

Accelerated TMS normalizes subgenual cingulate–default mode network coupling in depression: An observational 7 Tesla fMRI study

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Abstract

Background

Repetitive transcranial magnetic resonance imaging is an effective treatment for depression. Accelerated TMS-protocols (aTMS) are applied several times per day and hold promise to rapidly decrease depressive symptoms. This study used high-resolution 7-Tesla MRI to anatomically precisely investigate aTMS-induced alterations of resting state functional connectivity (rs-FC) of the subgenual anterior cingulate cortex (sgACC). We hypothesized that aTMS reduces hyperactivation of the sgACC by decreasing rs-FC with key cortical regions. Furthermore, we explore associations between sgACC related rs-FC alterations, depression severity and mindfulness, which is often impaired in depression.

Methods

Twenty-four patients with current depression underwent 7-Tesla MRI-scans before and after a two-week aTMS treatment series (target: left dorsolateral prefrontal cortex, total number of pulses: 24,000). Fifteen healthy controls were also scanned twice for comparison, without receiving aTMS. Group $\times$ time interactions of changes in sgACC seed-based rs-FC were calculated. In addition, we examined baseline group differences of sgACC rs-FC. Correlations between longitudinal changes in sgACC rs-FC, depression severity, and mindfulness, were calculated.

Results

aTMS reduced rs-FC between the sgACC and the precuneus (core part of the default mode network; DMN), normalizing elevated baseline rs-FC in depressed patients. No significant association was observed with changes in overall depression severity. However, decreases in sgACC–posterior DMN connectivity were significantly associated with improvements in mindfulness.

Conclusions

Treatment response in depression is associated with a normalization of rs-FC alterations between the sgACC and the DMN. Observed changes might reflect processes related to improvements in mindfulness.

Introduction

Major depressive disorder (MDD) is frequent and associated with a high disease burden, costs for society and significant room for treatment optimization (1, 2). Depressive episodes can be effectively treated with antidepressive medication and psychotherapy (3–5). Nevertheless, about a third of patients with difficult-to-treat depression (DTD) does not respond well to these treatments and efficacy of

pharmacological antidepressive trials decrease with each consecutive treatment failure (3). Thus, additional and complementary treatment modalities are warranted.

Treatment with repetitive transcranial magnetic stimulation (rTMS) is consistently recommended in guidelines for treating depression, due to high levels of evidence (6, 7). Recent clinical trials point to a more pronounced treatment response of rTMS in comparison to antidepressive switch or augmentation in patients with DTD (8, 9). Treatment with rTMS modulates large-scale brain networks by inducing focal electric currents in cortical tissue through electromagnetic induction generated by rapidly changing magnetic fields (10). Most commonly, an excitatory stimulation protocol is used targeting the left dorsolateral prefrontal cortex (dlPFC) (7, 11). A promising development is the application of accelerated TMS (aTMS, multiple TMS-sessions per day, normally in combination with an intermittent theta burst (iTBS)-protocol), which may facilitate more rapid treatment responses (12–15).

The efficacy of rTMS does not solely rely on local modulation of the dlPFC, but rather on modification of entire networks, which can be used for optimal TMS target localization (16–18). The subgenual anterior cingulate cortex (sgACC) may be of particular importance for the pathophysiology of mood disorders and treatment response. The sgACC is hyperactive in patients with depression (19–22), which may reverse following successful treatment (23). Furthermore, resting state functional connectivity (rs-FC) of the sgACC and regions of the default mode network (DMN) show potential to predict treatment response to both antidepressants and rTMS (17, 24–28). It is assumed that efficacy of rTMS is facilitated by reducing activity of the sgACC, which is functionally anticorrelated with the dlPFC (29, 30). This has led to rTMS-approaches that use rs-FC to specifically stimulate the subregion the left dlPFC that is most strongly anticorrelated with the sgACC (16, 31, 32). In this study, we used ultra-high field 7-Tesla MRI scans, which provide both a better signal-to-noise ratio than 3-Tesla MRI, and are applicable in patients with depression (33–35) to explore if aTMS of the left dlPFC normalizes pathological changes in rs-FC of the sgACC in patients with depression.

To capture additional clinically relevant domains beyond quantitative overall scores of heterogeneous symptoms of depression, we also assessed complementary psychopathological features associated with depression. Patients with depression often experience marked difficulties in emotion regulation which is closely linked to heightened rumination and negative affect, contributing to the persistence of depressive experiences (36). Rumination is a robust predictor of depressive relapse and recurrence and may improve with help of mindfulness-based interventions (37). This may in turn modulate functional connectivity of the DMN and the salience network (38–41), including the dlPFC, the target region of repetitive transcranial magnetic stimulation (rTMS) treatment in patients with depression.

