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Cerebral perfusion is related to antidepressant effect and cognitive side effects of Electroconvulsive Therapy

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ABSTRACT

Background: The mechanisms underlying the antidepressant effect and cognitive side effects of Electroconvulsive Therapy (ECT) remain elusive. The measurement of cerebral perfusion provides an insight into brain physiology.
Objective: We investigated ECT-related perfusion changes in depressed patients and tested whether these changes correlate with clinical effects.
Methods: A sample of 22 in-patients was examined at three time points: 1) within two days before, 2) within one week after, and 3) six months after an ECT series. Cerebral perfusion was quantified using arterial spin labeling magnetic resonance imaging. The primary regions of interest were the bilateral dorsolateral prefrontal cortices (DL-PFC) and hippocampi. The depression severity was assessed by the six-item Hamilton Depression Rating Scale, and cognitive performance by the Screen for Cognitive Impairment in Psychiatry. A linear mixed model and partial correlation were used for statistical analyses.
Results: Following an ECT series, perfusion decreased in the right (−6.0%, p = .01) and left DL-PFC (−5.6%, p = .001). Perfusion increased in the left hippocampus (4.8%, p = .03), while on the right side the increase was insignificant (2.3%, p = .23). A larger perfusion reduction in the right DL-PFC correlated with a better antidepressant effect, and a larger perfusion increase in the right hippocampus with worse cognitive impairment.
Conclusion: ECT-induced attenuation of prefrontal activity may be related to clinical improvement, whereas a hippocampal process triggered by the treatment is likely associated with cognitive side effects.

1. Background

Electroconvulsive therapy (ECT) is the most effective treatment for severe depression [1]. The treatment considerably reduces the risk of suicide [2] and is safe [3–5]. However, there is a substantial variation in its use worldwide, even between socioeconomically comparable countries [6,7]. One of the reasons may be a stigma due to an insufficient understanding of the mechanisms underlying its action and side effects. Clarifying these mechanisms may reduce the stigma and facilitate further development of this treatment.

In the past two decades, many structural MR studies have reported significant gray matter volume increases in the hippocampus and other brain regions [8–10], suggesting that ECT works by boosting brain neuroplasticity. Our investigations of ECT's effects on hippocampal subfields and cortical thickness have contributed to this evidence [11,12]. However, these volume increases seem to be unrelated to the clinical effect [9,13,14], and it is unlikely that the structural MR studies alone can elucidate the mechanisms of ECT action. Fortunately, functional MRI can add valuable information to this research field. One way to investigate brain function is to track changes in cerebral perfusion (cerebral blood flow, CBF), as a regional increase in neuronal activity is followed by increased perfusion called “functional hyperemia” [15].

CBF and cerebral metabolic rate of glucose after ECT have primarily been investigated in older studies using single photon

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emission computed tomography (SPECT) and positron emission tomography (PET) [16–18]. Arterial spin labeling (ASL) can quantify CBF and is non-invasive since it does not require radioactive tracers [19]. Only two studies have used ASL to investigate depressed patients treated with ECT, yielding inconsistent results [20,21].

The current understanding of ECT-related CBF changes is limited. The results of studies are divergent, likely due to methodological differences, but the most replicable findings are reduced prefrontal metabolism [16–18] and increased hippocampal metabolism [16,22,23]. Prefrontal hypometabolism has been associated with clinical improvement [24,25], supporting the hypothesis that the improvement is mediated by the anticonvulsant properties of ECT [26,27]. Other anticonvulsive effects, such as pronounced slowing on an ictal EEG, a slow-wave pattern on a postictal EEG, and an increasing seizure threshold during an ECT series, have also been linked to the clinical effect [24,26–28].

In 2014, Abbott and colleagues proposed a model of ECT's working mechanism combing the anticonvulsive and neurotrophic effects [16]. According to this model, reduced prefrontal metabolism following ECT (the anticonvulsive effect) is responsible for immediate remission but is not sufficient for sustained remission. An increase in the hippocampal volume (the neurotrophic effect) [29–33] should be essential for sustained remission. However, most studies have not found associations between hippocampal volume enlargements and the clinical effect [8,9,13,14]. In contrast, recent studies suggest a link with cognitive side effects [34–36]. Indeed, the hippocampus is vital for memory formation [37], and ECT impairs this function [38,39]. This link is further strengthened by observations that higher electric charges are not only related to worse cognitive outcome, but also to larger hippocampal increases [13,40]. We, therefore, assumed that ECT causes temporary hippocampal dysfunction by triggering a biological process, increasing CBF in this region. However, whether increased hippocampal CBF is related to cognitive side effects has not yet been studied.

We hypothesized that reduced prefrontal CBF after ECT would be related to the antidepressant effect and increased hippocampal CBF would be associated with cognitive impairment.

