Dorsomedial prefrontal cortex repetitive transcranial magnetic stimulation (dmPFC-rTMS) in the augmentation of antidepressants (DOPRERA study). Efficacy, tolerability and neurophysiological changes.

Background

Depression is a major debilitating psychiatric disorder. Current antidepressant drugs are often associated with side effects or treatment resistance.

Conventional repetitive transcranial magnetic stimulation (rTMS)

Over the last decades repetitive rTMS has received increasing attention as a therapeutic tool in the treatment of major depressive disorder (MDD). RTMS is considered a safe intervention with limited and transient side-effects. Conventional rTMS for MDD employs left high-frequency (HF) or right low- frequency (LF) dorsolateral prefrontal cortex (DLPFC) stimulation, with response and remission rates between 50-55% and 30-35%, respectively [1]. HF-rTMS combined at the outset with antidepressants (ADs) is effective for accelerating and enhancing response (62% vs 46%) and remission (54% vs 39%) rates comparing to sham stimulation [2]. Acute treatment with rTMS for depression is typically comprised of a series of once-daily sessions over 4–6 weeks [3]. Neuroimaging methods identified several regions (DLPFC, orbitofrontal cortex (OFC), anterior cingulate (ACC) particularly, subgenual ACC (sgACC), insula) which activity and mutual connectivity at the baseline or during the treatment were associated with change of depressive symptoms parameters [4]. These regions are also principal parts (hubs) of large neural networks involved in the pathophysiology of MDD [5,6]

The higher (anterior) peak individual alpha frequency (IAF) values, lower power in the fronto-central theta frequency band, smaller P300 amplitudes at Pz during task, and increased prefrontal delta and beta cordance values distinguished responders and nonresponders in previous neurophysiological study, but these findings were not replicated [7,8]. Recent study confirmed negative correlation between IAF prox (absolute value of the distance from IAF to 10 Hz) and reduction of depressive symptoms [9]. Beyond investigations of IAF, work is still underway to investigate cordance, theta power, alpha power and theta connectivity EEG as considered markers of rTMS response [4,10-12]. Our group has demonstrated predictive efficacy of the prefrontal theta cordance reduction after the first week of the treatment with LF-rTMS over the right DLPFC [12].

Deep rTMS

The penetration depth of "conventional" rTMS coils such as the figure-of-8-coil in brain tissue is limited to superficial cortical areas. Newly developed coils (e.g. Magventure COOL D-B80 A/P- "double-cone" angulated coil (DCC)) allow modulation of deeper located brain structures (e.g. ACC) but spatial targeting is partially limited. RTMS using a DCC has been shown to modulate the neural activity in the dorsal anterior cingulate (dACC) by placing the coil over the dorsomedial prefrontal cortex (dmPFC); it is called anterior cingulate double-cone rTMS (ACDC-rTMS) or dmPFC-rTMS [13].

The role of dorsal anterior cingulate cortex in MDD

The ACC consists of four different subregions within Brodmann areas 24, 25 and 32 and is involved in different emotional, cognitive, sensory, and autonomic functions. In general, an 'affect subdivision' encompassing rostral (ventral) ACC (rACC) and sgACC areas and a dorsal 'cognitive subdivision' of the ACC (dACC) have been distinguished [14]. The sgACC plays a major role in the pathophysiology of depression [15,16]. Hyperactivity in rACC/sgACC regions and hypoactivity of dACC regions are commonly reported in MDD [13]. Furthermore, current metanalysis revealed that three regions, the both insulas and the dACC, showed significant gray matter loss across all psychiatric disorders [17].The dACC is closely connected to the prefrontal cortex and plays a critical role in cognitive-emotional processing [18]. The sgACC is involved in emotion recognition [19]. The activity of the dACC and the sgACC seem to be functionally anticorrelated, what has been shown in different conditions such as depressive states and experimentally induced sadness, and on the contrary during antidepressant treatment [20,21]. The interaction of dACC and sgACC has also been found in the only study that investigated the effects of dmPFC-rTMS by neuroimaging [22]. It revealed that cerebral blood flow was increased in the dACC and reduced in sgACC after 10 Hz dmPFC-rTMS.

