A and B and Supplementary Results S2.1).

During emotion regulation (see Fig. 2b, panels A and B), patients compared with controls showed decreased activity in left dlPFC ($p_{FWE-SVC} = 0.009$; fear regulation) and increased dmPFC activity ($p_{FWE-SVC} = 0.001$; OCD-related regulation). Analysis of main effect of task showed that over all participants ($N = 81$; Supplementary Fig. S1, panel C) and stimuli, reappraisal was associated with increased dmPFC and decreased rACC activity ($p_{FWE-SVC} < 0.005$). Within-group analyses (see Table 2, Supplementary Fig. S1, panel D) showed that emotion regulation was characterized by recruitment of bilateral dlPFC and left dmPFC in controls (fear regulation) and by left dmPFC activity in patients (OCD-related regulation).

In controls, activity of the right dlPFC [$\rho(df = 36) = 0.48$; $x/y/z = 30/35/28$, $Z = 3.8$, $BA9/36$, $k_e = 19$, $p_{FWE-SVC} = 0.004$] was associated with greater reduction of fear distress during fear regulation. In patients regulation success did not correlate with brain activity. Disease severity, however, correlated inversely with regulation-related activity in bilateral dmPFC ($p_{FWE-SVC} = 0.002$) and thalamus ($p_{FWE} = 0.04$; see Fig. 2b, panel C, Supplementary Table S3).

Post-hoc analyses showed that OCD patients with ($N = 24$) and without ($N = 19$) co-morbid diagnoses did not differ significantly on demographics, clinical data, baseline task performance (all $p > 0.05$), or brain activity during emotion regulation (data not shown).

Emotion regulation after rTMS

First, we compared groups during scan 2 (see Supplementary Table 4a). Single-session dlPFC rTMS was able to modulate dorsal frontal brain activity when we assessed the BOLD response related to the general process of picture appraisal regardless of instruction condition (condition-independent contrast): we observed sham-controlled excitation after HF rTMS in patients (left dmPFC: $p_{FWE-SVC} = 0.002$; right dlPFC: $p_{FWE-SVC} = 0.004$) and inhibition after LF rTMS in controls (left dlPFC $p_{FWE-SVC} = 0.08$, subthreshold). When assessing the effects of rTMS on emotion regulation specifically in controls, real *v.* sham LF rTMS did not affect ROI activity, but was at the uncorrected level associated with increased hippocampal activity. Patients receiving sham *v.* real HF rTMS had significantly increased dmPFC activity ($p_{FWE-SVC} = 0.009$) and at the uncorrected level, increased parahippocampal and opercular activity during emotion regulation. Task performance during scan 2 was not significantly different between the real *v.* sham rTMS groups (see Supplementary Table S2a, b; Supplementary Fig. S2).

Second, real *v.* sham rTMS did not significantly affect the relative change in task performance over sessions (see Supplementary Table S2a, b; Supplementary Fig. S2). In controls after sham LF rTMS the fear attend distress rating was reduced during session 2 compared to session 1 ($p = 0.01$). This was not the case after real LF rTMS ($p = 0.51$), and the between-group (sham *v.* real LF rTMS) interaction effects was not significant ($p = 0.21$). In patients the fear attend change score showed opposing effects, with a near-trend decrease in fear distress over sessions in patients after real HF rTMS ($p = 0.11$), a lack of decrease in the sham HF rTMS group ($p = 0.74$), and a non-significant group interaction ($p = 0.17$). When comparing the relative change in brain activity from session 1 to session 2, the real HF *v.* sham HF patients showed a relative decrease of dmPFC ($p_{FWE-SVC} = 0.001$) and, at the uncorrected level, occipital cortex, activity on the condition-independent contrast (see Fig. 3 and Supplementary Table S4a, b for all additional rTMS results). The real LF *v.* sham LF controls showed no significant ROI-corrected results over sessions. At the uncorrected level we found a relative increase of visual processing area activity on the condition-independent contrast. *Post-hoc* analysis showed that the changes in fear attend distress ratings correlated with relevant ROI brain activity (Supplementary Results S2.2).

