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RESEARCH ARTICLE

Changes in postictal cerebral perfusion are related to the duration of electroconvulsive therapy-induced seizures

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Abstract

Objective: Postictal symptoms may result from cerebral hypoperfusion, which is possibly a consequence of seizure-induced vasoconstriction. Longer seizures have previously been shown to cause more severe postictal hypoperfusion in rats and epilepsy patients. We studied cerebral perfusion after generalized seizures elicited by electroconvulsive therapy (ECT) and its relation to seizure duration.

Methods: Patients with a major depressive episode who underwent ECT were included. During treatment, 21-channel continuous electroencephalogram (EEG) was recorded. Arterial spin labeling magnetic resonance imaging scans were acquired before the ECT course (baseline) and approximately 1 h after an ECT-induced seizure (postictal) to quantify global and regional gray matter cerebral blood flow (CBF). Seizure duration was assessed from the period of epileptiform discharges on the EEG. Healthy controls were scanned twice to assess test–retest variability. We performed hypothesis-driven Bayesian analyses to study the relation between global and regional perfusion changes and seizure duration.

Results: Twenty-four patients and 27 healthy controls were included. Changes in postictal global and regional CBF were correlated with seizure duration. In patients with longer seizure durations, global decrease in CBF reached values up to 28 mL/100 g/min. Regional reductions in CBF were most prominent in the inferior frontal gyrus, cingulate gyrus, and insula (up to 35 mL/100 g/min). In patients with shorter seizures, global and regional perfusion increased (up to 20 mL/100 g/min). These perfusion changes were larger than changes observed in healthy controls, with a maximum median global CBF increase of 12 mL/100 g/min and a maximum median global CBF decrease of 20 mL/100 g/min.

Significance: Seizure duration is a key factor determining postictal perfusion changes. In future studies, seizure duration needs to be considered as a confounding factor due to its opposite effect on postictal perfusion.

KEYWORDS
arterial spin labeling, cerebral blood flow, depression, epilepsy, seizure duration

1 | INTRODUCTION

Following epileptic seizures, patients may display unresponsiveness, impaired cognition, headache, nausea, myalgia, and delirium as well as psychiatric or other neurologic manifestations.[1,2] These postictal symptoms may result from cerebral hypoperfusion as a consequence of seizure-induced vasoconstriction.[3,4] Postictal cerebral hypoperfusion has been observed up to 1 h after seizures, with widespread and regional perfusion and metabolic decreases. The brain regions involved may relate to the seizure onset zone.[3,5–8] Increased postictal cerebral perfusion has also been observed, but these studies were all hampered by small sample sizes and lack of correction for test–retest variability.[3,9–12] Seizure duration, seizure type, age, or timing of perfusion measurements may explain such divergent observations.[3,9–14]

Assessment of seizure duration and cerebral perfusion after spontaneous seizures is challenging. This has motivated us to study postictal perfusion in patients treated with electroconvulsive therapy (ECT)-induced seizures.[9,15] In ECT, mainly as treatment for severe depression, focal to bilateral tonic–clonic seizures are elicited by using an electrical stimulus, applied through two electrodes on a patient's head under anesthesia and with proper muscle relaxation.[9,16] Several characteristics of ECT-induced seizures, such as the type of ictal discharges and postictal electroencephalography (EEG) and clinical symptoms, appear similar to those of generalized seizures in epilepsy patients.[17] This suggests that findings in studies that explore ECT-induced seizure characteristics, such as duration, and cerebral perfusion may be extrapolated to patients with epilepsy.

After ECT-induced seizures, previous studies showed divergent patterns of increased as well as decreased postictal cerebral perfusion in widespread bilateral cortical regions, in particular in specific frontal (i.e., inferior frontal gyrus, cingulate gyrus, insula) and subcortical regions (i.e., caudate, putamen, thalamus, midbrain, amygdala, hypothalamus, vermis).[9,11,12,15] These opposite perfusion changes may be explained by differences in the timing of perfusion assessment. Perfusion measurements early in the postictal state (i.e., 10–30 min) mostly show increased cerebral perfusion, whereas later measurements (i.e., 45–60 min) may show decreased postictal perfusion. Measured after the complete ECT course (i.e., multiple induced seizures, mostly 10–20 sessions), increased cerebral perfusion in the thalamus was associated with worse cognitive impairment.[18] Longer ECT-induced seizure duration was related to an increased risk of developing postictal delirium.[19] To our knowledge, no studies examined the effect of seizure duration on global or regional cerebral perfusion after ECT-induced seizures.

Key Points

- ECT-induced seizures lead to reductions in postictal global and regional cerebral blood flow, depending on seizure duration
- Longer seizures are associated with decreased postictal perfusion, whereas shorter seizures are associated with increased postictal perfusion 1 h after ECT
- Investigating postictal perfusion after ECT-induced seizures is feasible

In this study using arterial spin labeling magnetic resonance imaging (ASL-MRI) in patients with ECT-induced seizures, we investigated changes in postictal global and regional cerebral perfusion, compared to normal variation in healthy controls, and we related changes in perfusion to seizure duration.

2 | MATERIALS AND METHODS

2.1 | Study design

This study is a post hoc analysis of ASL-MRI data of patients included in the preregistered prospective SYNAPSE study (NCT04028596), which had a randomized crossover design to test vasodilatory drugs to reduce postictal symptoms.[20] For the current analysis, we used ASL-MRI scans at baseline (<1 week before start of the ECT course) and 1 h after an ECT-induced seizure from each patient, but only in the control ("placebo") condition of SYNAPSE (i.e., a cup of water administered 2 h before ECT). To correct for normal variability over time and test–retest effects of the repeated ASL-MRI measurements, a group of healthy controls was included (ERB study number 2020-BC-12375), who were measured on the same MRI-scanner at two separate time points (i.e., baseline and after 6 weeks). Clinical variables (i.e., age, sex, regular smoking), electrode placement (i.e., unilateral [UL] or bifrontotemporal [BL]), number of ECT sessions at ASL-MRI measurement (i.e., number of previous seizures before perfusion measurement), and applied charge to induce the seizure (in millicoulombs [mC]) were registered.