2. Material and methods

2.1. Study design

This prospective study examined a cohort of in-patients with severe depression treated with ECT. The study protocol was registered on ClinicalTrials.gov before the participant enrollment (NCT 03040388). The patients were assessed at three time points: at baseline (pre-ECT, within two days before an ECT series), immediately after an ECT series (post-ECT, within one week after the last ECT session in an ECT series, median = 39 h, range 5–144 h), and finally, at a six-month follow-up. Overlapping samples were used in our investigation of the ECT's effect on hippocampal volume [11,34], serum S100B-protein concentration [41], and in a cortical thickness study [12].

The recruitment took place between 2017 and 2019. The eligibility criteria were 1) age: between 18 and 95 years, 2) admission to the Mental Health Center of the Capital Region of Denmark and treatment with an ECT series due to Major Depressive Disorder (MDD) or bipolar depression according to ICD-10 and DSM-IV. The exclusion criteria were 1) a severe physical disease potentially affecting the brain, 2) head trauma with unconsciousness lasting for more than 5 min, 3) ECT in the past six months, 4) dependency on psychoactive substances according to ICD-10, 5) schizophrenia, 6) high risk of suicide or severe psychotic symptoms, making patient transportation impossible, 7) any compulsory treatment, 8) MRI contraindications, including pregnancy.

The diagnosis of depression was validated using the Mini-International Neuropsychiatric Interview [42]. To exclude any organic causes of depression, all patients underwent physical and neurological examination, a blood sample screening (including B12-vitamin, folic acid, and thyroid-stimulating hormone), and an electrocardiogram. Urine tests were conducted to exclude any ongoing abuse of psychoactive substances.

2.2. Ethics statement

The Regional Ethical Committee of the Capital Region of Denmark approved the study before patient enrollment (H-16042082). All patients signed informed written consent. All study procedures comply with the ethical standard on human experimentation and are in accordance with the Helsinki Declaration.

2.3. ECT procedure

The treating clinicians solely made all decisions regarding the patients' treatment. All patients received a series of bitemporal ECT administered three times weekly by a Thymatron System IV device (Somatics, LLC, USA). Bitemporal treatment is in accordance with the guidelines of the Danish Psychiatric Association. A constant brief pulse width between 0.5 and 1.0 ms was applied. The initial percent charge was calculated as half of the patient's age (100% charge corresponding to 504 milliCoulombs). The following charges were based on the electroencephalogram (EEG) and clinical information. The patients continued ECT until 1) the remission, 2) no further improvement and increasing severe side effects. Anesthesia was achieved using Thiopental (2–4 mg/kg) and muscle relaxation by Suxamethonium (0.75 mg/kg). All patients continued psychotropic medication, and we calculated the intake in terms of the defined daily dose (DDD) used by the World Health Organization. Friedman's test showed that the doses did not change during the study (Supplementary information, Table S1).

2.4. Clinical data

The clinical assessment was conducted by the same researcher (KG) in all patients at three time points. The depression severity was measured by the six-item version of the Hamilton Rating Scale for Depression (HRSD-6) [43] because it has a sensitivity comparable to the 17-item version but is more homogenous as it measures core depressive symptoms [44]. The percentage change in HDRS-6 after the ECT series was calculated as follows: (post-ECT HDRS-6 score − pre-ECT HDRS-6 score)/pre-ECT HDRS-6 score x 100. A corresponding formula was applied for a percentage change in cognitive performance. Response was defined as a more than 50% reduction in the baseline HRSD-6, remission as an HRSD-6 score of 4 or less, and relapse as worsening the depressive symptoms in remitters, fulfilling the criteria for a depressive episode.

The cognitive performance was assessed by a Danish version of the Screen for Cognitive Impairment in Psychiatry (SCIP) [45], which has been described in detail in our previous publication [34]. The SCIP comprises five subtests 1) Immediate verbal learning, 2) Delayed verbal learning, 3) Working memory, 4) Verbal fluency, and 5) Processing speed, corresponding to comprehensive neuropsychological tests [45]. The SCIP is sensitive and specific to detecting cognitive impairment in patients with depression, and the cut-off score of impairment is 74 [45]. However, it does not measure retrograde amnesia for autobiographical information. We used three parallel versions of this instrument to reduce learning effect.

2.5. CBF definitions

CBF refers to cerebral perfusion, defined as the blood volume (ml) delivered to 100 ml of brain tissue in a time unit (a minute) and is expressed in ml/100 g/min, assuming a tissue density of 1 ml/g. Mean gray matter CBF is the average CBF to the whole cerebral gray matter. Regional CBF to each ROI was normalized for mean gray matter CBF to obtain relative CBF (relative CBF = regional CBF/mean gray matter CBF x 100). The relative CBF to a given ROI thus reflects the percentage of CBF to the entire gray matter.

