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The effect of electroconvulsive therapy on cerebral monoamine oxidase A expression in treatment-resistant depression investigated using positron emission tomography

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ABSTRACT

Background: Electroconvulsive therapy (ECT) constitutes one of the most effective antidepressant treatment strategies in major depression (MDD). Despite its common use and uncontested efficacy, its mechanism of action is still insufficiently understood. Previously, we showed that ECT is accompanied by a global decrease of serotonin-1A receptors in MDD; however, further studies to investigate the involvement of the serotonergic system in the mechanism of action of ECT are warranted. The monoamine oxidase A (MAO-A) represents an important target for antidepressant treatments and was found to be increased in MDD. Here, we investigated whether ECT impacts on MAO-A levels in treatment-resistant patients (TRD).

Methods: 16 TRD patients (12 female, age 45.94 ± 9.68 years, HAMD 25.12 ± 3.16) with unipolar depression according to DSM-IV were scanned twice before (PET1 and PET2, to assess test-retest variability under constant psychopharmacotherapy) and once after (PET3) completing a minimum of eight unilateral ECT sessions using positron emission tomography and the radioligand [^{11}C]harmine to assess cerebral MAO-A distribution volumes (V_T). Age- and sex-matched healthy subjects (HC) were measured once.

Results: Response rate to ECT was 87.5%. MAO-A V_T was found to be significantly reduced after ECT in TRD patients (−3.8%) when assessed in 27 *a priori* defined ROIs ($p < 0.001$). Test-retest variability between PET1 and PET2 was 3.1%. MAO-A V_T did not significantly differ between TRD patients and HC at baseline.

Conclusions: The small effect size of the significant reduction of MAO-A V_T after ECT in the range of test-retest variability does not support the hypothesis of a clinically relevant mechanism of action of ECT based on MAO-A. Furthermore, in contrast to studies reporting elevated MAO-A V_T in unmedicated depressed patients, MAO-A levels were found to be similar in TRD patients and HC which might be attributed to the continuous antidepressant pharmacotherapy in the present sample.

Introduction

Electroconvulsive therapy (ECT) constitutes a rapidly acting and highly potent - though clearly unspecific - treatment option in psychiatry, where a generalized seizure is induced under controlled circumstances and expected to alleviate mental symptoms [1]. The

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potential of ECT is very high with response-rates up to 80% in the main indication major depression (major depressive disorder, MDD) [2,3]. Even when it comes to treatment-resistant conditions (treatment-resistant depression, TRD) [4,5] remission rates between 40 and 50% can be expected after ECT [6]. Interestingly, in spite of its common use and well-documented efficacy in MDD since over 80 years [7], its complex mechanisms of action are still relatively unclear and no consensus has been reached in this concern. Several lines of evidence have been pursued to clarify the issue, but were only partially successful in detecting neurobiological markers that correlate with treatment effects of ECT [8–10]. In this context, special attention has been paid to the neuroendocrine system, by investigating functional changes of the hypothalamic-pituitary-adrenal (HPA) axis after ECT [11], and adult neurogenesis, by assessing levels of brain-derived-neurotrophic factor (BDNF) [12] during a course of ECT as well as gray matter volume changes after treatment, particularly in the hippocampus region [13,14,78]. Thirdly and most prominently, effects of ECT on brain function in terms of glucose metabolism and cerebral blood flow as surrogate markers of neuronal activity as well as specific neurotransmitter systems using molecular neuroimaging techniques have been intensively studied [8,15]. However, a differentiation between imminent seizure-associated alterations and actual treatment-related changes could not be ascertained in these investigations [12,13,16].

Regarding the impact of ECT on specific neurotransmitter systems, the wealth of data retrieved from preclinical research has led to the common view that ECT enhances monoaminergic neurotransmission, more specifically dopaminergic, noradrenergic and serotonergic signaling, and that this boost of monoamines explains the powerful effects of ECT in treating severe mental states [17]. However, evidence in humans regarding the effects of ECT on neurotransmission is very limited and lacks replication. Only three studies have hitherto directly investigated this relationship in depressed patients by means of positron emission tomography (PET) and were able to report effects. We previously showed that ECT leads to a widespread reduction of serotonin-1A receptor density in the cortex and the hippocampus-amygdala complex [18], unlike in rodents but similar to observations reported under treatment with selective serotonin-reuptake inhibitors (SSRI) [19]. Similarly, Yatham et al. demonstrated that ECT goes along with a reduction of cortical serotonin-2A receptors in depressed patients [20], which is equally similar to antidepressants and unlike the pattern shown in animal studies. Lastly, ECT was shown to be accompanied by a reduction of dopamine D2 receptor density in the rostral anterior cingulate cortex [21].

One central monoaminergic molecule is the monoamine oxidase A (MAO-A). It is the key enzyme responsible for the degradation of serotonin, norepinephrine and dopamine and its adequate function specifically maintains the homeostasis of cerebral serotonin concentrations in humans [22,23]. MAO inhibitors (MAOI) represent an important element in the therapeutic armamentarium of psychiatrists, notably the irreversible MAOI such as tranylcypromine were shown to be highly effective in TRD and atypical depression [24,25]. Due to less dietary restrictions and interactions with other serotonergic agents, reversible MAOI such as moclobemide are more commonly in use in clinical practice and studies support this class of antidepressants of being equally safe and tolerable as SSRIs [26,27]. In accordance with the monoamine hypothesis of depression [28], Meyer et al. showed that elevated cerebral MAO-A density measured using PET represents one of the main serotonin-lowering processes in medication-free depressed patients and may even constitute a trait marker of major depression [29,30]. In fact, studies find that MAO-A levels were 34–40% higher in MDD than in healthy controls [30,31]. This relative difference constitutes one of the largest discrepancies between depressed and healthy subjects in terms of a molecular endophenotype of MDD. A significant elevation of MAO-A was also found in the hypothalamic regions in postmortem brains of suicide victims [32]. Furthermore, increased MAO-A expression has been associated with the early postpartum period [33], perimenopause [34], and severe, atypical depression [35]. Brain MAO-A availability was shown to be affected by moclobemide and MAO-A occupancy levels of 74% were proposed as a desirable threshold level to have therapeutic impact in MDD [36,37].