2.2 | Participants

We included 24 ECT patients and 27 healthy controls. Patients aged ≥18 years, diagnosed with (mostly

pharmacotherapy-resistant) major depressive episode (established according to the Mini Neuropsychiatric Interview [MINI]), and treated with ECT in Rijnstate Hospital, Arnhem, the Netherlands, were included.[21] Exclusion criteria were chronic use of acetaminophen, calcium antagonists, or nonsteroidal anti-inflammatory drugs, and contraindications for undergoing MRI or EEG. Healthy controls had no history of psychopathology (established with the MINI), had no contraindications for undergoing MRI, and were matched to patients on the group level based on age, sex, and level of education. All participants provided oral and written informed consent.

2.3 | ECT procedure

ECT was administered according to the Dutch treatment guideline.[22] Electrode placement was left to the discretion of the treating psychiatrist, and included UL (according to d'Elia[23]) and BL (also known as bitemporal) positioning. A Thymatron System IV device (Somatics) was used, delivering a constant-current (0.9 A) with bidirectional square waves in brief pulses (1 ms). All patients were preoxygenated with 100% O_2, and most received etomidate as sedative and succinylcholine as muscle relaxant. Stimulus charge was determined based on either the half-age method (i.e., in case of BL electrode placement) or dosage titration (i.e., with right or left UL electrode placement). In the case of severe postictal confusion, midazolam 2–5 mg was provided intravenously.[17] A detailed overview of the study protocol is given elsewhere.[20,24]

2.4 | Seizure duration based on EEG

All patients were monitored with continuous EEG during the treatment and in the postictal state, until electrodes were removed for MRI preparation. Prior to each ECT session, 12 silver/silver chloride cup electrodes were applied according to the international 10–20 system. EEGs were recorded using a NeuroCenter EEG recording system (Clinical Science Systems) and a full-band direct current-coupled amplifier (TMSi). Depending on ECT electrode placement, temporal or frontal electrodes were re-placed. For patients treated with BL ECT electrodes, the EEG electrodes T3 and T4 were placed 10% behind the predefined position to ensure enough space for the ECT electrodes. EEGs were sampled at 256 Hz, and impedances were kept below 5 kΩ. Seizure duration was determined visually and defined as the time interval in seconds between the onset of rhythmicity or spike–wave complexes and the onset of postictal generalized suppression in all channels.

2.5 | Clinical assessment of the postictal state

Reorientation time (ROT) was assessed by a questionnaire, consisting of five items concerning reproducing the patient's name, age, birthday, current location (i.e., the name of the hospital), and the day of the week, which patients were asked in a 5-min interval.[25] If a minimum of four of five questions were answered correctly, compared to baseline answers, the score was indicated in minutes. Scores ranged from 5 to 100 min.

A visual analogue scale assessed subjective intensity of postictal headache, nausea, and myalgia on a scale from 0 (i.e., no pain) to 10 (i.e., worst pain).[26] These questions were asked at 1 h postictally.

The postictal suppression index (PSI), estimated by the Thymatron device, was reported to indicate the amount of postictal suppression, based on two frontal EEG channels.[27] The index is given as a percentage, with 100 indicating perfect postictal suppression.

2.6 | MRI acquisition and preprocessing

Resting-state ASL-MRI and T1-weighted (T1W) images in patients and healthy controls were acquired using the same 3T Ingenia MRI scanner (Philips Healthcare) using a 15-channel head coil. ASL-MRI images were acquired with pseudocontinuous ASL (pCASL) labeling and a three-dimensional gradient-and-spin-echo readout module. Scan parameters were as follows: labeling duration = 1800 ms, postlabel delay = 1900 ms, four background suppression pulses, repetition time (TR) = 4057 ms, echo time (TE) = 12 ms, flip angle = 90°, field of view (FOV) = 240 × 240 × 126 mm^3, matrix size = 64 × 60, voxel size = 3 × 3 × 6 mm^3, 21 transverse slices, and no slice gap. Labeling planes were placed perpendicular to the distal ascending portions of the internal carotid.[28] The ASL-MRI data consisted of four label–control pairs. An M0 image was acquired for each participant using the imaging parameters identical to the ASL acquisition, without labeling and background suppression to calibrate the ASL signals. Total scan duration was 5.5 min. T1W images were acquired with an isotropic voxel size of 1.1 mm, TR = 7.5 ms, TE = 4.6 ms, FOV = 256 × 238 mm^2, and 145 sagittal slices. All scan parameters were kept constant for patients and healthy controls.