2.6. MR data

All participants were scanned on a 3 Tesla Philips Achieva scanner using a 32-channel receive coil. For structural delineation, a T1-weighted high-resolution scan was acquired and processed using the standard longitudinal segmentation pipeline [46,47] of FreeSurfer, version 6.0.0 (http://surfer.nmr.mgh.harvard.edu/) as introduced in our previous work [11,12]. ASL data was acquired using a "2D echo planar pseudo-continuous ASL sequence" (20 axial slices; inter-slice timing = 53 ms; labeling duration = 1650 ms; post-labeling delay = 1600 ms; 40 label-control pairs; repetition time = 4200 ms; echo time = 16 ms; flip-angle = 90°; field of view = 240 x 240 × 119 mm^3; acquisition matrix = 88 x 88; slice thickness = 5 mm). A M_0 scan with the same acquisition parameters as the ASL sequence (repetition time = 10000 ms) was recorded. Voxel-wise perfusion maps were calculated using oxford asl (a part of FSL software, 6.0.5, FMRIB Oxford, UK) with standard settings for T_1 values and priors. The T_1-weighted and recorded M_0 images were used for quantification and registration to T_1-weighted anatomical space. Slice-timing differences were corrected using the inter-slice timing of 0.53 milliseconds.

The relative CBF was obtained for 82 gray matter ROIs derived from FreeSurfer. The 68 cortical ROIs (34 for each hemisphere) were anatomical gyral-based regions according to the Desikan-Killiany cortical atlas [48], and 14 subcortical ROIs (7 for each hemisphere) comprised the hippocampus, amygdala, thalamus, caudate nucleus, putamen, pallidum, and accumbens area.

2.7. Statistical analyses

We used 1) a hypothesis-driven analysis involving four primary ROIs and 2) a data-driven analysis involving all 82 ROIs. We chose the right and left rostral middle frontal gyrus and the right and left hippocampus as our primary ROIs. To make our results comparable with other studies, we refer to the rostral middle frontal gyrus as the dorsolateral prefrontal cortex (DL-PFC) since a large part of the DL-PFC consists of this gyrus. The data-driven analyses were corrected for multiple testing using Benjamini and Hochberg's false discovery rate (FDR) method [49] with a threshold of q = 0.05. Raw (not FDR-corrected) p-values were reported. The hypothesis-driven analyses were considered significant at a p-value less than .05. All analyses were performed using SPSS Statistics (Armonk, NY: IBM Corp., version 25.0).

2.7.1. Longitudinal changes in CBF and clinical measures

Longitudinal changes were investigated using a linear mixed model (LMM), which examined the fixed effects of the time used as a categorical variable. The unstructured covariance pattern and the restricted likelihood method were applied. The missing observations were assumed to be missing at random (MAR). The reasons for the missing data are reported in Supplementary information (Table S2).

2.7.2. Relationship between CBF and clinical effects

We used partial correlation to test whether CBF changes immediately after an ECT series were associated with clinical improvement (the percentage change in HRSD-6 score) and cognitive side effects (the percentage change in total SCIP score). These analyses were adjusted for age and gender.

2.7.3. Exploratory analyses

We examined the effect of 1) the number of ECT sessions, 2) the cumulative charge, and 3) the cumulative duration of EEG seizures on relative CBF to primary ROIs. Moreover, we tested whether changes in relative CBF correlated with changes in hippocampal volume and cortical thickness of DL-PFC.

3. Results

3.1. Sample characteristics

The cohort consisted of 22 in-patients treated with an ECT series due to severe depression (Table 1). One, two, and six CBF measurements were missing at pre-ECT, post-ECT, and six-month follow-up assessments, respectively. One six-month follow-up depression score was missing. Finally, at pre-ECT and six-month follow-up assessments, two and one cognitive performance scores were lacking. The reasons for the missing data are reported in Supplementary information (Table S2). The mean number of ECT sessions received by remitters was 11.0 (SD = 3.9), whereas non-remitters were treated with 14.6 sessions (SD = 5.7).

3.2. The clinical effects of ECT

The ECT had a considerable antidepressant effect in the sample. Remission was achieved in 13 patients (59%) and response in 17 (77%). The HRSD-6 score dropped from 14.4 to 5.1 points (mean difference = − 9.2, t = − 12.0, p = <.001) and remained low six months later. The mean difference between a six-month follow-up and a baseline score was − 10.4 (t = − 10.6, p < .001).

The cognitive performance worsened somewhat immediately after an ECT series. The total SCIP score dropped from 75.0 points to 63.2 (mean difference = − 11.9, t = − 4.2, p < .001). The patients regained the cognitive function at a six-month follow-up (the mean SCIP = 77.8 points) as there was no significant difference between the long-term follow-up and baseline assessment (mean difference = 2.7, t = 1.3, p = .22).

After the end of ECT, all patients were followed by psychiatric outpatient services. At the six-month follow-up, all but two patients were still taking the medication. Eighteen out of 21 patients (1 missing) were treated with antidepressants, 11 with antipsychotics, five with anticonvulsants, three with lithium, and one with benzodiazepines. Most patients remained stable; however, two individuals experienced relapse.