It was the aim of this study to investigate aTMS-induced alterations of rs-FC of the sgACC. We hypothesizes that aTMS induces decreases in rs-FC between the sgACC and key cortical regions including parts of the DMN, which is crucial for emotion regulation and mindfulness (42), hereby potentially reversing group differences between patients with depression and healthy controls at baseline. Furthermore, we explore how these changes in rs-FC are associated with postulated

improvements of depression severity and mindfulness. As further secondary outcome measure, we investigated group differences in rs-FC of the sgACC at baseline.

Methods

Study participants

Patients of this observational study were recruited at the University Hospital of Psychiatry and Psychotherapy in Bern. Both inpatients and outpatients were included. Inclusion criteria for patients were age between 18 and 65 years, a current depressive episode, and planned enrolment in aTMS treatment. Both patients with major depressive disorder (MDD) and bipolar disorder (BD), according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by the American Psychiatric Association (43), were included. Exclusion criteria were psychotic disorders, substance use disorders other than nicotine, neurological disorders, claustrophobia, or other contraindications to perform a 7-Tesla MRI scan. The inclusion criterion for healthy controls was age between 18 and 65 years. Exclusion criteria were a current or lifetime history of a diagnosis of psychiatric or neurological disorders or a contraindication to perform a 7-Tesla MRI scan. Pregnancy was an additional exclusion criterion in all female participants. Written informed consent was obtained from all participants in the study. The study was approved by the local cantonal ethics committee (KEK-number: 2023 – 00134).

A total of 43 participants (26 patients and 17 healthy controls) were included. Two patients dropped out (1 due to side effects, and 1 due to harmful use of alcohol). Two controls were excluded (one control experienced claustrophobia, one control had a metal clip that posed a contraindication for the 7-Tesla fMRI-scan), resulting in a total of 24 patients with depression and 15 healthy controls. Twenty-three patients had a diagnosis of MDD and one patient had a diagnosis of bipolar depression type 2. Three patients had comorbid diagnosis of an anxiety disorder, and two patients had a comorbid attention deficit hyperactivity disorder (ADHD). All but two patients were on antidepressive medication during the aTMS treatment (selective serotonin reuptake inhibitors (SSRI) $n = 6$, dual antidepressants $n = 17$, tricyclic antidepressants $n = 3$, lithium $n = 5$, atypical antipsychotics $n = 7$). There was a wide range of number of episodes (minimum 1, maximum 26) and duration of episodes (minimum 1 month, maximum 32 months). Ten patients could not clearly state duration and number of episodes due to the chronic course of depression. The time interval between scans was 20 ± 5 days in patients and 21 ± 13 days in healthy controls. The difference in time interval was not statistically significant ($p = 0.79$).

Assessments

The Mini International Neuropsychiatric Interview (MINI) (44) was used for diagnosis of mental disorders according to DSM-5. Handedness was assessed with the Edinburgh Oldfield Inventory (45). Depression severity was assessed with the Montgomery Asberg Depression Rating Scale (MADRS) (46), and the Beck Depression Inventory II (BDI-II) (47). Mindfulness was assessed using the Comprehensive Inventory

of Mindfulness Experience CHIME (48, 49). Positive and negative affect were assessed using the Positive and Negative Affect Schedule (PANAS) (50)), providing independent scores for two broad affective domains. Positive affect reflects social activity and satisfaction, while negative affect relates to self-reported stress, coping difficulties, and health complaints. In healthy controls, questionnaires were applied once at the day of the first MRI scan. In patients with depression, questionnaires were administered at the day of the MRI scan before and after aTMS treatment.

Repetitive aTMS-treatment

aTMS-treatment was performed with a figure-8 coil using a MagPro R30 stimulator (Medtronic Functional Diagnostics). aTMS treatment was applied 5 times a week (Monday through Friday) for a period of 2 weeks, resulting in a total of 10 treatment days. The aTMS target site (left dlPFC) was determined with the Beam-F3 method (51). Resting state motor threshold was determined and stimulation performed with 120% resting state motor threshold of the right abductor pollicis brevis muscle (13). Four iTBS sessions were applied per day. Similarly to previous aTMS studies, there was a pause of 15 minutes between iTBS treatment sessions e.g. (52–54). Parameters for the iTBS-protocol were as described in (13): Triplets of 50 Hz bursts were repeated every 200 milliseconds (5 Hz). The 2-second trains were repeated every 10 seconds for a total of 600 pulses in an iTBS session. The duration was 3 minutes and 9 seconds per iTBS session. This resulted in 2,400 pulses per day and a total of 24,000 pulses during the 10 days of aTMS treatment.