Post-hoc frontal-limbic connectivity analyses

Results from the gPPI analysis showed that at baseline OCD patients, compared with controls, had less dmPFC-bilateral amygdala connectivity ($p_{FWE-SVC} <$

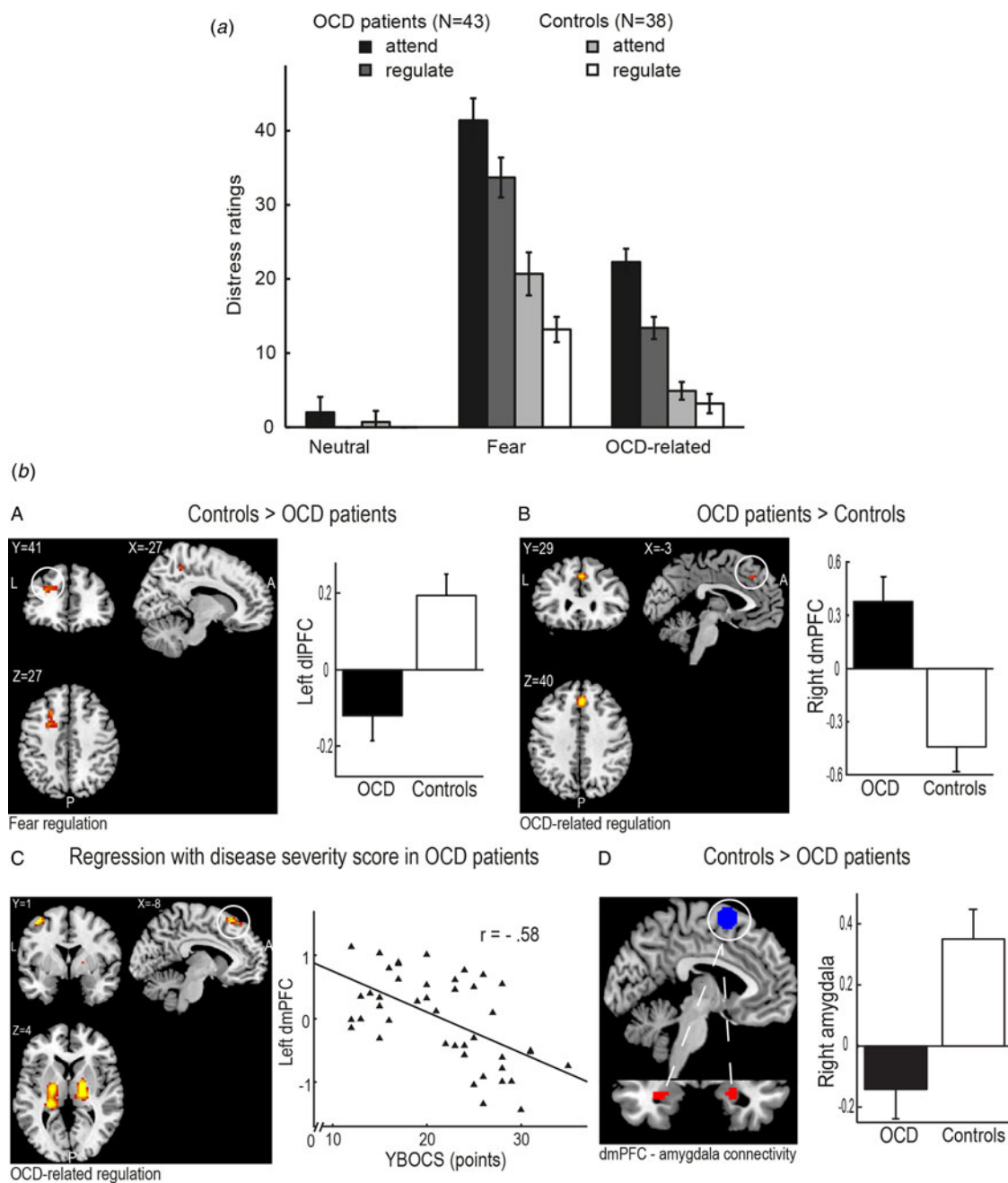


Fig. 2. (a) Baseline emotion regulation task performance. Bar graph depicting the mean (\pm standard error of the mean; s.e.m.) self-report distress rating per condition. (b) Neural correlates of emotion regulation at baseline (scan 1). **Panel A.** Decreased activity in left dmPFC ($x/y/z = -27/41/25$, $Z = 3.5$, $k_e = 42$) in OCD patients ($N = 43$) *v.* controls ($N = 38$) during fear regulation at baseline (contrast: fear regulate > attend). *Left:* Left dmPFC cluster from two-sample *t* test. *Right:* Parameter estimates of peak left dmPFC voxel in patients (black) and controls (white). At $p < 0.001$ whole-brain uncorrected level the dmPFC cluster also extends through BA 6/8 ($x/y/z = -21/17/40$, $k_e = 159$, $Z = 3.9$), and additional findings are left inferior parietal cortex ($x/y/z = -48/-31/22$, $Z = 3.8$, $k_e = 13$), right precuneus ($x/y/z = 15/-43/52$, $Z = 3.5$, $k_e = 12$), left precentral gyrus ($x/y/z = -45/-4/25$, $Z = 3.2$, BA 9, $k_e = 3$) and right superior frontal gyrus ($x/y/z = 21/26/37$, $Z = 3.2$, BA 8, $k_e = 3$). **Panel B.** Increased dmPFC activity ($x/y/z = 3/32/40$, $Z = 4.1$, $k_e = 40$) in OCD patients ($N = 43$) *v.* controls ($N = 38$) during OCD-related regulation at baseline (contrast: OCD-related regulate > attend). *Left:* Significant cluster in right dmPFC from two-sample *t* test. *Right:* Parameter estimates of peak right dmPFC voxel in patients (black) and controls (white). At the $p < 0.001$ uncorrected level an additional finding is the right anterior frontal cortex ($x/y/z = 27/59/1$, BA 10, $Z = 3.5$, $k_e = 4$). *t* values are displayed from $t = 3.2$ (threshold, red) to maximum (yellow; $t = 4.1$). **Panel C.