3.3. DL-PFC and hippocampus

3.3.1. Longitudinal CBF changes

The relative CBF to the right and left DL-PFC decreased significantly immediately after an ECT series by 5.6% and 6%, respectively (Fig. 1, Table 2). At the six-month follow-up, the relative CBF values were lower than pre-ECT values, but the differences were insignificant. The changes in relative hippocampal CBF went in the opposite direction (Fig. 1, Table 2). Immediately after an ECT series, the relative CBF to the right and left hippocampus increased by 2.3% and 4.8%, respectively; however, this was significant only on the left side. Six months later, the relative CBF to the right hippocampus

Table 1
Clinical characteristics of the cohort and ECT parameters.

DEMOGRAPHICS	
Patients (male/female), number	22 (11/11)
Age, years, mean (SD)	44.7 (11.4)
PSYCHOPATHOLOGY	
Patients with MDD/BD, number	21/1
Single/recurrent MDD	6/16
Duration of the current episode, months, median (IQR)	4.8 (7.0)
Duration of illness, years, median (IQR)	7.0 (14.0)
Age of onset of depressive disorder, mean (SD)	34.4 (12.4)
Baseline total HRSD-17 score, mean (SD)	28.0 (4.7)
Baseline total HRSD-6 score, mean (SD)	14.4 (2.5)
Patients with melancholia according to MINI, number	18
Patients with psychotic symptoms, number	6
PSYCHOPHARMACOLOGY	
Patients receiving psychotropic medication, number	22
Antidepressants	21
Antipsychotics	9
Antiepileptics	3
Lithium	2
Benzodiazepines	5
ECT	
Patients treated with bitemporal / right unilateral ECT, number	22/0
ECT-sessions in series, mean (SD)	12.5 (4.9)
Cumulative charge in series, %, median (IQR)	380.0 (340.0)
Cumulative EEG seizures duration in series, sec., mean (SD)	476.5 (240.0)

MDD: Major Depressive Disorder, BD: Bipolar depression, HAMD-17: 17-item Hamilton Rating Scale for Depression, HAMD-6: 6-item Hamilton Rating Scale for Depression, SD: Standard Deviation, IQR: Interquartile Range, MINI: Mini International Neuropsychiatric Interview. The charge of 100% corresponds to 504 millicoulombs.

was significantly lower than the baseline values, whereas no significant difference was present on the left side.

3.3.2. Relationship with clinical effects

There was a moderate positive correlation between the change in relative CBF in the right DL-PFC and depression score (Fig. 2A, Table 3). Patients with greater CBF reductions immediately after an ECT series had a better clinical effect. As depicted in Fig. 2A, all but