Magnetic resonance imaging

MRI data were acquired using a Siemens Magnetom Terra 7T scanner (Siemens Healthcare, Erlangen, Germany) equipped with a 32-channel head/neck coil (Nova Medical, Wilmington, MA) at the Swiss Institute for Translational and Entrepreneurial Medicine (SITEM), in Bern, Switzerland. High-resolution T1-weighted structural images were obtained with a bias-field corrected 3D MP2RAGE sequence for acquisition of two gradient volumes (INV1 and INV2) and computation of a high-contrast volume (UNI) (FOV = $240 \times 240 \text{ mm}^2$, matrix = 384×384 , slices = 256, voxel resolution = $1 \times 1 \times 1 \text{ mm}^3$, TR/TE = 5000/2.98 ms, TI = 700 ms and T2 = 2500 ms). Resting-state fMRI data were acquired using a multiband echo-planar imaging (EPI) sequence (360 volumes; 60 slices; voxel size = $1.4 \times 1.4 \times 1.4 \text{ mm}^3$; field of view = $204 \times 204 \text{ mm}^2$; matrix = 102×102 ; TR = 1000 ms; TE = 24 ms; acquisition time = 6:00).

MRI preprocessing

Resting-state fMRI data were preprocessed using CONN version 22a (RRID:SCR_009550) (55). The preprocessing pipeline included motion realignment, slice-timing correction, coregistration to the anatomical images (MP2RAGE), normalization to the MNI template, and spatial smoothing with a 3 mm Gaussian kernel (FWHM $\approx 2 \times$ voxel size). A band-pass filter (0.008–0.09 Hz) was applied to remove

physiological noise, and nuisance variables were regressed out, including the 5 time series extracted from segmented white matter and cerebrospinal fluid, as well as the 6 realignment parameters and their 6 first temporal derivatives.. Outlier volumes with global BOLD signal or framewise displacement (FD) exceeding the 95th percentile were scrubbed using the Artifact Detection Tools (ART) toolbox implemented in CONN. Afterwards, we used a bilateral binary sgACC mask (507 voxels, 4056 mm³), derived from the AAL3 atlas (56), as the seed region and computed its whole brain Pearson correlation-based rs-FC for each timepoint (baseline and follow up) and each participant.

Statistical analyses

We used the Statistical Package for Social Sciences SPSS 29.0 (SPSS, Inc., Chicago, Illinois) for data analyses. Demographic and clinical variables were compared between groups using two-sample t-tests or χ^2 tests as appropriate. Longitudinal changes of clinical assessments within the patient group were compared using paired t-tests.

We used the CONN toolbox to compare sgACC seed-based rs-FC maps between depressed patients and healthy controls. We performed baseline and group $\times$ time interaction using a full-factorial model. Six head motion parameters (three translations and three rotations) and their first temporal derivatives were regressed out at the first level. Second-level analyses were corrected with the regressors age and sex. We used a conservative voxel threshold of $p < 0.001$ and a cluster correction with a family wise error (FWE) correction of $p < 0.05$. Significant clusters of longitudinal changes in patients were extracted for Spearman correlation with changes in depression severity (MADRS) and mindfulness (CHIME). Spearman rank correlation analyses were conducted to examine associations between significant longitudinal imaging findings and clinical outcome measures (MADRS, CHIME) in patients.

Results

Clinical findings

Findings of the two-sample t-tests or χ^2 tests showed, that patients and controls did not differ regarding age, sex and handedness but in all clinical characteristics (see Table 1). Patients improved significantly regarding overall depression severity (MADRS ($t(23) = 6.25, p < 0.001$), BDI ($t(22) = 6.07, p < 0.001$)), mindfulness (CHIME ($t(21) = -2.83, p = 0.01$)), and positive affect (PANAS positive affect ($t(21) = -3.84, p < 0.001$) and negative affect (PANAS negative affect, $t(21) = 2.60, p = 0.02$)).