** *Left:* *t* statistic image of regression analysis between Yale–Brown Obsessive Compulsive Scale (YBOCS) and brain activity during OCD-related regulation patients at baseline. Significant results in right

Table 2. Main effect of emotion regulation within controls and patients per picture type at baseline (scan 1)

	BA	Side	k_e	MNI coordinates			Z	$p_{FWE-SVC}$
				x	y	z		
Controls (N = 38)								
<i>Contrast: fear regulate > attend</i>								
Dorsolateral prefrontal cortex	9/10/46	R	53	33	44	37	4.11	0.001*
				27	38	31	3.51	
		L	2	-30	41	25	3.15	0.025
Postcentral gyrus	4	L	31	-48	-10	52	3.94	-
Dorsomedial prefrontal cortex (ACC/pre-SMA)	24/6	L	13	-15	2	43	3.66	0.006*
			2	-9	5	58	3.14	
Inferior frontal gyrus	44	L	21	-51	5	22	3.65	-
		R	3	45	11	10	3.19	-
Middle frontal gyrus	8	L	25	-21	20	46	3.54	-
<i>Contrast: OCD-related regulate > attend: n.s.</i>								
OCD patients (N = 43)								
<i>Contrast: fear regulate > attend: n.s.</i>								
<i>Contrast: OCD-related regulate > attend</i>								
Dorsomedial prefrontal cortex (SMA)	6	L	43	-6	-1	70	3.59	0.007*
				-9	8	64	3.33	
Caudate nucleus/Putamen	n.a.	R	9	18	17	4	3.54	-
		L	3	-18	2	7	3.39	-
		L	2	-15	14	7	3.10	-
Middle temporal gyrus	21	L	13	-51	-34	-8	3.37	-
			3	-57	-9	-8	3.21	-
Frontal operculum inferior	44	L	4	-57	8	10	3.31	-
Anterior insula	13	R	3	39	14	7	3.19	-

BA, Brodmann Area; ACC, anterior cingulate cortex; n.s., not significant; SMA, supplementary motor area.