FSL 6.0.3 (FMRIB Software Library, Functional Magnetic Resonance Imaging of the Brian Center, Department of Clinical Neurology, University of Oxford) and Permutation Analysis of Linear Models (PALM) in a MATLAB R2022b environment (MathWorks) were used for offline data processing.[29] A mean perfusion image of

the four subtraction images (control—label) was created. Cerebral blood flow (CBF) was quantified using multi-component modeling with Bayesian Inference for Arterial Spin Labeling MRI (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BASIL).[30] CBF quantification was performed by kinetic model inversion, calibration with M0 scans, and registration with the function oxford_asl.[31] CBF values were corrected for the four background suppression pulses.[32] T1W images were preprocessed using a standardized pipeline (i.e., fsl_anat) involving brain extraction, cortical and subcortical segmentation, and registration to standard space (i.e., Montreal Neurological Institute).[32] We derived individual gray matter (GM) probability maps (threshold > 0.2 probability for incorporating most GM voxels) that were binarized and then merged to create a binarized group-based GM mask. pCASL data were registered to standard space via the T1W image, which resulted in a CBF GM image with a 2-mm isotropic resolution. For each participant, we derived a GM partial volume corrected and smoothed CBF image. The GM partial volume images were multiplied with the group-based GM mask, resulting in GM CBF images excluding white matter. Global CBF in GM was calculated by averaging CBF within each image. Subtraction (difference) images of baseline and postictal (or follow-up) images were calculated and used for voxelwise analyses. A schematic overview of the preprocessing flow is presented in Figure S1. Assuming that regional postictal perfusion decreases may be predominantly found in seizure onset zones, 10 bilateral regions of interest were selected based on ictal ECT literature (i.e., inferior frontal gyrus, cingulate gyrus, insula, caudate, putamen, thalamus, midbrain, amygdala, hypothalamus, vermis).[9,11,12,15] Bilateral regions of interest (ROIs) were defined based on anatomical locations of the Talairach Daemon Labels. Binary masks were created for all ROIs, multiplied with individual partial volume corrected GM CBF images. Mean regional perfusion was calculated for each ROI.

2.7 | Statistical analysis

Clinical, demographic, and global and regional CBF data were analyzed with R version 4.2.3.[33] Median and interquartile range (IQR) were reported for quantitative variables. Patients and healthy controls were compared with *t*-tests and chi-squared tests for differences in age, sex, and level of education between groups. Pearson correlation coefficients between independent variables were investigated for multicollinearity. Probability values of <.05 were considered statistically significant.

For all analyses involving healthy controls, we used Bayesian estimation (BEST) analyses, whereas for between-patient analyses, we used Bayesian regression models with R packages brms.[34,35] BEST is a Bayesian equivalent to a *t*-test using Markov chain Monte Carlo simulation as part of the model. This analysis approaches the data structure most accurately without the restricting assumptions of traditional frequentist analyses (i.e., homogeneity of variances and normally distributed noise), generally provides more informative results about the samples, and provides quantitative certainty about the results.[34,35]

First, we investigated baseline CBF differences and average CBF changes over time (global and regional, ΔgCBF and ΔrCBF, respectively) in patients compared to healthy controls to account for test–retest effects with group by time interactions. Second, we examined whether global or regional postictal perfusion changes were related to seizure duration. To assess the possible influence of age on seizure duration (because elderly ECT patients tend to show shorter seizures than younger patients) and baseline perfusion, a Bayesian regression model was implemented.[36] Corrections for age (as this is a well-known confounder of perfusion differences), time interval between ECT stimulus and ASL-MRI scan, number of previous ECT-induced seizures, electrode placement, and smoking were implemented.[37] The association between ROT and ECT charge was investigated in a separate Bayesian regression model. In another regression model, ROT and PSI were investigated as fixed effects on perfusion outcomes, including age and seizure duration to assess their influence on global and regional postictal perfusion changes. Independent variables were investigated to determine degree of multicollinearity.

2.7.1 | Additional exploratory analyses

Voxelwise analyses were performed to investigate whether other brain regions showed perfusion changes over time, controlling for normal variation in healthy controls. Three analyses were performed with GM CBF difference images using PALM with threshold-free cluster enhancement to investigate (1) baseline perfusion differences between patients and healthy controls (corrected for age and sex), (2) differences in perfusion changes in patients versus healthy controls (corrected for sex and age), and (3) perfusion changes over time in patients corrected for covariates of no interest (i.e., age, sex, electrode placement, and time interval between ECT stimulus and ASL-MRI scan).[38] Voxels were reported as significant if these survived correction for multiple comparisons (family wise error rate; $p < .05$).

2.7.2 | Interpretation of Bayesian results

In Bayesian data analysis, a posterior distribution of parameters of interest is generated, which may be used to make decisions on whether the true parameters lie within a "region of practical equivalence" (ROPE) that is defined as an interval including zero.[39] For this, a 95% highest density interval (HDI) is calculated from the posterior distribution, which covers 95% of the most credible values. We defined the ROPE interval as (−.1, .1), which may be interpreted as a practically negligible effect.[40–42] If the HDI falls partly within the ROPE, we cannot conclude with certainty that there is an effect (i.e., *nonconclusive*). If the HDI falls outside the ROPE, we interpret the parameter values as having *credible* effect. Thus, the ROPE may be viewed as a Bayesian alternative to a *p*-value that can be used to accept or reject an explicitly formulated null hypothesis (i.e., interval −.1, .1). Bayesian results will be presented as median parameter estimates of the posterior distribution together with its 95% credibility interval (CI95). The credibility interval is defined as the range containing 95% of probable parameter estimate values of the posterior distribution.[35] The following settings were used in all Bayesian analyses: 8000 iterations, four chains, and default priors.

3 | RESULTS

Twenty-four patients were included in this study (median age = 50 years [±22.5 IQR, range = 24–82], 15 females [63%]). Fifteen patients were treated with BL (at the end of the ECT course) and nine exclusively with UL electrode placement (i.e., one patient received left UL electrode placement). Two patients were left-handed, one of whom received left UL electrode placement. The other left-handed patient was treated with BL electrode placement. During the ECT course, median seizure duration on EEG was 56 s (±24.2 IQR, range = 24.9–114). Median number of ECT sessions in the course was 12 (±8 IQR, range = 8–100), which lies within the normal range reported by others.[43,44]

Twenty-seven healthy controls were included to examine test–retest CBF variability, with a median age of 55 years (±22.5 IQR, range = 27–84), including 15 female participants (56%). Neither age ($p = .954$), sex ($p = .826$), level of education ($p = .227$), nor the number of smokers ($p = .056$) differed significantly between patients and healthy controls. Patient characteristics are presented in Table 1.