At present, it is a challenge to reliably assess the direct or indirect impact of antidepressant treatments on MAO-A in depression. As a logical consequence the present study aimed at investigating the availability of MAO-A in its role as major monoamine-regulatory enzyme with respect to the most effective therapeutic tool currently available in the treatment of depression, namely ECT. The development of accurate neuroimaging techniques and specific radioligands has broadened the possibilities of analyzing the major components of the monoaminergic system. As the current state-of-the-art investigational tool for examining central MAO-A in humans, [^{11}C]harmine (7-[^{11}C]methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole) is a highly selective, reversible MAO-A ligand for PET allowing *in vivo* measurements of the volume of distribution (V_T) of MAO-A, an index of MAO-A expression or density [30,38,39]. Here, we determined MAO-A V_T in TRD patients before and after a course of ECT compared to healthy subjects using PET and the tracer [^{11}C] harmine in order to expand our previous findings regarding the effect of ECT on serotonin-1A receptor levels [18] and provide a further coherent explanatory model for ECT's mechanism of action.

Material and methods

Subjects and study design

Two groups of subjects were enrolled in the study: 16 inpatients with severe unipolar depression (mean age ± SD = 45.94 ± 9.68 years, 12 women) and 16 carefully matched healthy subjects (mean age ± SD = 44.69 ± 8.74 years, 12 women). Depressed participants were scanned with [^{11}C]harmine PET three times: twice before (PET1, PET2) and once after (PET3) a minimum of eight ECT sessions. All three measurements were carried out during continuous and unmodified psychopharmacological treatment. The first two baseline scans (PET1, PET2) were carried out within one week before the first ECT session to determine the test-retest variability under medication. Illness severity assessed by means of the 17-item Hamilton Rating Scale for Depression (HAM-D) was recorded at screening visit (baseline), before the 1st ECT session (PET2) and after ECT termination (PET3). Control subjects were scanned once. All subjects were in the age range between 18 and 60 years. A pregnancy test was performed at study inclusion and before PET to exclude pregnancy in female participants. Demographical data of both groups is displayed in Table 1.

Depressed patients were elected for inclusion in this imaging study after establishment of the indication for ECT by their respective treating physician at the Department of Psychiatry and Psychotherapy of the Medical University of Vienna, Austria. All patients fulfilled the criteria for TRD and had accomplished at least two trials with antidepressants including augmentation strategies of different pharmacological classes at sufficient dosage and duration in the current episode [3,5,40]. The diagnosis was confirmed using the Structured Clinical Interview for DSM-IV (SCID), while HAM-D scores had to be equal to or higher than 23 points (severe depression). All patients also met criteria for major depressive disorder according to DSM-5 (assessed retrospectively, https://www.psychiatry.org/psychiatrists/practice/dsm). All subjects suffered from recurrent

Table 1
Demographical data.

Demographic data		min	max	mean	SD	T	p
TRD patients	Age (years)	24	58	45.94	9.68	–	–
	Sex	12F, 4M	–	–	–	–	–
	Age at onset (years)	20	55	33.88	11.8	–	–
	Illness duration (years)	<1 year	30	12.06	11.34	–	–
	N of patient with and without psychotic depression	4, 12	–	–	–	–	–
	Number of ECT sessions	8	11	8.56	0.96	–	–
	Seizure duration (seconds)	24.88	59.38	40.42	10.79	–	–
	Mean stimulation charge (mC)	163.80	472.50	326.29	136.23	–	–
	HAM-D before ECT (screening visit)	22	33	25.13	3.16	–	–
	HAM-D before ECT (PET 2)	8	33	22.63	6.17	–	–
	HAM-D after ECT	1	18	7.44	4.98	–	–
	mean difference of baseline HAM-D (baseline vs. PET 2)	–	–	2.50	−3.01	1.44	0.16
	mean HAM-D reduction after ECT (compared to baseline)	–	–	17.68	−1.82	12.00	<0.001
	mean HAM-D reduction after ECT (compared to PET 2)	–	–	15.19	1.19	7.66	<0.001
HC	Age	24	58	44.69	8.74	–	–
	Sex	12F, 4M	–	–	–	–	–

Demographic data of patients suffering from treatment-resistant depression (TRD) and healthy control (HC) subjects are summarized. F = female, M = male, Min = minimum, max = maximum, SD = standard deviation, ECT = electroconvulsive therapy, HAMD = Hamilton Depression Rating Scale, mC = millicoulomb, PET, positron emission tomography.