Table 1
Demographical and clinical characteristics of groups

Age (years)	Patients (n = 24)	Controls (n = 15)	P Value
	45.8 ± 13	43.9 ± 13	0.46
Female (n, %)	14, (58%)	9, (60%)	0.92
Right handedness (n, %)	22, (92%)	14, (93%)	0.24
Duration of episode (months)	11.7 ± 8.9	n/a	n/a
Number of episodes	6.6 ± 7	n/a	n/a
BDI-II (T1)	26.9 ± 7.1	2.5 ± 2.1	< 0.001
MADRS (T1)	26.3 ± 9.1	1.5 ± 1.6	< 0.001
CHIME (T1)	3.2 ± 0.6	4.5 ± 0.5	< 0.001
PANAS positive affect (T1)	1.0 ± 0.7	3.2 ± 0.4	< 0.001
PANAS negative affect (T1)	1.6 ± 0.8	0.5 ± 0.4	< 0.001
Duration of episode (months)	14.9 ± 18.2	n/a	n/a
BDI-II (T2)	19.2 ± 10	n/a	n/a
MADRS (T2)	13.8 ± 8	n/a	n/a
CHIME (T2)	3.3 ± 0.7	n/a	n/a
PANAS positive affect (T2)	1.4 ± 0.6	n/a	n/a
PANAS negative affect (Follow-up)	1.3 ± 0.8	n/a	n/a
n (remitter)	5 (20. 8%)	n/a	n/a
n (responder)	14 (58.3%)	n/a	n/a

Abbreviations: remitter: MADRS < 8 points; responder or remitter: MADRS reduction > 50%; n/a: not applicable; T1: Timepoint one (baseline); T2: Timepoint two (follow-up). Age, sex and handedness were compared between patients and healthy controls using χ^2 tests. Clinical variables were compared between patients and healthy controls using two-sample t-tests.

Changes in rs-FC of the sgACC

Analyses revealed a significant group $\times$ time interaction in longitudinal sgACC resting-state functional connectivity (rs-FC) across multiple cortical regions, predominantly located within the DMN (see figure 1). Within the depressed patient group, rs-FC between the sgACC and the bilateral precuneus

($MNI_{x,y,z} = 2, -66, 46$; cluster size = 39; $p\text{-FWE} = 0.00097$) showed a significant reduction over time (see figure 2). No significant longitudinal changes were observed in healthy controls. At baseline, patients exhibited greater sgACC rs-FC compared to healthy controls in the superior division of the left lateral occipital cortex ($MNI_{x,y,z} = -16, -66, 42$; cluster size = 28; $p\text{-FWE} = 0.036$) (see figure 3). No regions showed higher sgACC rs-FC in healthy controls relative to patients.

Correlational analyses

Correlational analyses revealed that a reduction in rs-FC between the sgACC and posterior DMN showed a non-significant positive association with reduction in depressive symptom severity (MADRS: $r = 0.29$, $p = 0.18$). Decreases in sgACC–posterior DMN connectivity were significantly associated with improvements in mindfulness ($r = -0.44$, $p = 0.039$) (see figure 4).

Discussion

This is the first study that used 7-Tesla MRI-scans to investigate aTMS-induced alterations in sgACC rs-FC in patients with depression. Treatment with aTMS decreased sgACC-DMN rs-FC in patients with depression, normalizing increased rs-FC between the sgACC and the DMN at baseline.

Our study extends previous work investigating aTMS induced neuroplasticity. We found an aTMS induced decrease of sgACC-DMN overactivation at baseline. This complements previous studies linking (predominantly) rTMS-induced decreases of sgACC rs-FC and metabolic activity to depressive symptom reduction (24, 28, 57, 58)). The sgACC is a core hub of the affective network, which has been consistently implicated in the generation, maintenance and alleviation of depressive mood states (19-21, 23). The DMN plays a crucial role for processing emotions, self-referential mentalization, and the recollection of prior experiences (59-61). The normalization of pathologically increased sgACC–DMN connectivity, together with the reversal of baseline group differences, suggests that aTMS selectively downregulates a network configuration thought to support self-focused, repetitive negative thinking and thus directly targets a system-level substrate of maladaptive rumination (62).