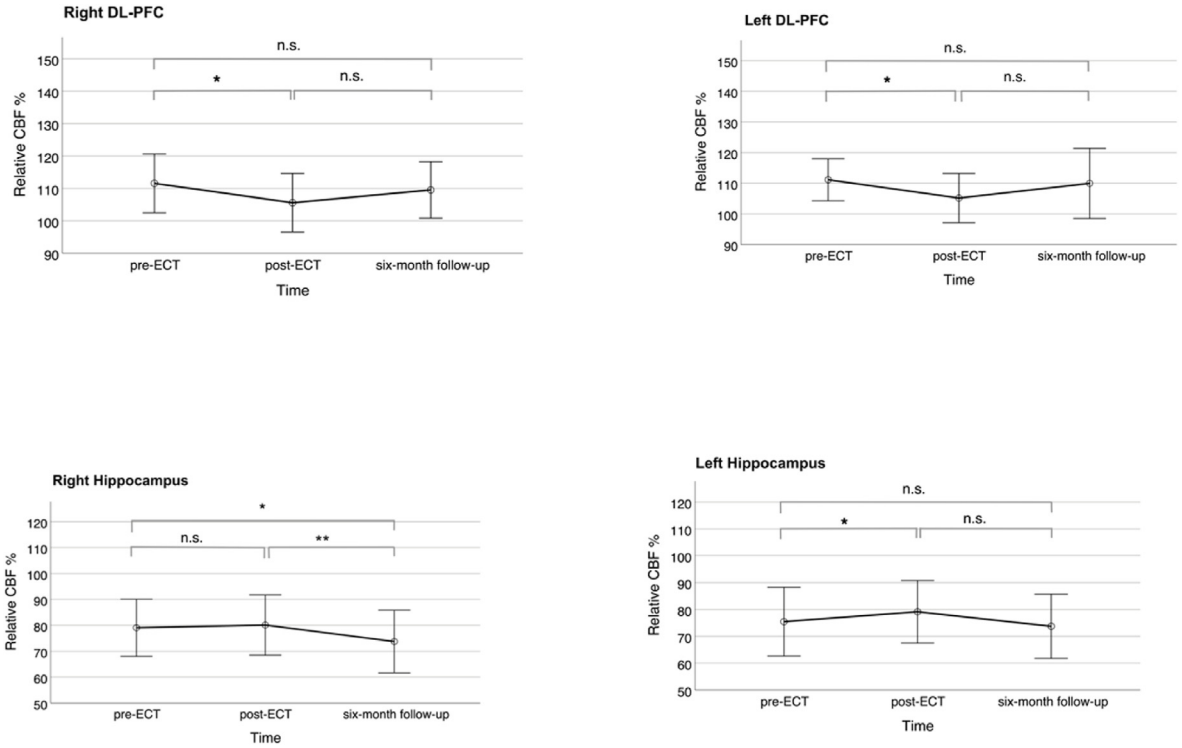

Fig. 1. The change in mean relative CBF to DL-PFC (upper row) hippocampus (lower row)
The asterisks indicate the significance level: <0.05*, <0.01**, <0.001***. Error bars depict one standard deviation of the sample mean. n.s.: non-significant, DL-PFC: Dorsolateral prefrontal cortex corresponding to the rostral middle frontal cortex (derived from FreeSurfer), CBF: Cerebral blood flow, pre-ECT: within two days before an ECT series, post-ECT: within one week after the series, six-month follow-up: 6 months after the series.

Table 2
The change in relative CBF to DL-PFC and hippocampi.

ROIs	Mean relative CBF (%) [a]								
	Pre-ECT (n = 21)			Post-ECT (n = 20)			Follow-up (n = 16)		
	Mean	(SE)		Mean	(SE)		Mean	(SE)	
Right DL-PFC	111.7	(2.0)		105.7	(2.0)		109.4	(2.1)	
Left DL-PFC	111.3	(1.5)		105.7	(1.8)		109.8	(2.8)	
Right Hippocampus	78.6	(2.4)		80.9	(2.6)		74.0	(3.2)	
Left Hippocampus	74.9	(2.8)		79.7	(2.6)		74.4	(2.8)	
ROIs	Mean change in relative CBF (%) [b]								
	Post-ECT vs Pre-ECT			Follow-up vs Post-ECT			Follow-up vs Pre-ECT		
	Mean	(SE)	p	Mean	(SE)	p	Mean	(SE)	p
Right DL-PFC	−6.0	(2.2)	0.014	3.6	(2.7)	0.186	−2.3	(3.0)	0.452
Left DL-PFC	−5.6	(1.4)	0.001	4.1	(3.1)	0.202	−1.6	(3.2)	0.638
Right Hippocampus	2.3	(2.0)	0.268	−6.9	(1.7)	0.001	−4.6	(2.1)	0.043
Left Hippocampus	4.8	(2.0)	0.026	−5.2	(2.5)	0.053	−0.4	(2.2)	0.842

Uncorrected p-values are reported. Pre-ECT: within two days before an ECT series, Post-ECT: within one week after the series, Follow-up: six months after the series, CBF: Cerebral blood flow, DL-PFC: Dorsolateral prefrontal cortex corresponding to rostral middle frontal cortex (derived from FreeSurfer). SE: Standard error, p: p-value, ROIs: Regions of interest.
[a] Estimated marginal means (derived from the Linear Mixed Model).
[b] Post-hoc pairwise comparisons based on the estimated marginal means.

one responder showed CBF reductions in the right DL-PFC. In contrast, three out of five non-responders showed increased CBF. A spaghetti plot showing changes in the right prefrontal CBF and depression score in individual subjects is available in Supplementary information (Fig. S1A). Our post hoc analyses revealed that the correlation was driven by an excellent responder showing a large CBF reduction (− 35%). After removing this individual, the correlation became weaker and was significant at a trend level (r = 0.48, p = .06, df = 14).

There was a moderate negative correlation between the change in relative CBF in the right hippocampus and the cognitive performance score (Fig. 2B, Table 3). Patients with larger CBF increases in this region had worse cognitive impairment. A spaghetti plot showing changes in the right hippocampal CBF and cognition in individual subjects is available in Supplementary information (Fig. S1B). We did not detect any significant correlations in the remaining primary ROIs (Table 3).

3.4. Data-driven analyses

3.4.1. Longitudinal CBF changes

In the data-driven approach, 82 ROIs were analyzed for CBF changes, and FDR correction for multiple testing was applied. Immediately after an ECT series, relative CBF to 20 regions changed significantly at p < .05 uncorrected (Supplementary information, Table S3). Of them, 13 cortical regions are presented in Fig. 3A, and seven subcortical regions are in Fig. 3B. Only two regions showed significant CBF changes after FDR correction: the left precentral gyrus and the left DL-PFC (Fig. 3A, the ROIs in gray boxes). At a six-month follow-up, the relative CBF did not differ significantly from baseline values in any of the 82 ROIs after FDR correction.

3.4.2. Relationship with clinical effects

Post-ECT changes (mostly decreases) of relative CBF in 12 out of 82 ROIs immediately after an ECT series were related to a better antidepressant effect at p < .05 (Supplementary information, Table S4). However, the results were not statistically significant after FDR correction. None of the 82 tested ROIs showed significant associations with cognitive side effects after FDR correction, but eight were significant at p <. 05 (Supplementary information, Table S4).