depression, 12 without and four with psychotic symptoms. Illness duration and age of onset was assessed by interviewing the patients and based on the previously recorded medical history. Depressed participants had to fulfill inclusion criteria for ECT, including an internistic and anaesthesiological approval (electrocardiography, thoracic X-ray, laboratory measurements, physical examination). Exclusion criteria were concomitant major neurologic illness, current substance abuse (including nicotine abuse as cigarette smoking has been associated with lower MAO-A levels [33]), schizophrenia or schizoaffective disorder and previous ECT. Current substance abuse was ruled out using the SCID and a routine urine drug screening including cotinine. A causal relationship of mood disturbances and general medical conditions was further ruled out by routine laboratory measurements (electrolyte levels, complete blood cell count, thyroid function and virology). Treatment with drugs targeting directly the MAO-A, such as moclobemide, was not admitted and had to be discontinued at least for six month prior inclusion. For ethical reasons, antidepressant medication and augmentation therapy with antipsychotics was continued and had to be left unchanged during ECT and study participation (see Table A1 for an overview of psychotropic medication of the sample). Mood-stabilizers were similarly tolerated; however, dosages of drugs with anticonvulsant properties and lithium had to be reduced prior to study enrollment to not compromise ECT and prevent delirium [41,42]. All drugs had to be in steady state for at least ten days before inclusion, apart from benzodiazepines that were tolerated in varying dosage and administered on demand given the clinical indication (see Table A1). From the initially screened 21 patients, four patients were screening failures (due to refusal of arterial blood sampling and refusal of ECT, multi-morbidity, previous treatment with ECT), while one patient dropped out after the first PET measurement because of discontinuation of inpatient therapy before start of the first ECT session. Therefore, 16 patients were enrolled in the final analysis.

The age- and sex-matched control subjects were in part newly recruited for the study by local advertisement. Seven healthy subjects with compatible inclusion criteria had participated in an earlier PET study using [^{11}C]harmine at the Department of Psychiatry and Psychotherapy of the Medical University of Vienna (Austrian Science Fund, FWF P24359) [43] and the available image data were used (identical PET protocol, same PET scanner). PET measurements of healthy individuals had to be performed during the same season (fall/winter or spring/summer) as patients to rule out seasonal variations of MAO-A V_T which have been shown previously by our group [43]. Subjects had to be physically healthy, non-smoking and without any history of previous mental disorder or treatment with psychotropic medication. General health was ensured by physical examination, electrocardiography and routine laboratory measurements.

All subjects provided written informed consent after detailed explanation of the study by an experienced psychiatrist. The participants were reimbursed for participation. The study was approved by the Ethics Committee of the Medical University of Vienna and the General Hospital of Vienna.

Electroconvulsive therapy (ECT)

Electroconvulsive therapy was conducted using the Thymatron® System IV device (Somatics, LLC., Lake Bluff, Illinois, USA) according to the standard operating procedures of the Department of Psychiatry and Psychotherapy, based on international guidelines and consensus statements for ECT [3,44–46]. ECT was carried out twice or three times weekly under anesthesia with methohexital and administration of the muscle relaxant succinylcholine. The stimulation method was restricted to a unilateral electrode placement at the right frontotemporal position and a brief pulse width of 0.50 ms. The exclusivity of a unilateral treatment not only reduces the risk for cognitive side effects [47] but also the number of confounding variables potentially creating a greater MAO-A variability in the sample. If a switch to a bilateral treatment approach was indicated due to insufficient response, low ictal quality or acuity of the mental state, the patient had to be withdrawn from the study. Seizure duration was determined routinely by electroencephalography (EEG). Furthermore, an electromyogram (EMG) was recorded on one forearm to monitor the magnitude and duration of the generalized seizure in the muscle. Stimulus titration started with 50.4 mC (=10% of maximum charge at the Thymatron device); if necessary, re-stimulation was performed in increasing steps of 25.2 mC (=5% of maximum charge) until a successful treatment was achieved (assessment of seizure duration, seizure amplitude, central inhibition, ictal coherence and autonomic activation). This stimulus intensity was then defined as the seizure-threshold [48]. The 2nd treatment was administered with a stimulus dosage three-times the seizure threshold. Further ECT sessions were individually titrated according to the clinical antidepressant response of the patient and/or measurable EEG correlates (e.g., seizure duration, ictal power, postictal suppression) [45,49,50]. A minimum of eight ECT sessions were carried out between PET2 and PET3 depending on the availability of respective time slots for PET measurements after the 8th ECT. If no time slot was available at that stage,

unilateral ECT was continued until the PET could be carried out. Changes in depressive symptoms after ECT were assessed according to the HAM-D score.

Positron emission tomography (PET)

Synthesis and quality control of [^{11}C]harmine, (7-[^{11}C]methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole) was performed as published by our group [51]. All PET scans were carried out using a GE Advance full-ring scanner situated at the PET Centre, Division of Nuclear Medicine, at the Medical University of Vienna. For attenuation correction a transmission scan of 5 min was performed with ^{68}Ge rod sources. An intravenous bolus of [^{11}C]harmine (4.6 MBq/kg body weight) was administered simultaneously with the start of the dynamic PET scan. PET scans were acquired in 3D mode with a total scanning time of 90 min, separated into 51 optimized time frames, a spatial resolution of 4.36 mm full-width at half-maximum one cm next to the centre of the field of view and reconstructed in 35 transaxial section volumes with an iterative filtered back-projection algorithm (128 × 128 matrix). Automatic arterial blood sampling was carried out continuously for the first 10 min at a rate of 4 ml/min (ALLOGG, Mariefred, Sweden) and manually at 5, 10, 20, 30, 45, 60, and 80 min after [^{11}C]harmine injection [38]. A cross-calibrated gamma counter was used to calculate radioactivity concentrations in plasma. Radioactive metabolites of the tracer were determined using high-performance liquid chromatography (HPLC) [52].

Magnetic resonance imaging (MRI)

For co-registration of PET data in SPM (Wellcome Trust Centre for Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/), every subject underwent a T1-weighted structural MRI scan performed using a 3 Tesla PRISMA MR or 3 Tesla Biograph mMR Scanner (Siemens Medical, Erlangen, Germany, 1 × 1 mm voxel size, 1.1 mm slice thickness, 200 slices), or a 3 Tesla Achieva MR Scanner (Philipps, Best, Netherlands, 0.47 × 0.47 mm voxel size, 0.88 mm slice thickness, 180 slices).