On a mechanistic level, our finding lends further support to the assumption that targeting the dlPFC which is functionally anticorrelated with the sgACC may alleviate depressive symptoms by modifying an extended sgACC network (16, 31, 32). While aTMS-treatment led to significant improvements in depressive symptoms, positive and negative affect, and mindfulness, the observed neurobiological normalization of sgACC-DMN rs-FC was specifically associated with enhanced mindfulness, rather than overall symptom reduction. Mindfulness may mitigate depressive psychopathology by targeting core emotion regulation vulnerabilities such as rumination, negative attentional bias, and experiential avoidance. It also fosters a more flexible, acceptance-based stance toward internal experience (63-65). Mindfulness-based interventions reliably increase the use of adaptive regulation strategies and reduce reliance on maladaptive ones, which mediates reductions in depressive symptoms (66-69). Neuroimaging studies indicate that these behavioral changes co-occur with functional and structural

plasticity in prefrontal–cingulo-opercular control systems, limbic regions, and default mode hubs involved in self-referential processing (70, 71). Improvements in core depressive symptoms achieved through interventions such as aTMS may, in turn, facilitate mindfulness skills and more adaptive emotion regulation. This points to potentially bidirectional relationships between symptom change and regulatory capacities that warrant testing in longitudinal studies.

Finally, this study has some limitations that arise from the observational design. First, all but two patients were on antidepressant medication which may impact both neuroimaging measures and clinical course. Second, treatment effects may be overestimated due to lack of blinding (patients and raters) and efficacy of additional therapies (pharmacology, psychotherapy). However, this observational design increases external validity, and we conducted a comprehensive assessment of psychopathology using self-rated and third party questionnaires. Strengths of the study are the inclusion of a healthy comparison group with longitudinal assessments and the application of ultra-high resolution 7-Tesla MRI with innovative sequences enabling an improved signal to noise ratio.

In conclusion, our 7-Tesla rs-fMRI data demonstrate that aTMS normalizes pathologically increased coupling between the sgACC and the DMN in patients with depression. This network-level modulation was linked to symptom improvement in mindfulness. These findings highlight the sgACC–DMN axis as a critical target of rapid antidepressant response and provides mechanistic insights into the neurobiological effects of accelerated TMS.