One-sample t tests per group per contrast. Results are corrected for multiple comparisons at the voxel-level ($*p_{FWE-SVC} < 0.0125$; trends $p_{FWE-SVC} < 0.025$) in *a priori* regions-of-interest by small-volume correction with 10 mm sphere after thresholding at $p < 0.001$ uncorrected. Exploratory whole-brain results are presented at $p < 0.001$ uncorrected with a minimal cluster extent of 3.

0.0125; Fig. 2b, panel D). Repeated-measures ANOVA with factors rTMS group (real *v.* sham) and session (scan 1 *v.* 2) showed altered dmPFC-amygdala connectivity after real rTMS compared with sham in OCD patients (rTMS \times session interaction effect at trend-level in left amygdala [$F(36,1) = 3.7$, $p = 0.06$; right amygdala = n.s.: $p = 0.22$]). This interaction effect was due to dmPFC-left amygdala connectivity showing opposing effects after real TMS (mean beta day 1 = 0.06; day 2 = -0.18) compared to sham rTMS (mean

beta day 1 = -0.06; day 2 = 0.18). There were no significant effects in controls (all $p > 0.3$).

Discussion

To our knowledge this is the first study assessing the neural correlates of effortful emotion regulation in OCD patients *v.* healthy controls. Further, this is also the first study to experimentally probe the differential modulatory

thalamus ($Z = 4.5$) and left dmPFC ($Z = 4.0$). Image is thresholded at $p < 0.001$ whole-brain uncorrected. t values are displayed from red ($t = 3.3$ threshold) to yellow ($t > 4.5$). *Middle/right*: Scatter plot of parameter estimate of left dmPFC peak voxel and disease severity. **Panel D.** Decreased dmPFC-amygdala connectivity in patients *v.* controls during fear regulation (contrast: fear regulate > attend). *Left*: Top: seed region in dmPFC [blue; 10 mm sphere around ($x/y/z = -9/8/64$)]. *Bottom*: Results from two-sample t test of general psycho-physiological interaction analysis [red; right amygdala ($x/y/z = 24/-7/-20$, $z = 3.4$, $k_e = 3$); left amygdala ($x/y/z = -33/-10/-23$, $Z = 3.4$, $k_e = 15$)]. For illustration purposes image is thresholded at $p < 0.005$ uncorrected. *Right*: Parameter estimate of right amygdala peak voxel. S, Superior; P, posterior; L, left; A, anterior; r , Pearson's rho; k_e , cluster extent; dlPFC, dorsolateral prefrontal cortex; dmPFC, dorsomedial prefrontal cortex; All parameter estimates are in arbitrary units. Error bars represent s.e.m.