DmPFC-rTMS in the treatment of MDD

Only several studies examined efficacy of dmPFC-rTMS in the acute treatment of MDD (n=9, 3 chart reviews, 3 open-label studies, 2 double-blind (DB) studies). All projects were designed as **add-on treatment** to various ADs with different mechanisms of action and other psychotropic compounds that had been applied several weeks before start of the stimulation.

Open-label and chart review studies demonstrated response rate from 36 to 51% and no difference between once-daily and twice daily stimulations [13]. DB study (n=45) comparing HF-rTMS of left DLPFC and dmPFC-rTMS and sham rTMS (15 sessions, 110%MT, 10 Hz, 2000 stimuli a day – for both active groups) found significant effect for dmPFC-rTMS vs HF-rTMS, but not for dmPFC-rTMS vs sham and no difference were detected among groups in terms of response (dmPFC: 46%, left DLPFC:20%, sham DLPFC: 25% ; p=0,29) and remission [23]. The recent DB study (n=120, 30 sessions, dmPFC, 120% MT, 20 Hz, 1520 pulses per hemisphere vs 120% MT, 1 Hz, 360 pulses per hemisphere vs sham) there was a significant main effect of time across all arms, active dmPFC-rTMS was not superior to sham [24]. Response rate did not significantly differ by treatment arm (1 Hz: 13.51%; 20 Hz: 31.43%, sham: 16.67%).

Only a few, small neuroimaging studies (functional connectivity fMRI and 18 FDG PET) were concerned on changes over the course of treatment and association with treatment outcome. The first study (n=25) has identified several baseline predictors related to positive outcome, including greater connectivity of dmPFC to sgACC, greater connectivity of sgACC to DLPFC, as well as lesser cortico-thalamic, corticostriatal, and cortico-limbic connectivity [25]. In the next study nonresponders showed significantly lower connectivity through a classical reward pathway comprising ventral tegmental area, striatum, and a region in ventromedial prefrontal cortex [26]. Responders and nonresponders also showed opposite patterns of hemispheric lateralization in the connectivity of dorsomedial and dorsolateral regions to this same ventromedial region. Tastevin et al. demonstrated that increase in metabolic values in the precuneus after dmPFC-rTMS was related to score improvements in the rating scale and baseline metabolic values in the caudate nucleus predicted score improvements in the rating scales of depression [27]. The studies mapping QEEG parameters during the dmPFC-rTMS are lacking.

Our previous works

Submitted project builds on our previous works in the field of neurostimulation (DB studies comparing of the LF-rTMS and transcranial direct current stimulation to venlafaxine (MDD) and using HF-rTMS in the treatment of bipolar depression - AZV n. 16-31380A) as well as prediction of treatment outcome for antidepressants and rTMS (early change of depressive symptoms, theta cordance, alpha asymmetry, brain-derived neurotrophic factor) [12,28-32].

Knowledge gap and project description

Available studies have mapped the efficacy and tolerability of dmPFC-rTMS only as add-on antidepressant treatment (i.e. after several weeks of unsuccessful antidepressant treatment). According to our knowledge there is no study examined efficacy and tolerability of dmPFC-rTMS in the **augmentation** of ADs **applied from the beginning of the treatment trial.**

The planned study will provide evaluation of efficacy and tolerability/acceptability of dmPFC-rTMS in the augmentation of ADs (selective serotonin re-uptake inhibitors; SSRI) from the outset of the treatment trial compared to conventional HF-rTMS and sham stimulation in depressed subjects. The project will also examine the ability of dmPFC to accelerate and enhance the reduction of depressive symptoms. Moreover, the study will elucidate the course of QEEG changes (source cortical activity and cortical connectivity) during the treatment in the region of interests (ROI; (dACC BA 24, sgACC BA 25, left and right DLPFC BA 9/46 , dmPFC BA 10/32, precuneus BA 7, posterior cingulate PCC BA23/31) involved in the pathophysiology of MDD and treatment response to rTMS. Another study aspect will be to identify ability of clinical and neurophysiological parameters in the prediction of the treatment outcome as well as to confirm predictive potential of some previously considered QEEG predictors (IAF prox, early change of theta prefrontal cordance value) of response to rTMS.