3.5. Exploratory analyses

Higher cumulative charges correlated with larger relative CBF increases to the left hippocampus when adjusted for age and

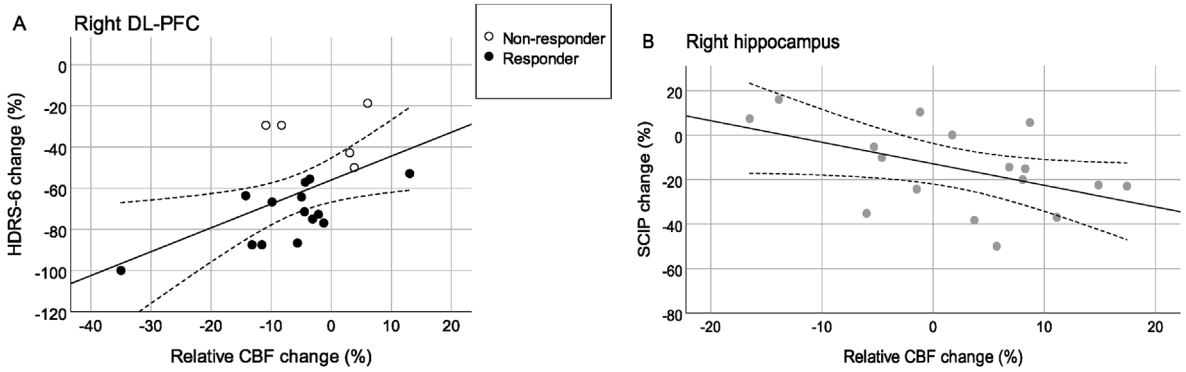

Fig. 2. The relationship between change in CBF immediately after ECT series (post-ECT) and clinical effects: (A) change in right relative prefrontal CBF and clinical improvement, (B) change in right relative hippocampal CBF and cognitive impairment.
The solid lines represent the regression line for all individuals, and the dashed lines indicate a 95% confidence interval. DL-PFC: Dorsolateral prefrontal cortex corresponding to the rostral middle frontal cortex (derived from FreeSurfer), CBF: Cerebral blood flow, HRSD-6: 6-item Hamilton Depression Rating Scale; SCIP: Screen for Cognitive Impairment in Psychiatry.

Table 3
The correlation[a] between relative CBF change (post-pre ECT) and clinical effects.

Relative CBF change (%) in:	HRSD-6 change (%) n = 19		SCIP change (%) n = 17	
	r	p-value	r	p-value
Right DL-PFC	0.70	0.002	0.47	0.080
Left DL-PFC	0.19	0.475	0.51	0.052
Right Hippocampus	−0.31	0.232	−0.65	0.009
Left Hippocampus	−0.02	0.941	−0.27	0.333

Uncorrected p-values are reported. Post-pre ECT: the difference between post- and pre-ECT assessment, n: the number of subjects, r: partial correlation coefficient, SCIP: Screen for cognitive impairment in psychiatry, HRSD-6: 6-item Hamilton rating scale for depression, DL-PFC: Dorsolateral prefrontal cortex corresponding to rostral middle frontal cortex (derived from FreeSurfer).
[a] Partial correlation with age and gender as covariates.

gender (r = 0.51, p = .037). The number of ECT sessions and the cumulative duration of EEG seizures were not associated with the change in relative CBF to the primary ROIs. Furthermore, we found no significant associations between the change in relative CBF to the primary ROIs after ECT and increases in hippocampal volume and cortical thickness reported in our previous publications [11,12].

4. Discussion

This study examined whether regional CBF changes after ECT were related to its clinical effects. The main finding is that, compared to baseline, a decrease in prefrontal perfusion correlated with the antidepressant effect of ECT, and a hippocampal increase in perfusion correlated with cognitive side effects.

Our results are in line with two previous ASL studies investigating CBF following ECT in depressed patients [20,21]. The largest (57 patients) [20] found that hypoperfusion in frontoparietal regions and hyperperfusion in the thalamus and motor cortex were related to response. Our study corroborates and extends the results. However, we could not replicate an association between hyperperfusion in the thalamus and motor cortex and clinical effect, which may be due to methodological differences. Our sample was more homogenous regarding electrode placement (only bilateral) and diagnosis (mostly MDD), and our patients had a higher