Declarations

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Competing interests

All authors report no conflicts of interest

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Figures

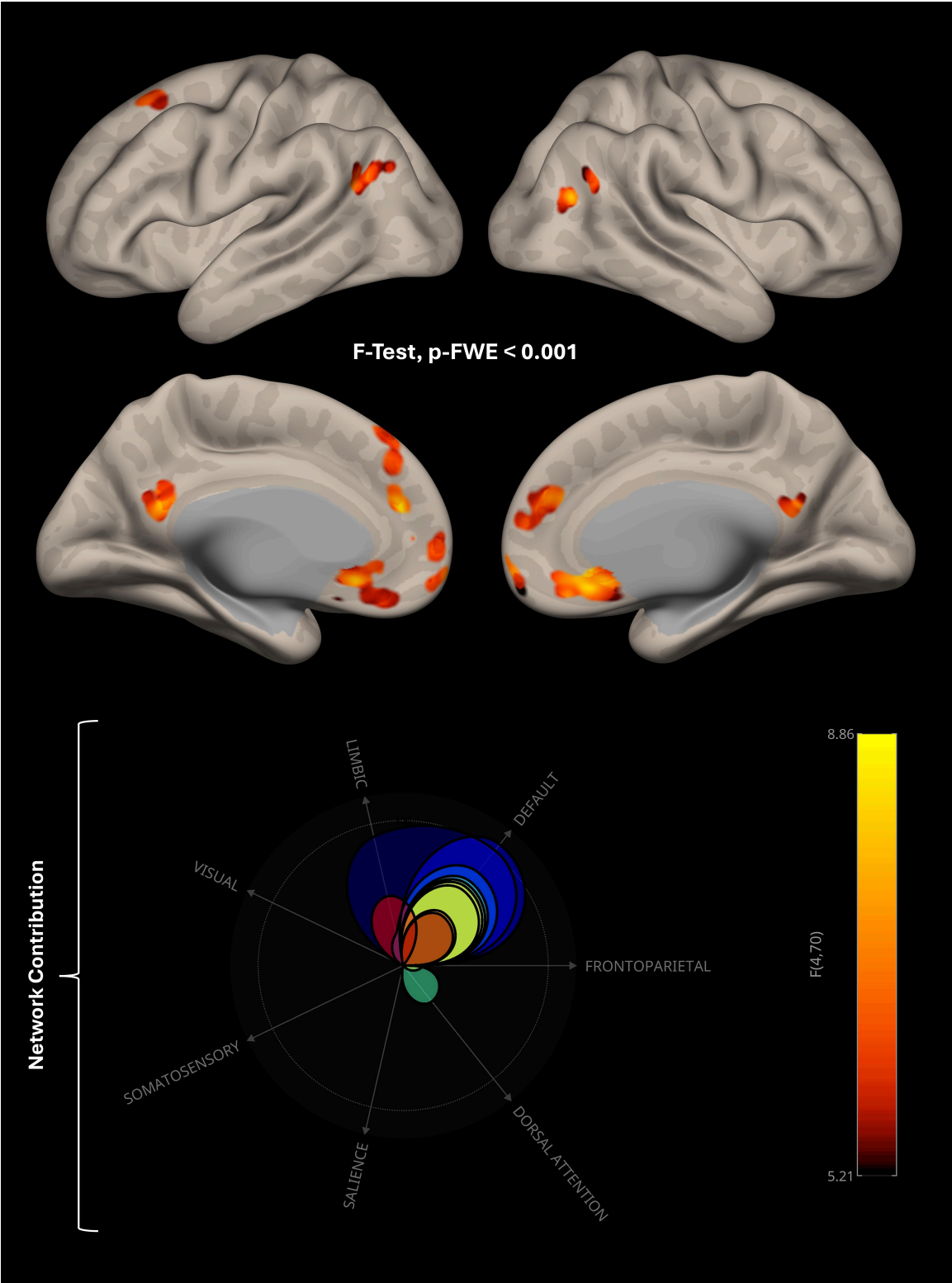


Figure 1

Group by time effects of seed-based rs-FC of the sgACC.

The lower panel depicts the relative contribution of canonical functional brain networks (Visual, Somatosensory, Limbic, Default, Salience, Dorsal Attention, Frontoparietal), with radial extent and color indicating each network's weight in the observed pattern.