3.1 | Clinical description of the postictal state

Eight of 24 patients reported postictal headache, nausea, or myalgia after ECT, before entering the MRI scanner (see Table S1). Symptom severity scores ranged from 2 to 7. Headache was the most reported symptom (6/8 patients), followed by nausea and myalgia. The two patients with the longest seizure duration (i.e., 101 and 114 s) both reported high scores (i.e., 7) of postictal headache. None of the patients showed signs of nonconvulsive status epilepticus. Median reorientation time was 37.5 min (±21.3 IQR, range = 20–100). The maximum ROT score (i.e., 100) was given to four of 24 patients, indicating that they were still (somewhat) disoriented at the time of the ASL scan acquisition. These patients had seizure durations of 34, 44, 59, and 79 s. Two of these patients reported postictal headache. The other patients who had lower ROT scores (maximum 60 min) were adequate and reoriented. Median postictal suppression index was 85.2% (±55.7 IQR, range = 10–97.5). In nine patients (38%), the postictal suppression index was not available.

3.2 | Global and regional CBF in patients controlled for test–retest variability

3.2.1 | Global CBF

At baseline, the median gCBF in patients was 54.9 ± 21.9 mL/100 g/min. After the seizure, patients had decreased as well as increased gCBF values compared to baseline (median gCBF = 54.2 ± 25.1 mL/100 g/min); this median did not differ from baseline (difference = 2.0 mL/100 g/min $[-2.2, 6.3]_{CI95}$; Figure 1). In patients, the maximum decrease of postictal gCBF was 28.3 mL/100/min, and the maximum postictal increase was 19.6 mL/100 g/min. In healthy controls, median change in gCBF (i.e., ΔgCBF) was −3 mL/100 g/min (range = −20.7 to 12.6 mL/100 g/min). Baseline gCBF did not differ between patients and healthy controls (−4.4 mL/100 g/min $[-13.2, 4.5]_{CI95}$).

3.2.2 | Regional CBF

When comparing changes in rCBF (i.e., ΔrCBF) in patients to those in healthy controls, only interaction effects were observed in the amygdala ΔCBF (−4.8 mL/100 g/min $[-9.5, -.2]_{CI95}$; Figure 1), but not in any of the prespecified regions (Figure S2, Table S2). This means that relative amygdala ΔCBF was increased in patients in the

TABLE 1 Characteristics of patients with cerebral perfusion measures after ECT-induced seizures, using ASL-MRI.

Characteristic	Patients, $N = 24$
Age, years, median (range; IQR)	56 (24–82; 22.5)
Female, *n* (%)	15 (63)
Smokers, *n* (%)	9 (38)
BL electrode placement at the end of the ECT course, *n* (%)	15 (63)
Delivered charge at ECT session before ASL-MRI acquisition, median millicoulombs (range; IQR)	303 (125.6–659.7; 170.1)
Median seizure duration on EEG, s (range; IQR)	56 (24.9–114; 24.2)
Previous seizures, *n* (range; IQR)	4 (2–8; 4)
Reorientation time, min (range; IQR)	37.5 (20–100; 21.3)
Timing of postictal ASL-MRI scan during the ECT course, *n* (%)	
After ECT session 2	3 (13)
After ECT session 3	6 (25)
After ECT session 4	5 (21)
After ECT session 5	3 (13)
After ECT session 6	1 (4)
After ECT session 7	2 (8)
After ECT session 8	4 (16)
Interval between application of the ECT stimulus and start of postictal ASL-MRI sequence, median min (range; IQR)	66 (53–90; 12.3)
Concomitant psychopharmacological drug use, *n* (%)	
Antidepressants	18 (75)
Antipsychotics	17 (71)
Antiepileptics	4 (17)
Benzodiazepines	17 (71)
Lithium carbonate	2 (8)
Patients needing medication for severe postictal symptoms after ECT, *n* (%)[a]	8 (33)

Abbreviations: ASL-MRI, arterial spin labeling magnetic resonance imaging; BL, bifrontotemporal; ECT, electroconvulsive therapy; EEG, electroencephalogram; IQR, interquartile range.

[a]Postictal medication consisted of a single dose of midazolam, ranging between 2 and 5 mg.

postictal state, whereas at follow-up in healthy controls, amygdala ΔCBF was decreased. This effect was largely driven by ΔCBF changes in healthy controls.

We found a negative relation between age and baseline perfusion for both patients and healthy controls ($-.6$ mL/100 g/min $[-1, -.2]_{CI95}$), indicating that older participants had lower baseline perfusion values compared to younger participants, with a change of approximately 5 mL/100/min per decade (Figure S3).

3.2.3 | Seizure duration in relation to CBF changes

All independent variables were investigated for possible correlations before analyses. A moderate negative correlation was found between seizure duration and age, meaning that older patients showed shorter seizures ($\rho = -.6$, $p < .001$). This moderate correlation may prevent definitive conclusions about the individual contribution of seizure duration (or age) in the models. No relations between global and regional cerebral perfusion with electrode placement, number of previous seizures, or smoking were established (see Table 2). This motivated exploration of both the gCBF and rCBF analyses with and without age as a covariate to assess their relation with seizure duration.