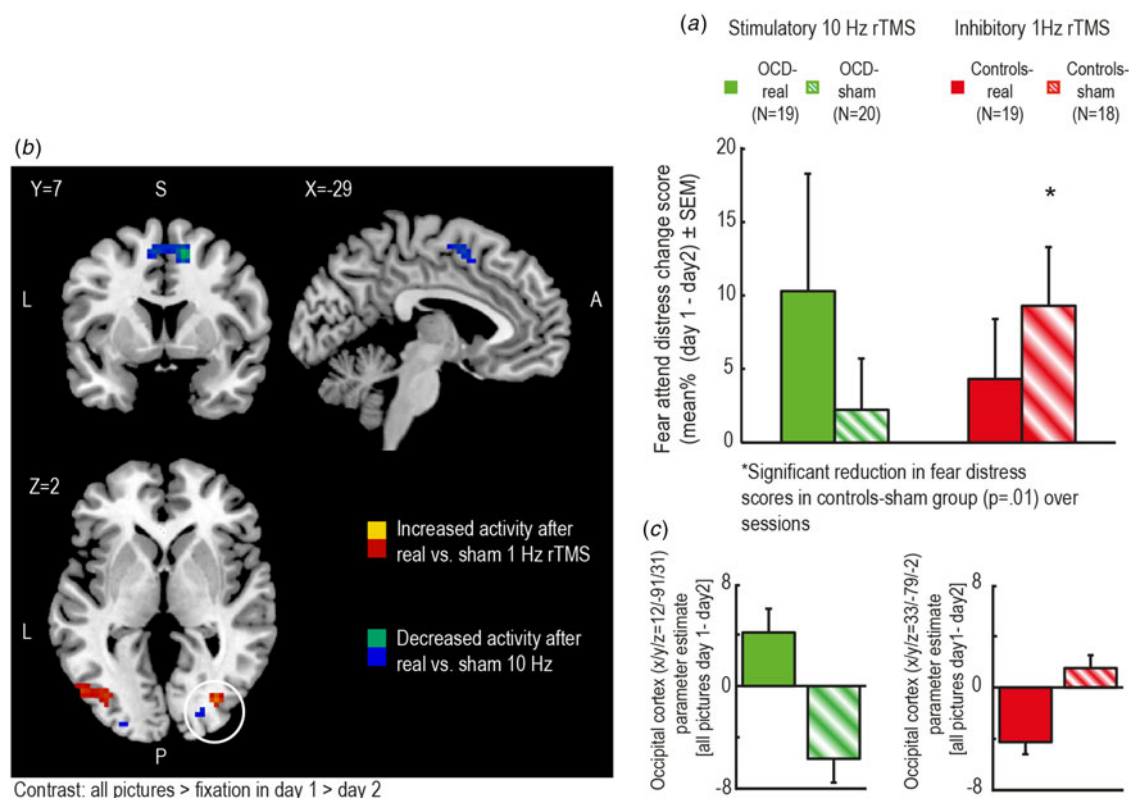


Fig. 3. Differential effects of real *v.* sham high-frequency (10 Hz) and low-frequency (1 Hz) left dlPFC repetitive transcranial magnetic stimulation (rTMS) on the change of fear distress ratings and brain activity from scan 1 to scan 2. (a) Bar graph depicting decrease of fear attend distress ratings from day 1 to day 2 after real (dlPFC) *v.* sham (vertex) stimulatory (10 Hz; OCD patients) and inhibitory (1 Hz; controls) rTMS. Within-group fear attend distress reductions (day 1–day 2) as tested with Wilcoxon-signed rank tests: OCD real ($Z = -1.6$, $p = 0.11$); OCD sham ($Z = 0.3$, $p = 0.74$); controls real ($Z = -0.7$, $p = 0.51$); controls sham ($Z = -2.4$; $*p = 0.01$). Between-group (real *v.* sham) effects were not significant ($p > 0.1$). (b) *t* statistic image, for illustration purposes thresholded at $p < 0.005$ uncorrected; *t* values are displayed from red ($t = 2.7$, controls) and blue ($t = 2.7$, patients) to yellow/green ($t > 5.0$). (c) Parameter estimate plot of the change of visual cortex activity in OCD patients (left) and controls (right) after rTMS. dlPFC, dorsolateral prefrontal cortex; %, percentage; error bars represent s.e.m.; parameter estimates are in arbitrary units.

effects of sham-controlled HF and LF single-session rTMS over left dlPFC on emotion processing and regulation-related brain activity in OCD patients and controls.

Emotional reactivity

OCD patients showed increased self-reported distress and abnormal activity in the amygdala and occipital cortex during processing of disease-related and general fear stimuli. This converges with prior findings of involvement of these regions in the processing of emotional intensity (Vaughn *et al.* 2010), and replicate findings of increased emotional reactivity in generally smaller samples of (often medicated) OCD patients (van den Heuvel *et al.* 2004; Rotge *et al.* 2008). Deviant timing of amygdala responses in OCD patients corroborates findings in spider phobics (Larson *et al.* 2006). Accounting for such changes may increase sensitivity of data analysis, since timing

rather than amplitude of the BOLD response may be altered in psychopathology (Caseras *et al.* 2010; Vaughn *et al.* 2010).