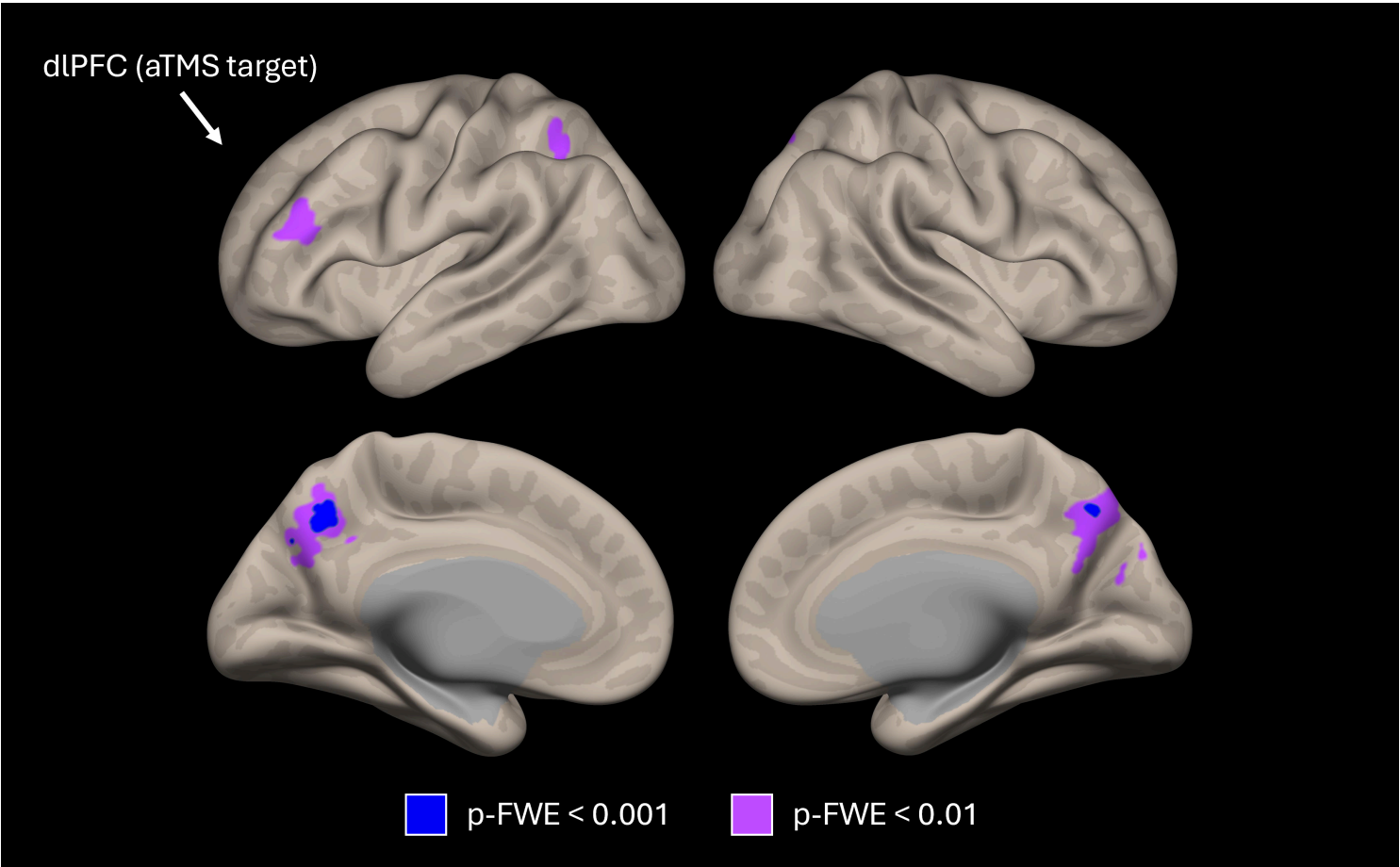


Figure 2

Reduction of rs-FC between sgACC and posterior DMN after aTMS

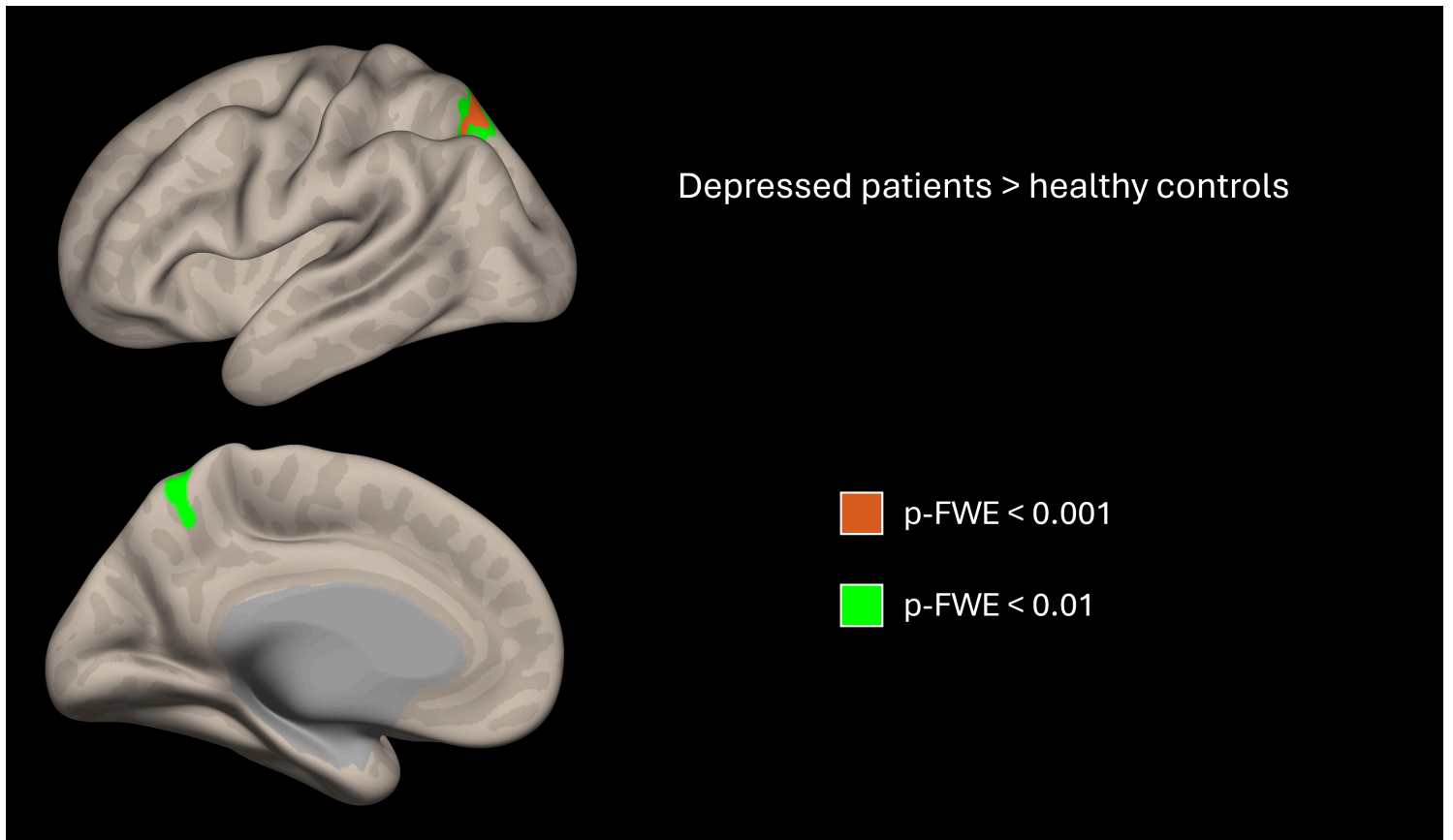


Figure 3

Increased baseline rs-FC between sgACC and posterior DMN in depressed patients.