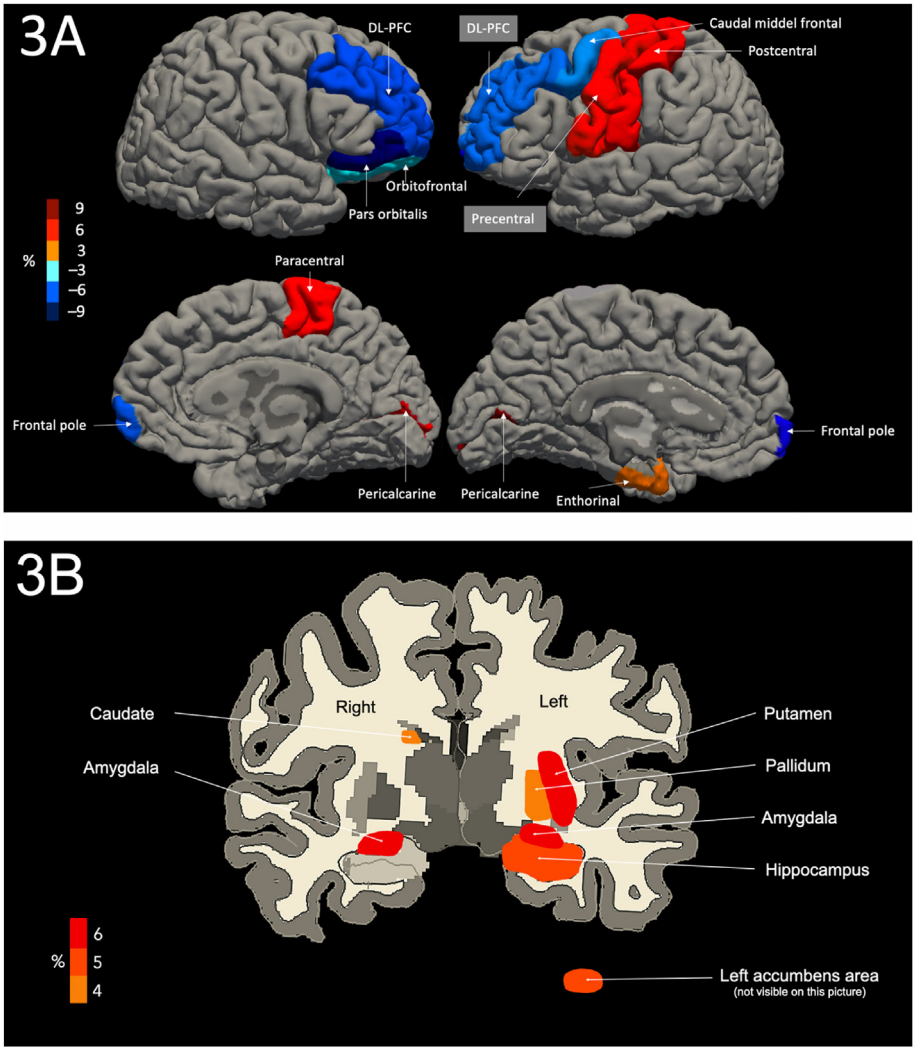

Fig. 3. Relative CBF changes immediately after an ECT series in (A) cortical and (B) subcortical ROIs.
Orange and red indicate CBF increases, and blue indicates CBF decreases at a significance level of < 0.05 (20 ROIs: 13 cortical and 7 subcortical). The bars display relative CBF changes in %. The changes in relative CBF are significant after FDR correction only in two out of these 20 ROIs: the left DL-PFC and the left precentral gyrus, depicted in Fig. 3A in the gray boxes. Estimates of relative CBF changes in the 20 ROIs are available in Table S3 (Supplementary information). DL-PFC: Dorsolateral prefrontal cortex corresponding to the rostral middle frontal gyrus (derived from FreeSurfer). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

response rate. Our results are also in concordance with a smaller study [21] that found reduced prefrontal CBF. Finally, our results align with SPECT and PET studies [16–18], pointing to reduced prefrontal perfusion [24,50] and metabolism [22,23,25,51–53] and increased metabolism in medial temporal lobes [22,23].

4.1. Prefrontal hypoperfusion and clinical effect

Our findings of an association between prefrontal CBF reductions and clinical improvement corroborate studies using SPECT [24] PET [25], and ASL [20]. CBF is regarded as a proxy for neural activity [15]. CBF reductions after ECT are thought to be related to cortical inhibitory mechanisms induced by seizures [17,27]. Indeed, larger CBF reductions after ECT are related to higher increases in seizure threshold [27]. These inhibitory mechanisms may mediate the anticonvulsive effects of ECT mentioned in the introduction [26,27]. Thus, our finding supports the anticonvulsive hypothesis of ECT's action [27].

We found reduced CBF to the DL-PFC bilaterally; however, the reduction correlated strongly with the clinical outcome only on the right side, while the correlation on the left side was very weak and insignificant. This asymmetry apparently fits with observations that depression is linked with the interhemispheric imbalance, i.e., a relative overactivity of the right hemisphere compared to the left hemisphere [54,55]. There is evidence indicating that inactivation of the right hemisphere leads to euphoria, while inactivation of the left-hemisphere results in depression [54,56,57]. Furthermore, right-sided strokes are associated with elevated mood [58], and right hemisphere hypoactivity are linked with mania [59]. Finally, inhibition of the right DL-PFC is the putative mechanism of low-frequency transcranial magnetic stimulation in depression [60]. Taken together, rebalancing interhemispheric activity may underly the mood stabilizing effects of ECT.