Seizure duration was negatively related to ΔgCBF when including age ($-.4$ mL/100 g/min $[-.7, -.2]_{CI95}$) and when excluding age ($-.3$ mL/100 g/min $[-.6, -.1]_{CI95}$) in the models (Table 2, Figure 2). Seizure duration was also negatively related to ΔrCBF in the cingulate gyrus ($-.5$ mL/100 g/min $[-.8, -.2]_{CI95}$), inferior

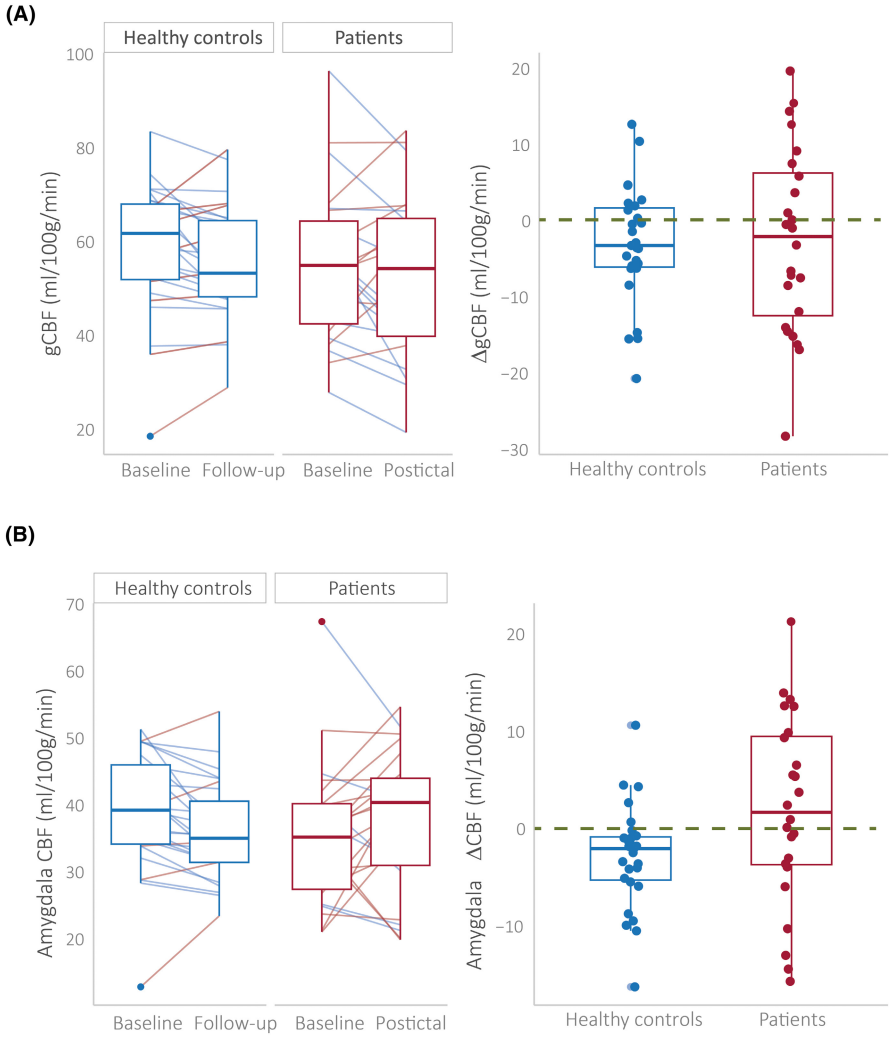

FIGURE 1 (A) Global cerebral blood flow (gCBF, left) and change in gCBF between baseline and postictal/follow-up (ΔgCBF, right) in electroconvulsive therapy patients ($n = 24$) and healthy controls ($n = 27$), essentially indicating that there was a negligible global CBF change between baseline and the postictal state when controlling for test–retest variation in healthy controls. ΔgCBF did not differ between groups (.4 mL/100 g/min, 95% credibility interval [CI95] = −5.7, 6.5), but global CBF decreased in healthy controls over time (−2.9 mL/100 g/min $[-4.9, -.8]_{CI95}$). (B) Regional cerebral blood flow in the amygdala (left) and change in amygdala CBF between baseline and postictal/follow-up (ΔCBF, right) highlight a relative increase in postictal amygdala CBF in patients compared to a relative decrease in healthy controls at follow-up (−4.8 mL/100 g/min $[-9.5, -.2]_{CI95}$). However, this difference was largely attributable to changes in healthy controls rather than only to changes in patients, because the amygdala perfusion changed in healthy controls, but not in patients (−2.9 mL/100 g/min $[-4.9, -.8]_{CI95}$ and 2.0 mL/100 g/min $[-2.2, 6.3]_{CI95}$, respectively). Blue lines indicate an individual decrease in CBF, and red lines indicate an individual increase in global CBF respective to baseline. Green dashed lines indicate no change respective to baseline.

frontal gyrus (−.5 mL/100 g/min $[-.9, -.1]_{CI95}$), and insula (−.4 mL/100 g/min $[-.7, -.1]_{CI95}$). ΔrCBF in the amygdala, caudate, and putamen showed inconclusive relationships with seizure duration (see Table 2). Seizure duration was not related to ΔrCBF in the hypothalamus, thalamus, midbrain, or vermis (Figure S4).