The objectives are: 1) to compare efficacy/tolerability of dmPFC-rTMS and HF rTMS over the left DLPFC with sham rTMS in the augmentation of standard antidepressant treatment (SSRI), 2) to identify the electrophysiological sequelae of dmPFC-rTMS, HF-rTMS of left DLPFC and sham rTMS in the augmentation of SSRI in the a priori defined ROI (current density, connectivity), 3) to identify clinical and electrophysiological predictors of treatment response

In the connection with the objectives, we are planning to test following hypotheses:

$H_{null\ 1}$: The reduction of depressive symptoms in MADRS[36] score is not different across three groups (dmPFC-rTMS, HF-rTMs over the left DLPFC and shame rTMS) after the week two and at the end of six- week study.

$H_{null\ 2}$: The number of responders and remitters are not different across three groups at the end of six- week study.
$H_{null\ 3}$: The number of subjects dropped-out from the study for any reason is not different across treatment groups.
$H_{null\ 4}$: The change in EEG spectral distribution or in electrical neuronal activity (current density) in individual frequency bands of a priori defined ROIs and connectivity among them are not different among responders and nonresponders within and between treatment groups from baseline to week 1 and four.
$H_{null\ 5}$: The response to treatment is associated with a decrease of prefrontal theta cordance at week 1 in all groups.
$H_{null\ 6}$: The baseline value of individual alpha peak frequency proximity (IAF-prox) does not correlate with change of depressive symptoms in all three groups.
Beyond the scope of the hypotheses, we will also analyze predictive ability of early reduction of depressive symptoms (after the first and second week of treatment) for the treatment outcome.
Study design: A 6-week, DB, three-arm, randomized, sham-and active comparator-controlled study.
Subjects: 60 patients suffered from MDD (based on power analyses - see below).
Inclusion criteria: 1. Patients (outpatients or inpatients) suffering from MDD (recurrent or single episode) diagnosed according to Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-V), confirmed using The Mini-International Neuropsychiatric Interview - M.I.N.I., Czech Translation version 7.0.2 [33,34]. 2. Patients fulfilling at least Stage I (≥1 previous, unsuccessful, adequate, antidepressant treatment) criteria for resistant depression according to Thase and Rush [35]. 3. The mental ability to understand and sign Informed Consent Form, 4. The score in the Montgomery and Åsberg Rating Scale (MADRS) ≥25 [36]. 5. Male and female inpatients or outpatients aged 18-70 years old. 6. Right handedness. 7. Duration of current episode of depression >1 but ≤ 12 months.
Exclusion criteria: 1. History of any other DSM-V diagnosis other than MDD, except anxiety disorders in the last year. 2. Personality disorder that makes participation in the trial difficult 3. History of substance dependence in the last year except nicotine. 4. Contraindications of SSRI´s treatment according to SPC. 5. Contraindications of rTMS (history of epilepsy or any neurologic condition likely to increase risk of seizure, mass brain lesions, cerebrovascular accident, metal in the head, a history of major head trauma with unconsciousness. 6. Pregnancy or breast-feeding. 7. Patients with severe somatic disorders (cardiovascular disease, neoplasms, endocrinology disorders etc.) that could be associated with depression due to somatic diseases. 8. Patients treated with electroconvulsive therapy less than 3 months before enrollment or suffering from neurologic disorder (e.g., epilepsy, head trauma with loss of consciousness) and patients using any treatment which can strongly affect EEG. 9. Application of other concomitant medication that is not allowed in protocol (e.g. antipsychotics, mood stabilizers etc.). 10. Unsuccessful treatment with more than one SSRI antidepressants or rTMS treatment in the current episode of MDD. 11. Fluoxetine treatment before the enrollment to the study
Treatment in the study
Following an initial wash-out period (2-5 days), eligible subjects will receive 6-week treatment. They will be randomly allocated in a 1:1:1 ratio (no stratification) to either dmPFC-rTMS +SSRI, HF-rTMS left DLPFC + SSRI and sham stimulation+SSRI groups (see Table 1 and Figure 1). RTMS will be delivered using the MagPro R30 stimulator (MagVenture, Denmark) and Cool D-B80 A/P (dmPFC-rTMS)/Cool-B65 A/P (conventional rTMS) with both an active and a placebo side that enables the rTMS operator to stay blinded. To empower the masking process, surface electrodes connected to the electric stimulator will be used for all treatments to mimic scalp sensation accompanying active rTMS. Patients in all three groups will undergo 20 sessions of rTMS (active ones or shame) each weekday (Mon-Fri) within the four weeks. The rTMS parameters (number of stimuli and trains, stimulation frequency, intensity etc. are derived from Kreuzer study (see above) except higher number of sessions [23]. Resting motor treshold (RMT) that will be determined for the right abductor digiti minimi muscle. Stimulation protocol is in line with current guidelines and reflects results of recent metaanalysis [3,37,38].
a. DmPFC-rTMS +SSRI group (Group 1): Patients assigned to group 1 will take antidepressants from SSRI class (fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram) in flexible doses within the range cited in the Summary of Product (SPC) for six weeks. The new SSRI will be chosen according to clinical