Data preprocessing and monoamine oxidase A quantification

Quantification was carried out using PMOD 3.509 (PMOD Technologies Ltd., Zurich, Switzerland; www.pmod.com). By multiplication of whole blood activity, plasma-to-whole blood ratio and the fraction of intact radioligand in the plasma, the final arterial input function (AIF) was obtained. MAO-A volume of distribution V_T was quantified by using the constrained two-tissue compartment model (2TCM). To assure a stable outcome, the fit of K_1/k_2 was carried out by coupling the frontal, temporal, parietal, occipital and cingulate cortex, amygdala and hippocampal complex, insula, striatum, thalamus, midbrain and the cerebellar gray matter [38]. Regional V_T were delineated by regions-of-interest (ROIs) from the AAL atlas [53,54], in combination with a delineation of the midbrain in standard space, and fitted along with the kinetic modelling procedure.

The primary endpoint of the analyses was MAO-A V_T in 27 ROIs (13 homologous areas in both hemispheres and one central structure), namely the superior, middle and inferior frontal gyrus, superior, middle and inferior temporal gyrus, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), hippocampus, amygdala, caudate, putamen, thalamus, separated for both hemispheres, and midbrain (AAL atlas) [53]. ROI-selection was based on previous findings in the context of MAO-A expression in depression as well as our previous PET study investigating the serotonin-1A receptor [18,29,30].

Statistical analysis

IBM SPSS statistics 23 was used for statistical analysis

First, we performed a linear mixed model analysis to assess the effects of ECT on regional MAO-A V_T using time point (PET1, PET2 and PET3), ROI and hemisphere as fixed factors and subjects as the random factor. Of note, the factor hemisphere was introduced in the statistical model as a right-unilateral stimulus method was used during ECT procedure potentially bearing lateralized effects on MAO-A distribution. Non-significant interactions were dropped from further analyses and *post-hoc* pairwise computations were corrected for multiple comparisons using the Bonferroni procedure. Residuals showed a normal distribution although values from the main model were positively skewed. Thus, additional non-parametric analyses on predicted values from the mixed model were performed to validate our findings. Further, to test for potential confounders, additional models were computed to assess effects of age, age of disease onset, illness duration as well as seizure duration. The covariance structure for each model was chosen based on the Akaike information criterion. Cohen's d was computed to estimate the effect size of MAO-A V_T changes.

Secondly, we performed a linear mixed model analysis to assess baseline differences in regional MAO-A V_T between TRD subjects (PET1) and healthy controls using group as between-subjects factor, ROI and hemisphere as repeated factors and subjects as the random factor.

To assess treatment response to ECT, a paired *t*-test was performed contrasting pre-treatment and post-treatment HAMD scores in the patients' group.

The significance level was set at 0.05 in all analyses. Further exploratory evaluations of data are presented at an uncorrected significance level.

Results

There was no significant difference in depression severity between screening visit and the visit before the 1st ECT session ($t = 1.44$, $p = 0.16$, see Table 1). ECT led to a significant reduction of HAM-D scores in TRD patients ($t = 12.00$, $p < 0.001$, see Table 1), corresponding to a response rate of 87.5%. Of 16 treated patients, 14 were considered as treatment responders, given a reduction of the baseline HAM-D by $\geq 50\%$. 10 (62.5%) of the latter were even considered as remitters with HAM-D$\leq$7 after ECT. Two patients failed to respond to ECT. Patients were treated with an average of 8.56 ± 0.96 (mean ± SD) right-unilateral ECT sessions and showed mean seizure duration of 40.42 ± 10.79 s (see Table 1).

Linear mixed model analysis assessing the effect of ECT on MAO-A V_T in depressed patients revealed a main effect of time ($F = 14.21$, $p < 0.001$) and ROI ($F = 51.68$, $p < 0.001$) and an interaction between hemisphere and ROI ($F = 3.37$, $p < 0.001$). The three-way interaction as well as other two-way interactions and main effects were non-significant. Post-hoc comparisons revealed a significant decrease of overall MAO-A V_T at PET3 compared to PET1 and PET2, and at PET2 compared to PET1 (both $p \leq 0.01$, corrected). Friedman's two-way analysis of variance (ANOVA) by ranks and Wilcoxon tests confirmed MAO-A V_T decreases over time (all $p < 0.001$, corrected). The estimates of mean MAO-A V_T over all 27 ROIs were 22.75 ± 1.12 (mean ± standard error, SE) at PET1, 22.06 ± 1.11 at PET2 and 21.23 ± 1.14 at PET3 (see Fig. 1). The test-retest variability of mean MAO-A V_T values between PET1 and PET2 was 3.1%, as calculated using the equation (PET1-PET2)/[(PET1+PET2)/2]x100 (Cohen's $d = 0.25$). Comparably, the effect of ECT on MAO-A V_T was 3.8%, calculated as (PET2-PET3)/[(PET2+PET3)/2]x100 (Cohen's $d = 0.29$). Using paired-samples *t*-test, change scores of MAO-A V_T between PET1 and PET2 were compared to change scores of MAO-A V_T between PET2 and PET3,