Exemplarily, in the patient with the longest seizure duration (i.e., 114 s), postictal global cerebral perfusion decreased by 28.3 mL/100 g/min and postictal regional cerebral perfusion in the inferior frontal gyrus decreased by 38.2 mL/100 g/min. This corresponded to a 52% and 88% decrease in CBF compared to baseline, respectively. The patient with the shortest seizure (25 s) showed relatively small increases in postictal gCBF (15.4 mL/100 g/min) and rCBF in the cingulate gyrus, inferior frontal gyrus, and insula (19.6, 16.0, and 11.4 mL/100 g/min, respectively). Figure 2A illustrates this contrast in the two patients having the longest and shortest seizure duration. ROT was not associated with administered stimulus charge (2.20 mC $[-.03, 4.38]_{CI95}$). ROT and PSI were not associated with global or regional postictal perfusion (see Table S3).

TABLE 2 Summary of global and regional ΔCBF in relation to seizure duration, electrode placement, age, time to ASL acquisition, number of previous seizures, and smoking.

	Global ΔCBF, mL/100 g/min		ΔCBF amygdala, mL/100 g/min		ΔCBF caudate, mL/100 g/min	
Predictor	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Intercept	52.9	−3.7 to 110.2	51.3	1.8–100.4	64.2	20.0–109.1
Seizure duration (s)	−.4	−.7 to −.1	−.3	−.5 to −.0	−.3	−.5 to −.1
Electrode placement (bilateral)	−2.4	−12.7 to 7.8	−2.6	−11.6 to 6.4	−.6	−9.0 to 7.4
Age	−.3	−.7 to .2	−.2	−.6 to .2	−.3	−.6 to .1
Time to ASL acquisition (min)	−.1	−.7 to .5	−.3	−.8 to .3	−.3	−.8 to .2
Number of previous seizures	−3.9	−10.3 to 2.5	−1.8	−7.3 to 3.8	−5.0	−10.0 to .2
Smoking	3.9	−6.6 to 14.3	1.0	−8.1 to 10.0	2.4	−5.8 to 10.6
ROPE interpretation of seizure duration	Credible		Inconclusive		Inconclusive	

Abbreviations: ASL, arterial spin labeling; CI, credibility interval; ROPE, region of practical equivalence; ΔCBF, change in cerebral blood flow.

3.2.4 | Exploratory voxelwise analyses in patients and healthy controls

Additional exploratory voxelwise analyses were performed to investigate whether specific regions showed baseline perfusion differences between patients and healthy controls and whether perfusion changed over time between both groups. In patients, voxelwise perfusion changes in the postictal state were explored. None of these analyses showed significant differences in any analyses across all GM voxels, after correction for multiple comparisons.

3.3 | Sensitivity analyses

Eight patients (33%) received midazolam 2–5 mg iv after ECT and before the ASL-MRI acquisition because of severe postictal confusion. Studies on the influence of acute benzodiazepine administration have reported decreased CBF, cerebral metabolic rate, oxygen consumption, and intracranial pressure by enhancing the inhibitory effect of γ-aminobutyric acid type A receptors.[45,46] The use of benzodiazepines may be associated with increased risk for ischemic stroke.[47] To verify whether our results were not driven by the administration of midazolam, we examined the groups of patients with or without postictal midazolam more closely and performed sensitivity analyses. The median postictal gCBF of patients who received postictal midazolam ($n = 8$) was 47.9 mL/100 g/min (IQR = 26.3), whereas in the group without postictal midazolam ($n = 16$) median postictal gCBF was 57.5 mL/100 g/min (IQR = 25.0). The median values for the selected ROIs are described in Table S4 and Figure S5.

When excluding the group with postictal midazolam administration, the relation between ΔgCBF and seizure duration remained credible (−.5 mL/100 g/min $[-.7, -.3]_{CI95}$) as well as with ΔrCBF in the insula (−.4 mL/100 g/min $[-.8, -.1]_{CI95}$; see Table S5 and Figure S6). The ΔrCBF in the cingulate gyrus and inferior frontal gyrus showed a negative trend in the association with seizure duration (−.6 mL/100 g/min $[-1.1, -.1]_{CI95}$ and −.6 mL/100 g/min $[-1.1, -.1]_{CI95}$, respectively). The group by time interaction in the amygdala (controlled for test–retest effects) disappeared (−5.6 mL/100 g/min $[-11.6, .3]_{CI95}$). These results, however, may be partly explained by the smaller sample size ($n = 16$).

4 | DISCUSSION

In this ASL-MRI study, seizure duration in patients after ECT-induced seizures was related to global and regional postictal perfusion changes. On the group level, median global and regional CBF values did not differ between baseline and in the immediate postictal state, controlled for test–retest variability. However, seizure duration was related to changes in postictal perfusion, where longer seizures were associated with larger decreases of global and regional postictal perfusion and shorter seizures were associated with increases in postictal perfusion. In some patients, regional postictal perfusion was reduced to 50% of baseline values.

ΔCBF cingulate gyrus, mL/100 g/min		ΔCBF inferior frontal gyrus, mL/100 g/min		ΔCBF insula, mL/100 g/min		ΔCBF putamen, mL/100 g/min	
Estimate	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
57.7	−8.6 to 121.3	62.9	−7.6 to 136.1	56.7	6.5–107.5	61.1	17.1–104.5
−.5	−.8 to −.2	−.5	−.9 to −.1	−.4	−.7 to −.1	−.3	−.5 to −.1
−.1	−11.8 to 11.5	−4.3	−17.5 to 9.0	−1.2	−10.2 to 8.0	.3	−7.6 to 8.1
−.3	−.8 to .2	−.2	−.8 to .3	−.2	−.6 to .2	−.3	−.6 to .1
−.2	−.8 to .6	−.2	−1.0 to .5	−.3	−.8 to .3	−.3	−.7 to .2
−2.9	−10.1 to 4.6	−4.0	−12.2 to 4.0	−3.4	−9.1 to 2.2	−4.1	−9.1 to .8
7.2	−4.6 to 19.0	6.6	−6.4 to 20.0	6.4	−2.9 to 15.9	2.9	−4.9 to 11.1
Credible		Credible		Credible		Inconclusive	