judgment of the attending psychiatrists and with respect to the history of previous treatments, clinical status (anxiety, insomnia, psychomotor retardation etc.). The SSRI that has been ineffective in the treatment of the current episode will be excluded. The SSRI class was chosen as an efficacious, standard and well tolerated treatment of MDD.

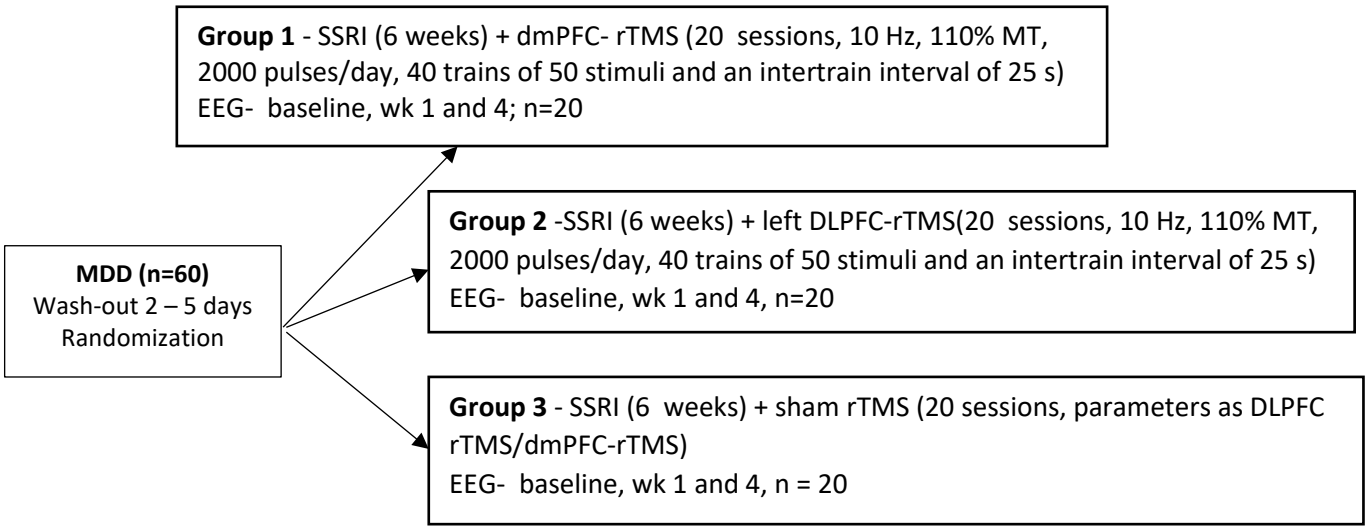
Table 1 Procedures in the study

Group I: SSRI + dmPFC-rTMS Group 2: SSRI + left DLPFC-rTMS Group 3: SSRI + sham-rTMS	**V -1 (screening)**	**V 0 (baseline)**	**V 1**	**V 2**	**V 3**	**V 4**
day	-5 - -2	0	7±1	14±1	28±2	42±2
MINI, demographic data	+					
EHI	+					
MADRS , CGI, QIDS SR	+	+	+	+	+	+
ASEC, TMS acute side effects questionnaire		+	+	+	+	+
EEG		+	+		+	
Previous and concomitant treatment	+	+	+	+	+	+