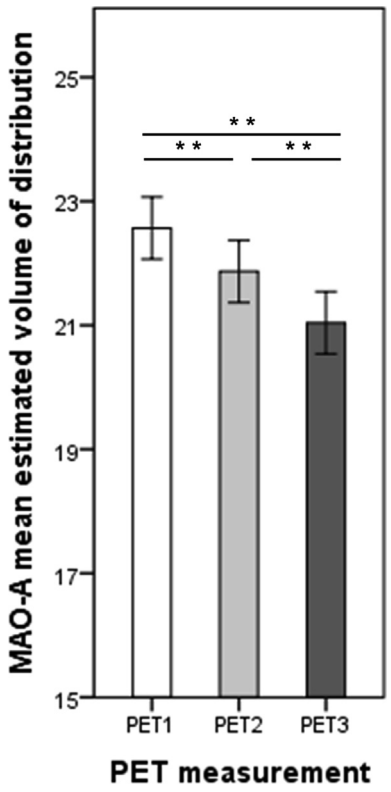

Fig. 1. Bar plot showing the estimates of mean MAO-A V_T over all 27 ROIs in 16 depressed patients. Error bars represent ±2 standard errors (SE). Differences in MAO-A V_T were significant when comparing PET1 and PET3, PET2 and PET3 as well as PET1 and PET2 (all $p < 0.01$, corrected). ** corresponds to $p \leq 0.01$. Between PET1 and PET2 MAO-A V_T decreased by 3.1% (test-retest assessment before start of treatment), between PET2 and PET3 by 3.8% (assumed effect of electroconvulsive therapy in the range of test-retest variability).

showing no significant difference (left hemisphere $p = 0.49$, right hemisphere $p = 0.24$). An exemplary MAO-A volume of distribution map of the patients' group before ECT is shown in Fig.2 with a specific delineation of all ROIs investigated in the statistical analysis.

An exploratory evaluation of ECT-induced MAO-A V_T changes for each ROI separately revealed no significant main effect of time. Furthermore, post-hoc comparisons showed no significant difference, though a numerical reduction of V_T after ECT could be observed in each of the ROIs investigated (see Table 2 and Fig. 3). Repeating the analysis only including women (four men excluded from the analysis) revealed a significant reduction of MAO-A V_T after ECT in the superior temporal gyrus ($p = 0.045$) and a trend for MAO-A V_T reductions in the ACC, PCC and amygdala (all $p < 0.09$, uncorrected). Excluding the two non-responders or excluding the four patients with additional psychotic symptoms had no effect on our findings, respectively. Moreover, testing for an effect of age, age at disease onset, illness and mean seizure duration had no influence on the non-significance of our results.

Comparing MAO-A V_T between healthy controls and patients at baseline (PET1) revealed a significant main effect of ROI ($F = 133.96$, $p < 0.001$) as well as a significant interaction between group and hemisphere ($F = 9.69$, $p = 0.002$) and between hemisphere and ROI ($F = 6.58$, $p < 0.001$). Post-hoc separate analyses per hemisphere, however, revealed only numerical differences between groups, indicating slightly lower mean MAO-A V_T in healthy controls compared to TRD patients in the right (21.28 ± 1.3 versus 22.95 ± 1.3, mean ± SE), and left hemisphere (21.38 ± 1.3 versus 22.31 ± 1.3, mean ± SE). Mean regional MAO-A V_T in HC is summarized in Table 2. Disentangling the interaction between hemisphere and ROI revealed higher MAO-A V_T in the right compared to the left hemisphere for the superior frontal gyrus middle temporal gyrus, putamen and thalamus, and higher MAO-A V_T in the in left compared to right hemisphere in the middle frontal gyrus, ACC, PCC and superior temporal gyrus (all $p < 0.05$, uncorrected). When excluding the four men from the analysis, the mixed model comparing MAO-A V_T between healthy controls and TRD patients at baseline (PET1) revealed a main effect of group ($F = 8.92$, $p = 0.007$) and ROI ($F = 111.83$, $p < 0.001$), a significant interaction between group and hemisphere ($F = 9.43$, $p = 0.002$), group and ROI ($F = 2.68$, $p = 0.001$) and hemisphere and ROI ($F = 5.72$, $p < 0.001$), but no significant three-way interaction. However, using a paired *t*-test we further explored ROI-wise the effect of group showing an increased MAO-A V_T in TRD women compared to healthy controls in nearly every ROI investigated (see Table B1, all p values uncorrected). Finally excluding the four patients suffering from psychotic depression from the analysis had no effect on our findings.

Discussion

The main finding of this longitudinal PET study is that MAO-A distribution volume assessed over 27 regions of interest was

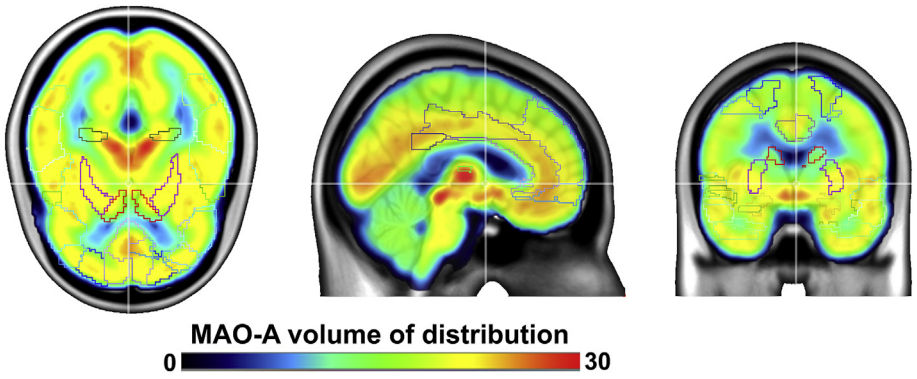

Fig. 2. Exemplary map of monoamine oxidase A volume of distribution (MAO-A V_T) before ECT displayed on a triplanar view superimposed on T1-weighted MRI images. Shown are mean MAO-A V_T in all patients before ECT. The regions of interests (ROI) used for statistics are indicated by colored lines. Selected ROIs are: superior, middle and inferior frontal gyrus, superior, middle and inferior temporal gyrus, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), hippocampus, amygdala, caudate, putamen, thalamus, separated for both hemispheres, and midbrain (AAL atlas [53]). The color table indicates MAO-A V_T. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Mean regional MAO-A V_T in treatment-resistant depression (TRD) patients and healthy controls (HC).