4.1 | Global and regional perfusion in patients and healthy controls

Median GM perfusion at baseline in our patients was 54.9 and 61.7 mL/100 g/min in healthy controls, both of which compare to values in the literature, reporting GM perfusion values of 40–52 and 18.4–83.4 mL/100 g/min, respectively.[48,49]

Also, in line with the literature, our CBF values decreased with age (approximately 5 mL/100 g/min/decade; see Figure S3), which supports the reliability of our results.[37,50,51] In our healthy controls, a median decrease of global perfusion was shown (i.e., −3 mL/100 g/min [±7.8]), which may be interpreted as test–retest effect of two measurements taken at different time points. CBF values in patients above or below this "normal" limit likely result from an effect of the ECT-induced seizures on perfusion in patients.

On the group level, median global and regional CBF values did not differ between baseline and in the immediate postictal state, controlled for test–retest variability. This may be explained by the timing of the postictal scans (i.e., median 66 min), because postictal cerebral perfusion changes after ECT-induced seizures may be more pronounced shortly after the seizure. However, the most likely explanation is its relationship with seizure duration.

4.2 | Seizure duration relates to ΔgCBF and ΔrCBF

Although on group level, medians of global and regional perfusion measures in patients did not change in the postictal state compared to baseline, we did observe that a longer duration of ECT-induced seizures was associated with decreased postictal global perfusion up to a maximum of 28.3 mL/100 g/min, whereas shorter seizures were associated with a relative increase in postictal perfusion. In addition, seizure duration was also negatively related to regional postictal perfusion in the cingulate gyrus, inferior frontal gyrus, and insula. These relations appeared independent of the patients' age, whereas age was also negatively related to seizure duration. Our findings are comparable with those of a study in epilepsy patients that showed larger decreases in regional perfusion in the postictal state in patients having longer seizures.[3] In ECT patients, longer seizure duration may result in more severe postictal clinical symptoms.[52] Previous ECT studies have reported mixed patterns regarding regional perfusion changes, primarily reporting decreases in frontal and temporal cortices.[7,8,11,12] In our sample, neither mean global nor regional perfusion changed on the group level between baseline and the postictal state, which is most certainly explained by the influence of seizure duration on CBF changes. Another explanation for these null findings may be differences in time intervals between seizure activity and perfusion measurements. These new insights may promote future studies regarding more regional perfusion analyses or clinical consequences of (longer) seizure duration, or intervention studies regarding minimalization of seizure duration and postictal hypoperfusion to improve patient outcomes.

4.3 | Pathophysiological considerations

The maximum decreases in regional CBF in the postictal state ranged from 9 to 38 mL/100 g/min, corresponding