Abbreviations: ASEC - Antidepressant Side Effect Scale, CGI- Clinical Global Impression Scale, dmPFC –dorsomedial prefrontal cortex, DLPFC - dorsolateral prefrontal cortex, EHI-Edinburgh Handedness Inventory, EEG-electroencephalography, MADRS- Montgomery and Åsberg Rating Scale, M.I.N.I. – Mini International Neuropsychiatric Interview, rTMS – repetitive transcranial magnetic stimulation, QIDS-SR-Quick Inventory of Depressive Symptomatology - Self-rated, SSRI – selective serotonin reuptake inhibitors, V-visit

DMPFC-rTMS will be delivered at 110% of RMT) at 10 Hz, for a total of 2000 pulses in 40 trains of 50 stimuli and an intertrain interval of 25 s). Coil positioning will follow the protocol described by Hayward et al. positioning the coil 1.5 cm anterior to one third of the distance from the nasion to the inion with the handle of the coil oriented in sagittal direction along the midline [22].

Figure 1: Scheme of the study



Abbreviations: MDD-major depressive disorder, DLPFC-dorsolateral prefrontal cortex, dmPFC-dorsomedial prefrontal cortex, EEG-electroencephalography, MT-motor threshold, rTMS-repetitive transcranial magnetic stimulation, s-second, SSRI-selective serotonin reuptake inhibitors, wk-week

b. HF rTMS left DLPFC + SSRI (Group 2): Patients will be treated with SSRI´s in the same manner as in Group 1. Coil will be positioned over DLPFC using F3 Beam algorithm [39] and be held tangentially to the scalp with its handle pointing back and away from the midline at 45°.

c. Sham stimulation +SSRI (Group 3): There are the same principles and limits for SSRI treatment as in Group 1. Sham rTMS/dmPFC-rTMS with sham coils will be applied either to left DLFPC or to dmPFC (randomly per ten subjects).

c. Concomitant treatment

The only concomitant treatments for both groups will be hydroxyzine (maximum 100 mg p.d.) for anxiety and zolpidem, zopitine or trazodone 50 mg (it should not be applied in the regular manner and not in the night before EEG exam) for insomnia during the study. The continuation of benzodiazepine medication will be allowed in unchanged dosage in patients who used them before the study.

Clinical measures

The depressive symptoms, overall clinical and side effects will be assessed with MADRS, Clinical Global Impression (CGI) [40], Quick Inventory of Depressive Symptoms – Self Rated (QIDS-SR) [41], Antidepressant Side Effect Scale (ASEC) [42] and TMS acute side effects questionnaire (according to Berenson-Allen Center for Noninvasive Brain Stimulation) before the wash-out period, at baseline, week 1, 2, 4 and at the end of the study (regular or early termination). Raters will be trained to the criterion of intraclass correlation of at least 0.80 for each clinician.

EEG procedures

The EEG data (10min eyes-closed, 5min eyes open) minutes in duration) will be recorded at baseline and after the 1st and 4th week of the study treatment under the standard condition (semi-recumbent position, eyes closed relaxed state) with at least 36 surface electrodes placed according to the extended International 10/20 system. Raw EEG data will be sampled at least 250 at 1000Hz. Three additional channels (horizontal and vertical electro-oculogram and ECG) will be recorded to control the biological EEG artefacts. For the analyses, artifacts detection will be performed visually and semi-automatically to select EEG epochs in a total length of min. 60 seconds containing no biological and technical artifacts, which will then be digitally filtered in the range of 1-40 Hz. Semiautomatic selection of epochs and QEEG calculation (spectral and coherence analysis) will be performed by specific software and a fast Fourier transform will be used to obtain the absolute and relative spectral values within the standard frequency bands. The EEG reviewer will be blind to patient´s treatment and the outcome of treatment.

sLORETA and eLORETA: Quantitative EEG analysis will further include the estimation of the sources of electrical neuronal activity (current density) and the analysis of functional connectivity by means of software eLORETA (available at http://www.uzh.ch/keyinst/loreta.htm)[43]. This will be used to calculate and estimate the distribution of current densities in the 3D cortical space, where the current density will be mapped to 6239 voxels of cortical gray matter with 5 mm3 spatial resolution, covering the entire cortex and hippocampus. Estimated eLORETA images show thus the electrical activity of each voxel (in neuroanatomical Talairach space) as the amplitude of the calculated current density (μA/mm2). Analysis of functional connectivity by the software eLORETA will allow to quantify the cortical functional connectivity between various Broadman's areas. The distribution of current densities and the analysis of functional connectivity by eLORETA will be performed at the baseline, week 1 and week 4 of treatment and then compared by statistical non-parametric mapping (SnPM) using unpaired (between-groups) or paired (within-groups) t-tests of log-transformed eLORETA values.