Abnormally low prefrontal CBF is a consistent finding in depressed patients [61,62], and prefrontal CBF correlates negatively with depressive symptoms [63,64,64]. Strikingly, ECT induces prefrontal hypoperfusion, correlating with the antidepressant effect [24,25]. This paradox has been known since the early 1990s [27] and is further supported by our study. This contrasts with findings that antidepressants normalize low prefrontal CBF in remitters [62,65,66], suggesting distinct working mechanisms of antidepressants and ECT. The letter may work through seizures-induced anticonvulsive mechanisms, especially in the prefrontal cortex, a part of the cortico-thalamic system involved in seizure generation [57]. An alternative explanation may be that the reduced prefrontal CBF is a surrogate effect, while the primary ECT impact is in deeper structures. For example, shutting the subgenual cingulate cortex hyperactivity by deep brain stimulation relieves depression [67,68]. Furthermore, baseline low prefrontal CBF may be a homeostatic mechanism activated due to an aberrant activity in other areas [66], according to a depression model proposed by Mayberg [65,66]. Finally, baseline prefrontal CBF abnormalities can be caused by processes not related to depression.

No CBF measurements were taken during the ECT course in the current study. Leaver and colleagues found that prefrontal CBF dropped already after two single ECT sessions only in responders [20]. Therefore, this early prefrontal CBF decrease could be a predictor of response.

4.2. Hippocampal hyperperfusion and cognitive side effects

Increased hippocampal CBF after ECT suggests a biological process demanding higher perfusion. Solid evidence supports the neurotropic effects of ECT, including neurogenesis [8,29,31,33,69,70], but other processes, for example, neuroinflammation, should be considered.

Novel findings of our study include that increased hippocampal CBF was correlated to cognitive impairment and higher charges correlated with larger CBF increases. We have recently reported that greater increases in hippocampal volume also correlated with worse cognitive outcomes [34], in line with other studies [35,36]. Noteworthily, higher charges have been linked to both worse cognitive outcomes [39] and larger hippocampal volumes [13,40]. These findings thus indicate that ECT triggers a hippocampal process related to the electrical charge. This process temporarily disturbs hippocampal function. Finally, ECT-related increased CBF was not related to clinical improvement in this study. This aligns with our previous report that did not find any association between larger volume increases and the antidepressant effect [11]. This is also in line with other studies [13,20].

4.3. Strengths and limitations

The present study has several strengths compared to two previous ASL studies [20,21]. Our sample was more homogenous, as discussed above. All participants were severely depressed inpatients, all but one had unipolar depression, many had melancholic features, and six had psychotic symptoms. This high illness severity may partially explain why the sample had as many males as female patients, as gender differences decrease with higher functional impairment [71,72]. However, due to this high illness severity in the sample, the results do not necessarily generalize to outpatients. Surprisingly, only one patient with bipolar depression participated. Removing this subject has not substantially changed the results. Furthermore, treating all patients with bilateral ECT contributed to the sample's homogeneity. However, bitemporal ECT as a default treatment is no longer encouraged in guidelines [73]. Other strengths are the exploration of the relationship between CBF and cognitive side effects and the CBF assessment at the long-term follow-up.

Some limitations must be acknowledged. Firstly, the study sample size is modest, which reduces the chance of detecting significant effects of ECT. Secondly, the study has no control group. Leaver and co-workers showed cerebral perfusion changes were absent in healthy individuals scanned twice four weeks apart [20]. However, the real issue is whether the prefrontal CBF reductions are the specific mechanism of ECT action. Several studies showed normalization of prefrontal CBF after remission achieved by antidepressants [62], suggesting that the prefrontal reductions are unique to ECT. However, controlling for the effects of medication is highly needed. Furthermore, the lack of healthy controls did not allow us to test for any baseline CBF abnormalities and their normalization by ECT. Thirdly, our patients continued their psychotropic medication, which could attenuate changes in CBF. Especially using antiepileptics (three patients) and benzodiazepines (five patients) during the ECT course could confound the results. However, the medication has been held relatively stable, and we did not find any statistical differences in the doses over time.

5. Conclusions

The antidepressant effect of ECT may be related to attenuation of prefrontal activity, which could be induced by inhibitory mechanisms triggered by seizures. On the contrary, cognitive side effects are likely associated with a hippocampal process, probably secondary to the electric charge. These findings should be interpreted with caution due to small sample size. Future studies should include healthy individuals and patients with depression treated solely with medication scanned twice. This design will address

whether prefrontal CBF reductions are unique to ECT and whether the treatment resolves any baseline abnormalities. Furthermore, measuring CBF after a few single ECTs could test whether early prefrontal CBF change predicts response. Finally, collecting larger samples will allow voxel-wise analyses, overcoming the limitations of analyses using anatomical ROIs.

CRediT authorship contribution statement

Krzysztof Gbyl: Conceptualization, Formal analysis, Funding acquisition, Investigation, Project administration, Visualization, Writing – original draft, Writing – review & editing. **Ulrich Lindberg:** Formal analysis, Software, Writing – review & editing. **Henrik Bo Wiberg Larsson:** Supervision, Writing – review & editing. **Egill Rostrup:** Supervision, Formal analysis, Software, Writing – review & editing. **Poul Videbech:** Funding acquisition, Conceptualization, Supervision, Project administration, Writing – review & editing.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.10.007.

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