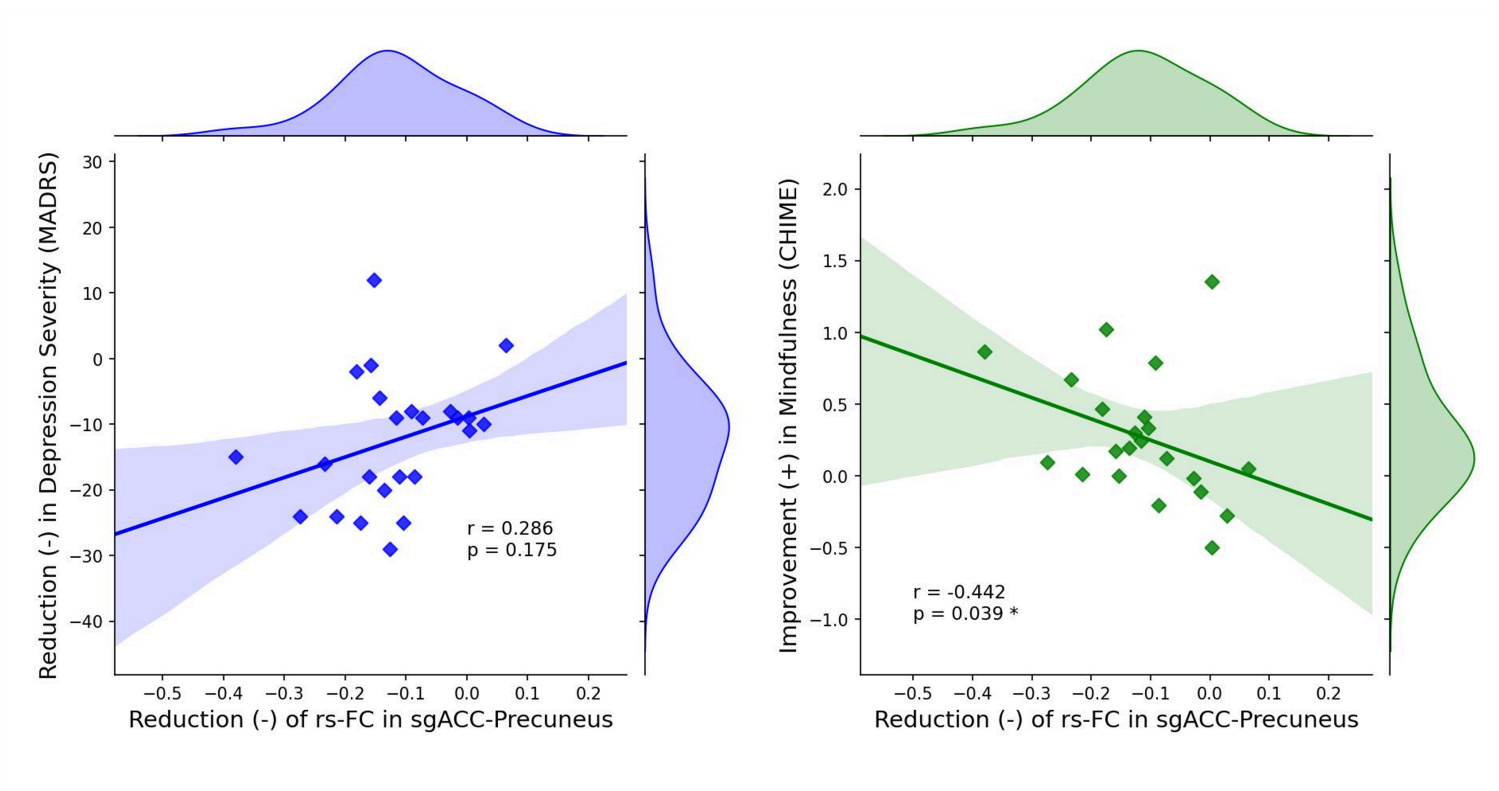


Figure 4

Exploratory correlations with symptom improvement in patients.