Cordance: QEEG cordance will be calculated by the EEG software (WaveFinder v.1.70, unimedis, Prague) using the algorithm which has been repeatedly described elsewhere in greater detail [12]. It contains three consecutive steps: First, absolute power values are reattributed to each individual electrode by averaging power from all bipolar electrode pairs sharing that electrode. In the second step, the maximum absolute and relative power values (AMAXf, RMAXf) in each frequency band (f) are determined to obtain normalized absolute (ANORM (s,f)) and normalized relative (RNORM (s,f)) power values (absolute and relative power values at each electrode site (s) and for each frequency band (f) are divided by AMAXf and RMAXf respectively). In the third step, the cordance values at each electrode site (s) for each frequency band (f) are calculated by summing the ANORM and RNORM values, after a half-maximal values (0.5 on the normalized scale) are subtracted: CORDANCE(s,f) = (ANORM (s,f) – 0.5) + (RNORM (s,f) -0.5). According to our hypotheses average cordance values from 3 frontal electrodes (Fp1, Fp2 and Fz) in theta frequency band (4-8 Hz) will be subjected to statistical analysis. Furthermore, cordance for Fz and Cz electrodes will calculated.

The individual peak alpha frequency peak (IAF) calculation:The IAF will be extracted from eyes closed resting states and calculated for F3 and F4. In short, calculating the IAF consisted of the following steps: 1) A Fast Fourier Transform will be applied to eyes closed data using 4 sec. segments with 50% overlap to get a power spectrum for each site, with a Hamming window applied to each segment; 2) The IAF for each site is determined by identifying the maximum value within the 7–13 Hz alpha range. If the power of the alpha frequency peak is lower than 1.5 Z-score below the mean, the patient is considered not to have a dominant IAF rhythm and thus was not included in the analysis. IAF-prox will be calculated as the absolute value of the distance from IAF to 10 Hz [9].

Statistical analysis: The primary outcome measure of change from baseline to week 6 in MADRS score will be analyzed on intend-to-treat dataset (data from subjects who were randomized and recieved at least one rTMS/sham treatment; Full Analysis Set, missing data will be replaced using Last Observation Carried Forward method) using an analysis of covariance with the treatment group as a fixed effect, and the baseline value as covariate. As a sensitivity analysis for primary endpoints a mixed-effects model for repeated measures applied on As Observed Analysis Set (without missing data imputation) with treatment, visit, and treatment-by-visit interaction as fixed effects, subject as a random effect will be used. Post hoc pairwise comparisons of least square means will be corrected following the Holm-Bonferroni method. The secondary endpoints (response to treatment-reduction of total MADRS score ≥ 50% after 6 weeks of treatment; remission- MADRS ≥10 points at the end of the study), and safety endpoints (incidence of side effects and number of drop-outs from the study from any reason) will be compared by chi-squared test, and in logistic regression. The changes in CGI and QIDS scores at the end of the study will be analyzed in the same way as the primary outcome. A priori defined EEG parameters at baseline, week 1 and week 4 as well as their change at the postbaseline visits will be analyzed using generalized mixed-effects model with As Observed Analysis Set. In addition, ROC analysis will be carried-out and predictive values (PPV and NPV) will be calculated for prefrontal theta cordance and its change as well as for other potential predictors identified by exploratory analyses (LORETA, eLORETA, early reduction of depressive symptoms).

Power analyses: To address the primary endpoint of the study total sample size of 54 subjects (18 per group) needs to be randomized to detect between-group MADRS change score difference of 5 points (and s.d. 8) if present, with a given alpha of 0.05 and 1-beta of 0.8. Sixty patients included in the study will prevent an eventual 10% pre-treatment withdrawal rate.

Literature:

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