Region of interest (AAL)	TRD						HC	
	PET 1		PET 2		PET 3		mean	SE
	mean	SE	mean	SE	mean	SE		
superior frontal gyrus_L	18.26	1.17	17.76	1.12	17.04	1.31	17.31	0.89
superior frontal gyrus_R	18.90	1.25	18.22	1.15	17.60	1.16	17.45	0.97
middle frontal gyrus_L	19.92	1.03	19.04	1.01	18.66	1.20	18.64	0.81
middle frontal gyrus_R	19.17	1.18	18.50	1.07	17.75	1.33	20.78	0.95
inferior frontal gyrus orbital part_L	19.22	1.35	18.86	1.23	18.13	1.62	19.12	0.91
inferior frontal gyrus orbital part_R	19.68	1.12	18.45	0.89	18.45	1.24	18.47	0.88
anterior cingulate cortex_L	25.09	1.44	23.98	1.27	23.57	1.27	23.62	1.16
anterior cingulate cortex_R	24.92	1.50	23.36	1.22	22.87	1.58	22.04	1.15
posterior cingulate cortex_L	23.06	1.44	21.42	1.12	20.78	1.14	20.38	0.87
posterior cingulate cortex_R	20.08	1.28	18.47	0.98	18.27	0,98	17.31	0.80
hippocampus_L	22.61	1.81	21.88	1.62	20.71	2.22	22.59	1.54
hippocampus_R	24.58	1.31	23.54	1.16	23.37	1.83	22.42	1.29
amygdala_L	26.71	1.72	27.11	1.88	25.19	2.25	26.41	1.85
amygdala_R	28.00	1.64	25.91	1.46	25.91	2.18	26.41	1.95
caudate nucleus_L	18.88	1.09	17.77	0.85	17.23	1.12	17.63	0.85
caudate nucleus_R	17.86	1.11	17.73	1.08	16.88	1.40	17.78	0.95
putamen_L	21.27	1.60	22.00	1.57	20.06	1.97	21.53	1.13
putamen_R	23.92	1.42	23.08	1.26	21.94	1.68	22.23	0.97
thalamus_L	26.65	1.80	26.36	1.62	24.83	2.23	26.27	1.61
thalamus_R	28.21	1.71	27.12	1.53	26.39	2.17	27.28	1.58
superior temporal gyrus_L	24.73	1.42	23.13	1.21	22.82	1.56	22.71	1.09
superior temporal gyrus_R	22.69	1.21	21.29	1.05	20.91	1.40	20.62	1.06
middle temporal gyrus_L	20.75	1.42	20.69	1.43	18.78	1.76	20.78	1.01
middle temporal gyrus_R	22.81	1.32	21.57	1.14	20.79	1.57	20.78	0.95
inferior temporal gyrus_L	21.47	1.45	21.05	1.32	19.88	1.70	21.01	1.10
inferior temporal gyrus_R	22.71	1.29	21.55	1.12	21.13	1.43	20.49	0.96
midbrain	27.69	2.04	27.23	1.86	26.19	2.70	27.37	1.53

Mean regional MAO V_T (and standard error, SE) of patients suffering from treatment-resistant depression (TRD) at PET1 (baseline), PET2 (before start of electroconvulsive therapy, to assess test-retest reliability between both baseline scans) and PET3 (after a series of eight to ten electroconvulsive therapies) and sex- and age-matched healthy controls (HC, measured only once), shown for each regions of interest separately. Though numerical reductions of MAO V_T after ECT can be observed in each of the investigated ROIs in the TRD sample, no significant difference in MAO-A V_T between scans could be determined in single ROIs. Baseline MAO-A V_T (PET1, PET2) in patients did not differ from MAO-A V_T in HC. AAL = automated anatomical labelling [53].

found to be unaffected by a series of minimum eight unilateral ECT sessions. More specifically, though MAO-A V_T was shown to be significantly reduced after ECT in depressed patients (linear mixed model), the small effect size of −3.8% was shown to lie in the range of the determined test-retest variability in this sample (3.1%). This was further underlined by a direct comparison (paired *t*-test) of change scores of MAO-A V_T between PET1 and PET2 (both baseline scans) and those between PET2 and PET3 which was not significant. A reduction of MAO-A V_T of 3–4% is unlikely to have clinically meaningful effects given that MAO-A occupancies range between 74 and 87% for moclobemide at different dosages and around 87% for phenelzine [37]. Therefore, our finding does not effectively support the hypothesis of a clinically relevant mechanism of action of ECT based on cerebral MAO-A expression. Nevertheless, on the basis of the assumed boost of monoaminergic neurotransmission following ECT which was shown in preclinical studies [17], on one hand one might have anticipated an upregulation of cerebral MAO-A levels in terms of a compensatory mechanism for the overload of released monoamines. On the other hand, building on the evidence retrieved from the PET studies published by Meyer et al. showing an increased MAO-A V_T in MDD patients [29,30], one might as well have expected a down-regulation, albeit indirectly triggered, in line with a "normalization" of monoaminergic neurotransmission following response to ECT. Regarding the latter, our negative finding is in accordance with a PET study showing that MAO-A V_T remained unchanged after a six-week trial with SSRI implying that the antidepressant-treated state does not equal the healthy state on a molecular level even when remission can be achieved [29]. Given the higher potency [55], broader spectrum of effects and diagnostic-unspecificity of ECT compared to SSRI [56], an effect on MAO-A levels could still have been expected. Also, as ECT was shown to affect serotonergic neurotransmission on multiple levels with previously published reports showing changes in serotonin-1A and 2A receptor density following a course of ECT [18,57], a relevant change in MAO-A expression after treatment might have seemed intuitive.