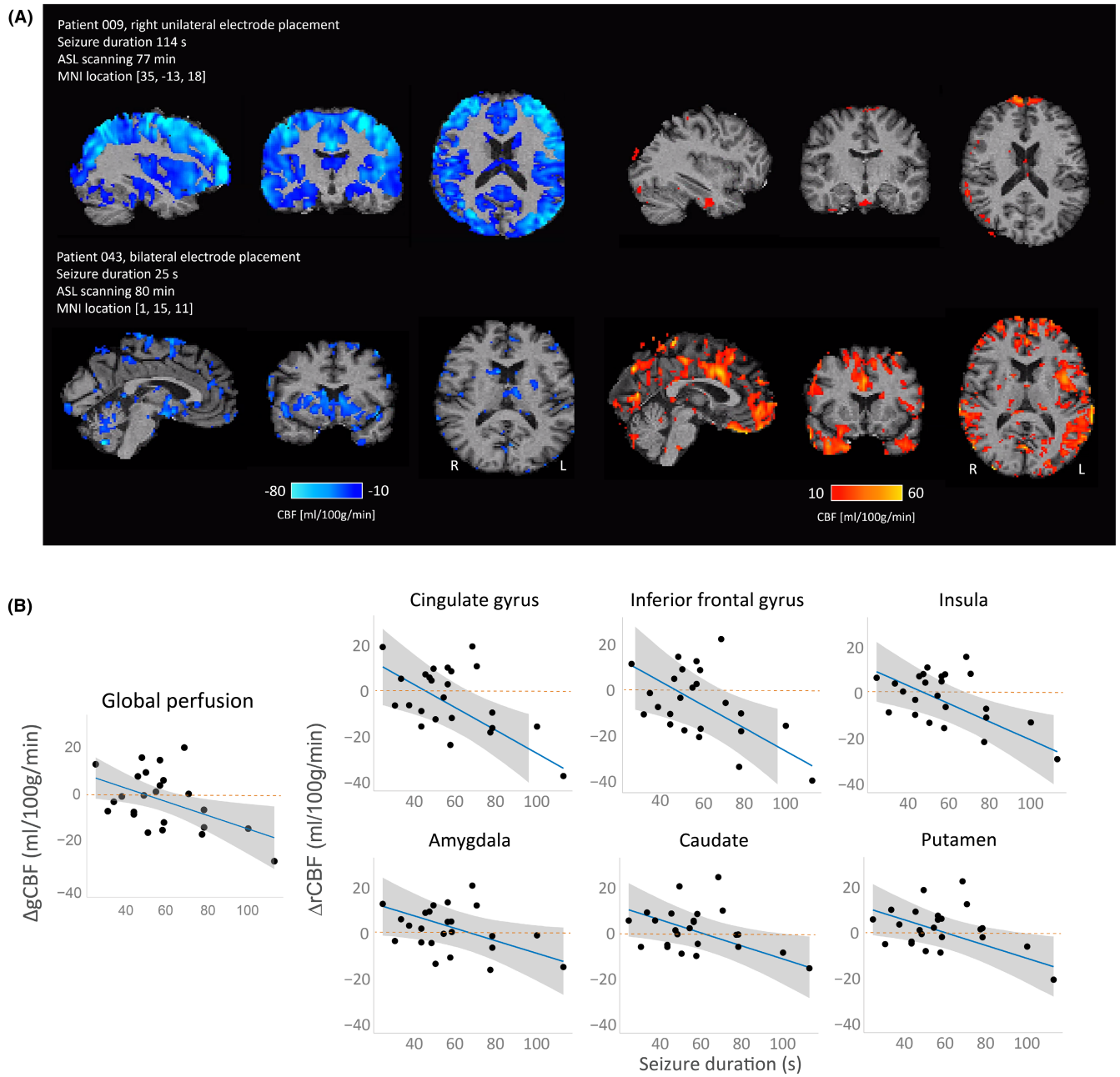

FIGURE 2 (A) Example of the relation between seizure duration and change of postictal cerebral blood flow (CBF) in a patient with the longest and in a patient with the shortest seizure. Subtraction CBF maps (postictal—baseline) of the patient with the longest seizure (Patient 9, 114 s) and the patient with the shortest seizure (Patient 43, 25 s) indicate profound and diffuse patterns of severe hypoperfusion (blue color) after the longest seizure, whereas for the shortest seizure hypoperfusion patterns were lower in magnitude and regionally restricted to midline and subcortical brain areas. The patient with the shortest seizure showed more widespread CBF increases (red color) compared to the patient with the longest seizure. Patient 9 was treated with right unilateral electrode placement, whereas Patient 43 was treated with bifrontotemporal electrode placement. Voxelwise CBF maps were superimposed onto the patient's T1-weighted anatomical image. (B) Seizure duration was negatively related to change in both global and regional perfusion (ΔgCBF and ΔrCBF, respectively) in the cingulate gyrus, inferior frontal gyrus, and insula. The amygdala, caudate, and putamen showed a nonconclusive negative relation with seizure duration. Trend lines show the conditional effects of the Bayesian models. The dashed orange lines indicate no change respective to baseline. ASL, arterial spin labeling; L, left; MNI, Montreal Neurological Institute; R, right.

to a maximum of 30–47% decrease from baseline. Similar changes during the postictal state were reported in patients with epilepsy, in a 4-aminopyridine (4-AP) seizure model in mice, and computed tomography perfusion measurements in adult patients with refractory epilepsy.[3,13,53] Both Farrell et al. and Lim et al. showed that the early hypoperfusion (30 min postseizure) was mainly induced by arteriolar constriction.[3,53] In the 4-AP mouse model, hypoperfusion

that persisted for >1 h resulted from increased capillary stalling induced by neutrophil adhesion to brain capillaries.[53] Similar mechanisms may be involved in the postictal state in our patients; however, these mechanisms cannot explain the increased perfusion observed in patients with short seizures (cf. Figure 2), of the order of 10 mL/100 g/min, which suggests that other processes are also involved. A candidate mechanism is increased activity of glia, to clear excessive extracellular potassium, which is known to be associated with regional CBF increases.[54–57] The relative strength of these counteracting mechanisms and their temporal relation may then define the net effect.

4.4 | Strengths and limitations

Strengths of our study include the prospective, systematic collection of clinical and ASL-MRI data shortly after ECT-induced seizures. Our methodology may enable studying postictal perfusion in a longitudinal fashion with repeated scans at regular time intervals. Furthermore, the inclusion of healthy controls, to control for test–retest effects, using the same scanner and settings, was important. Limitations include the relatively small sample sizes of patients and healthy controls. Also, the influence of the anesthetic agent (i.e., etomidate) in patients could have caused reductions in CBF.[46] However, this is unlikely, as the half-life of etomidate is 2–4 min and the postictal scans were acquired after approximately 1 h. Midazolam administration may have partly influenced our results, because the relation between rCBF and the cingulate gyrus and inferior frontal gyrus disappeared, when excluding patients receiving postictal midazolam. However, these results may also be explained by the smaller sample size. Postictal hypoperfusion in some patients may have already returned to baseline before the ASL-MRI measurements, although the regression models showed no independent relation with this time interval. A significant limitation to the interpretation is the potential cumulative effect of seizures on postictal perfusion changes, which may be addressed in future studies by scanning patients early in their ECT course. In addition, the patients' baseline ASL-MRI scans may not have been optimal, as these were not acquired after a sham procedure in the operation room. Finally, we could not obtain full brain coverage in all patients, precluding some brain regions from voxelwise analyses.

5 | CONCLUSIONS

Changes in global and regional postictal perfusion were related to the duration of ECT-induced seizures. Longer seizures were associated with larger decreases of global and regional postictal perfusion, whereas shorter seizures were associated with increases in postictal perfusion. Future studies may replicate these findings in a larger sample, investigating patients earlier in their ECT course.

AUTHOR CONTRIBUTIONS

Julia C. M. Pottkämper: Data acquisition; analyses; writing. **Joey P. A. J. Verdijk:** Writing. **Eva Aalbregt:** Data acquisition; analyses. **Sven Stuiver:** Data acquisition. **Laurens van de Mortel:** Analyses. **David G. Norris:** Analyses; writing. **Michel J. A. M. van Putten:** Writing. **Jeannette Hofmeijer:** Writing. **Guido A. van Wingen:** Analyses; writing. **Jeroen A. van Waarde:** Writing.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

CLINICAL TRIAL REGISTRATION

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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