Emotion regulation

Although distress ratings to general fearful and OCD-related stimuli were significantly higher in OCD patients than controls, even in the regulation condition, the groups showed similar rates of distress reduction after reappraisal. At the neural level, patients and controls showed overlapping as well as distinct recruitment of known emotion regulation brain areas (Kalisch, 2009). Both groups recruited the dmPFC during emotion regulation. Only controls recruited bilateral dlPFC, and this was related to reduction of fear distress, underscoring the behavioral relevance of the dorsal PFC for emotion regulation in healthy participants (Drabant *et al.* 2009).

Cognitive reappraisal was not associated with down-regulation of amygdala activity, which may be due to the fast and short-lasting response in this region (Hermann *et al.* 2009). Reappraisal, however, was in both groups associated with decreased rACC activity. The rACC is part of the ventral emotion processing system (Phillips *et al.* 2003a), is structurally and functionally connected with the amygdala during emotional reactivity (Pezawas *et al.* 2005; Ghashghaei *et al.* 2007), and has been related to self-monitoring of negative affect (Ochsner *et al.* 2004).

Overall, our data show that when cued within the context of an experiment, patients with OCD can implement reappraisal as a cognitive-linguistic strategy to down-regulate negative affect. When doing so, however, OCD patients compared with controls showed less recruitment of the dlPFC, less dmPFC-amygdala connectivity (during fear regulation), and enhanced recruitment of dmPFC (during OCD-related regulation). Such dissociation of finding different reappraisal-related brain activity between psychiatric patients and controls under similar task performance has been reported before (Goldin *et al.* 2009a; Kanske *et al.* 2012), and underscores the added value of fMRI to detect changes in emotion regulation mechanisms in OCD. Diminished dlPFC and frontal-limbic connectivity during reappraisal-mediated down-regulation of negative affect in OCD is in accordance with emotion regulation studies in anxiety and depression (Goldin *et al.* 2009a; New *et al.* 2009; Erk *et al.* 2010) and with findings during executive functioning in OCD (van den Heuvel *et al.* 2005a; Remijnse *et al.* 2006; de Vries *et al.* 2014). Emotion regulation-related dlPFC activity has been associated with sustained amygdala down-regulation in controls (Erk *et al.* 2010), and combined with the finding of diminished dmPFC-amygdala connectivity, our data suggests that this hypoactivity of the dlPFC may reflect diminished ability of patients to control pathological anxiety in everyday life over longer stretches of time. Differential recruitment of regulatory brain regions in patients (dmPFC) and controls (dlPFC) could also be related to the use of different regulation strategies (Kanske *et al.* 2012). Although not an *a priori* ROI, we observed parietal hypoactivity during fear regulation in patients as well. In the context of the wider OCD literature (Menzies *et al.* 2008; de Wit *et al.* 2012), our data suggest that impaired cognitive control in OCD is related not only to dysfunction of the dorsal PFC but to a wider distributed frontal-parietal network.

Interpretation of the observed dmPFC hyperactivity in OCD patients during OCD-specific reappraisal is not straightforward, due to the absence of a direct association between the behavioral and neural level in patients. Also, in controls reappraisal did not significantly affect distress ratings or brain activity during

OCD-related stimuli, probably related to the low emotional relevance of OCD-related stimuli for healthy participants. We cannot rule out, however, that dmPFC hyperactivity is an indication of a compensatory mechanism in patients related to frontal-parietal failure. OCD patients overall, and especially those with higher disease severity, reported less use of cognitive reappraisal to modulate emotions in everyday life. Additionally, greater disease severity was related to less recruitment of dorsal regulation-related brain areas (including the dmPFC) and less rACC down-regulation (trend) during emotion regulation. This suggests that only patients that are less affected by the disease are able to use reappraisal in the context of the experiment as well as in everyday life, which seems in line with the hypothesis that reduced cognitive control over (para)limbic regions is at least a contributing mechanism in OCD pathophysiology.