Compared to previously published neuroimaging studies in the field [29,30,33–36], the depressed sample included in the present study was medicated. We must assume that the psychopharmacological medication administered to the patients in this sample acting on different molecular targets may explain the fact that we could not reliably validate the previously reported higher MAO-A V_T in medication-free, severely depressed patients compared to healthy subjects [30,35]. These effects might be masked by medication-induced changes or interactions in our sample, considering that the potency of most of the drugs administered continuously during study participation (see Table A1) in inhibiting MAO-A (IC_{50}) is not known. Also, illness severity seems to be a crucial factor regarding the reported elevation of cerebral MAO-A density which could not be observed in previously investigated mildly to moderately depressed patients, even when unmedicated [35,36]. Here, we included only patients with a $HAMD_{17}$ greater than 23 referred to the department for the administration of ECT and fulfilling criteria for treatment-resistance [3,40,43]. TRD is associated with distinct sociodemographic, clinical and biological risk factors that are not necessarily associated with non-treatment-resistant depression [4,5,58–61] which might equally contribute to the fact that we could not ascertain the findings published by Meyer et al. [30]. Elevated MAO-A might indeed represent a trait marker of depression or at least increase the vulnerability to

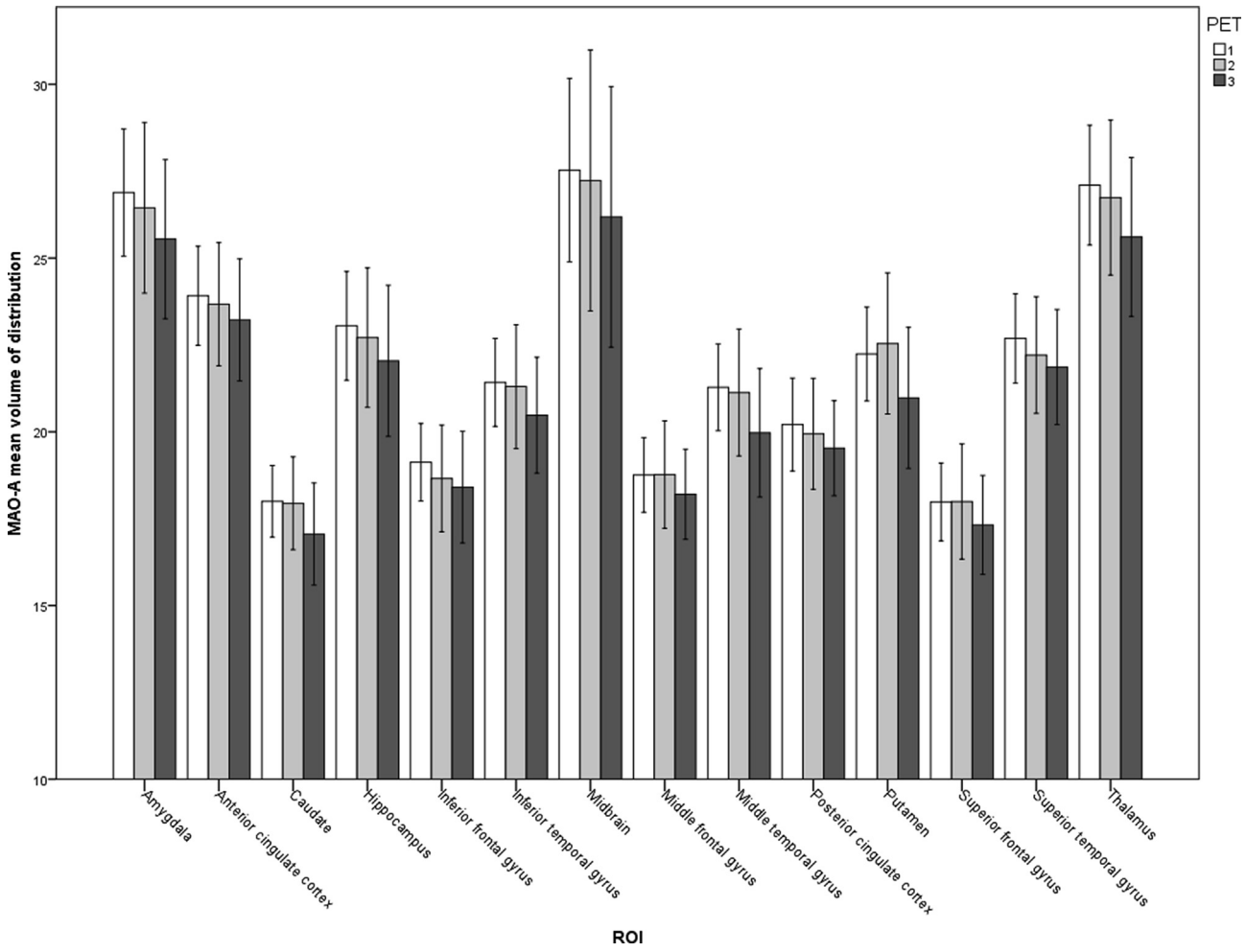

Fig. 3. Bar plot displaying mean MAO-A V_T in 27 regions of interest at PET1, PET2 and PET3. Error bars represent ±2 standard errors (SE). MAO-A V_T changes for each region of interest (ROI) revealed no significant main effect of time though a numerical reduction of V_T after electroconvulsive therapy (ECT) can be observed.

developing the disorder; however, based on the current evidence in this concern, no definitive conclusions can be drawn regarding MAO-A expression neither in TRD nor under long-term antidepressant treatment. Another relevant factor is that out of twelve women included in this study nine were over 45 years of age at study inclusion. MAO-A V_T was reported to be elevated by 34% in perimenopausal women compared with reproductive age and by 16% compared with menopause [34], an effect similar to the impact of MDD on MAO-A V_T [30] and therefore potentially biasing our findings. Though the exclusion of men did not have an impact on the non-significance of our longitudinal findings, the exploratory analysis performed on the baseline data (TRD vs. healthy women) showed elevated MAO-A V_T in nearly every ROI investigated in patients, conforming with previous data (see Table B1) [30]. We cannot rule out that changes of MAO-A V_T associated with peri- and postmenopause in our sample not only mask TRD-induced alterations of MAO-A density but also possible ECT-induced effects. However, as age- and sex-matched controls were included in our analysis, we consider these effects to be corrected for.

Though MAO-A density was shown to be unaffected by clinical response to short-term use of SSRI (six weeks) in previously untreated depressed patients [29], we must assume - as stated before - a relevant influence of long-term antidepressant treatment on MAO-A expression that potentially influences our findings. To minimize this bias, psychopharmacological treatment remained unchanged during study participation with the exception of benzodiazepines. Nevertheless, from a clinician's point of view and for ethical reasons, a discontinuation of treatment was inacceptable in this severely-ill TRD sample. Moreover, this sample rather reflects the real-world clinical situation that physicians are facing when dealing with treatment-resistant patients. In fact, in clinical practice antidepressant treatment is commonly continued during ECT (apart from punctual discontinuation before an ECT session to reduce risk for hypertension or delirium for noradrenergic agents or lithium, respectively) [41,42] as positive synergistic effects of both treatment options are expected [62,63], though this approach is not necessarily supported by controlled trials [64]. The present findings indirectly support the continuation of pharmacological antidepressant treatment after a course of ECT, which is generally performed to prevent relapse [65], by providing a rational for the use MAOI as an independent treatment option after completion of ECT as both seem to have distinct mechanisms of action and thereby bear synergistic potential in terms of antidepressant potency. Interestingly, both therapeutic options are usually considered when it comes to treatment-resistant conditions in MDD [26,66]. However, clinical studies are needed to substantiate this assumption as the present study was not designed to test this hypothesis. The theory that the combination of MAOI and ECT is associated with a higher cardiovascular risk was not supported by the literature [67,68].

Several limitations to the study must be addressed. We used only unilateral ECT in this investigation. This approach was chosen in order to unify our sample and limit cognitive side effects potentially associated with ECT and changes in MAO-A expression. Bilateral ECT often considered being more effective in depression [69], we cannot extrapolate from our present findings to the effects of bilateral ECT on MAO-A V_T. However, the factor hemisphere being incorporated in our statistical model, we could not detect lateralized effects of ECT on MAO-A V_T. The response rates of 87.5% achieved in our sample align with those commonly reported in the literature and support critical voices that consider high-dosage unilateral ECT as similarly effective as bilateral treatment [2]. Further, changes in menstrual cycle length (perimenopause) and menopause were not specifically assessed in our study. Women in this age class are at high risk for major depression [70,71] and therefore likely to be referred to a specific antidepressant treatment including ECT. Lastly, no psychometric scales apart from the HAMD were recorded in this study. Evidence points towards an association of MAO-A density with atypical depression [35], REM sleep deprivation which is closely associated with MDD [72] as well as glucocorticoid exposure (acute and chronic stress) [73,74]. In fact, the inpatient stay itself might impact on MAO-A levels via changes in experienced stress levels and associated sleep pattern deviations, thereby influencing test-retest variability of MAO-A V_T (−3.1%). Though depression severity remained unchanged in TRD patients before the start of ECT, we recommend future studies focused on MAO-A to specifically consider these factors.

In summary, we were able to detect a significant reduction of MAO-A V_T assessed over 27 regions of interest involved in the pathophysiology of depression after a course of ECT [30]. However, the effect size was small and similar to the test-retest variability determined in this study. We are led to conclude that MAO-A does not significantly contribute to the mechanism of action of ECT in treating depression. In the present analysis, MAO-A V_T of medicated TRD patients did not significantly differ from healthy controls. As ECT was shown to influence other major players involved in the pathophysiology of MDD, such as the serotonin-1A [18] and serotonin-2A receptor [57], further studies in this research direction seem necessary to complete the picture of ECT's effect on serotonergic neurotransmission. Moreover, our findings provide a theoretical basis for the use of MAOI in treatment-resistant patients after ECT, as both treatment options exhibit distinct mechanisms of action.

Conflict of interest

Without any relevance to this work, P. Baldinger-Melich declares that she has received an Erasmus + Staff Mobility Grant. S. Kasper declares that he has received grants/research support, consulting fees and/or honoraria within the last three years from Angelini, AOP Orphan Pharmaceuticals AG, AstraZeneca, Celegne GmbH, Eli Lilly, Janssen-Cilag Pharma GmbH, KRKA-Pharma, Lundbeck A/S, Neuraxpharm, Pfizer, Pierre Fabre, Schwabe and Servier. R. Lanzenberger received travel grants and/or conference speaker honoraria from Shire, AstraZeneca, Lundbeck A/S, Dr. Willmar Schwabe GmbH, Orphan Pharmaceuticals AG, Janssen-Cilag Pharma GmbH, and Roche Austria GmbH. M. Mitterhauser received speaker honoria from GE Healthcare. W. Wadsak received speaker honoraria from Bayer. R. Frey declares that he has received grant/research support from Bristol-Myers Squibb, AstraZeneca, Sandoz, Eli Lilly, and Janssen. D. Winkler received speaker Honoria from Angelini, Lundbeck, Medizin Medien Austria, and ProMente.

Preliminary findings of this study were presented at the 30th CINP congress in Seoul, South Korea [75], the 30th ECNP congress in Paris, France [76], and the 48th SfN (Society of Neuroscience) Annual Meeting in San Diego, California [77].

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Appendix A. Supplementary data

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