Neuromodulatory effects of repetitive transcranial magnetic stimulation

In the present study we set out to assess if high-frequency rTMS over the left dlPFC would boost regulatory control in OCD patients, and if low-frequency dlPFC rTMS would decrease emotion regulation capabilities in controls. The data show that stimulatory high-frequency rTMS resulted in a *condition-independent* increase in dorsal frontal activity, and conversely inhibitory low-frequency rTMS in a reduction of dlPFC activity. rTMS did not significantly affect task performance during scan session 2. An interpretation of the observed differences in brain activity we specifically observed during *emotion regulation* on scan 2 may be that inhibition in controls resulted in increased task-related cognitive effort (increased hippocampal activity) and stimulation in patients induced increased task-related neural efficiency (with relatively reduced dorsal frontal activity on the emotion regulation contrast compared to the sham condition).

Further, LF and HF rTMS may have differentially affected the change in emotional saliency network activity *over sessions* in patients and controls. Reduced fear distress over sessions in the real *v.* sham HF rTMS patient group was associated with decreased brain activity in visual emotion processing areas (occipital cortex, rACC, amygdala) and with alterations in dmPFC-amygdala connectivity. By contrast, in the real LF control group, relatively increased fear distress over sessions was associated with increased visual processing related (occipital cortex) brain activity.

Overall, our rTMS findings are in line with other reports of frontal rTMS effects on local as well as distant connected brain regions (van der Werf *et al.* 2010; Reithler *et al.* 2011; Volman *et al.* 2011; van den Heuvel *et al.* 2013). Our results seem to indicate that dlPFC

rTMS affected more automatic (condition-independent) rather than effortful (reappraisal task specific) regulatory processes (Gyurak *et al.* 2011). We speculate that HF rTMS over dlPFC may thus be beneficial for fear extinction learning, an implicit regulatory process that is known to be deficient in OCD (Milad *et al.* 2013).

Limitations and strengths

A limitation of this study is that, unlike previous studies in anxiety (Goldin *et al.* 2009b; Hermann *et al.* 2009), comparison of disease-specific *v.* disease-unrelated emotion regulation was hampered by the absence of sufficient emotion induction of OCD-related stimuli in the control group. Nonetheless, comparison of fear regulation across the groups enabled us to assess general emotion regulation brain activity in patients and comparison across the OCD-related regulation contrast allows us to speculate about the function of disease-specific emotion regulation systems in OCD.

Further, like other reports of trend-level or task-order dependent effects of rTMS (Guse *et al.* 2010; van den Heuvel *et al.* 2013), our behavioral results from the rTMS challenge were present at liberal trend-level only. Although additional evidence, relating the changes in distress to changes in brain activity in relevant emotion processing and regulation brain areas, point to a similar conclusion, our rTMS results should be interpreted with caution and await empirical replication. Although comorbidity did not influence emotion regulation capabilities at baseline, a possible interaction of co-morbid diagnosis and response to rTMS cannot be excluded, given the significantly higher incidence of co-morbid diagnoses in patients randomly assigned to real *v.* sham rTMS.

The present study also has important strengths. First, we assessed emotion processing and regulation in a relatively large medication-free OCD sample. Second, we accounted for differential timing of neural processes during emotion provocation in our analysis. Third, we aimed to optimize modulatory effects of rTMS by using a functionally-localized hotspot under neuronavigation (Sack *et al.* 2009).

Conclusion

To conclude, we observed frontal-limbic and frontal-parietal dysfunction during effortful emotion regulation in OCD. Modulation of cortical excitability using rTMS over left dlPFC appears to affect automatic emotion regulatory processes, possibly by changing frontal-limbic connectivity.

Supplementary material

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0033291715001026>.

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Declaration of Interest

None.

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