

## SUPPLEMENT ARTICLE

# Neuroimaging alterations related to status epilepticus in an adult population: Definition of MRI findings and clinical-EEG correlation

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## Summary

Magnetic resonance imaging (MRI) provides an opportunity for identifying perictal MRI abnormalities (PMAs) related to status epilepticus (SE). Extremely variable MRI alterations have been reported previously during or after SE, mainly in small selected populations. In a retrospective monocentric study, we analyzed brain MRI changes observed in the ictal/postictal periods of SE in an adult population. We included all consecutive patients observed in a 5-year period with an electroclinical diagnosis of SE and an MRI performed within 30 days from the beginning of SE. We identified 277 patients. Among them, 32 (12%) showed PMAs related to SE. The duration of SE was strongly associated with MRI alterations, showing a mean duration of 6 days vs 2 days ( $P = .011$ ) in the group with and without MRI alterations, respectively. Focal electroencephalography (EEG) abnormalities ( $P = .00003$ ) and in particular, lateralized periodic discharges (LPDs) ( $P < .0001$ ) were strongly associated with PMAs. MRI alterations were unilateral (23 patients, 72%), located in multiple brain structures (19 patients, 59%), and involving mesiotemporal structures (17 patients, 53%). Sixteen patients (50%) had good spatial correspondence between cortical PMAs and the focal EEG pattern; 12 patients (38%) with focal EEG pattern showed cortical PMAs plus MRI signal changes also involving subcortical structures. A follow-up MRI was available for 14 of 32 patients (44%); 10 patients presented a disappearance of PMAs, whereas in 4, PMAs were still present. This study demonstrates that a long duration SE and the presence of certain EEG patterns (LPDs) are associated with the occurrence of PMAs. A good spatial concordance was observed between cortical PMA location and the EEG focus.

## KEYWORDS

DWI, magnetic resonance imaging, neuroimaging, status epilepticus

## 1 | INTRODUCTION

Status epilepticus (SE) is conceptually defined as “a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead[s] to abnormally, prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.”<sup>1</sup> This new definition underscores the pathophysiologic mechanisms that sustain SE development and its maintenance, thereby increasing the risk of neuronal injury.<sup>2</sup>

Ongoing seizure activity is accompanied by an excessive release of glutamate, which activates postsynaptic *N*-methyl-D-aspartate (NMDA) receptors and triggers receptor-mediated calcium influx. This leads to desensitization and internalization of postsynaptic  $\gamma$ -aminobutyric acid A (GABA-A) receptors<sup>3</sup> and increased expression of proconvulsive neuropeptides,<sup>4,5</sup> creating a vicious cycle of self-sustained seizure. Calcium influx also causes a cascade of biochemical changes, mitochondrial dysfunction, oxidative stress<sup>6</sup> modification of gene expression, and initiation of cell death.<sup>7</sup> At the same time, the sustained seizure activity increases cerebral glucose metabolism, oxygen and adenosine triphosphate (ATP) depletion, and lactate accumulation, finally leading to hypermetabolic neuronal necrosis.<sup>8</sup>

Magnetic resonance imaging (MRI) provides an opportunity for early identification of alterations related to seizures activity. Variable periictal MRI alterations<sup>9,10</sup> (PMAs) have been reported in patients with SE, in either the ictal or the postictal period. Restricted diffusion (high signal in diffusion-weighted imaging [DWI] sequences and corresponding low apparent diffusion coefficient, ADC)<sup>9,11</sup> and hyper-intensities in T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences that could even appear simultaneously,<sup>12</sup> are the most frequently encountered alterations. These changes represent a continuum of cytotoxic (increased DWI and decreased ADC signal) and vasogenic edema (increased DWI and increased T2 without decreased ADC signal) mostly depending on the timing of MRI performance.<sup>9,10</sup> Rarely a T2 hypointensity can be seen in patients with ongoing SE.<sup>9</sup> Moreover, ictal hyperperfusion in MR perfusion (MRP) sequences,<sup>11</sup> corresponding increased vascularity in MR angiography (MRA), and contrast enhancement, which are co-localized with aforementioned alterations, may be seen.<sup>9,13,14</sup>

PMAs have been observed in different cortical areas,<sup>9,15–17</sup> as well as involving subcortical structures. Previous studies also highlighted some preferential

### Key Points

- MRI is a useful, noninvasive, and easily available tool for identifying acute/subacute SE related alterations
- A long duration of SE with LPDs is strongly associated with periictal MRI abnormalities
- Acute/subacute MRI changes are generally reversible, but long-term, permanent consequences could be generated

susceptibility regions or networks: the mesolimbic structures,<sup>9,10,15,18</sup> the pulvinar nucleus of thalamus,<sup>13,18,19</sup> the splenium of corpus callosum,<sup>18,20</sup> the contralateral cerebellum (a sign known as crossed cerebellar diaschisis),<sup>13,18,21,22</sup> the insular cortex and basal ganglia,<sup>9,13</sup> and the claustrum.<sup>10,23</sup> The majority of these cases had focal SE<sup>18,24</sup> and showed PMAs both locally, in the cortical area of the ictal activity, as well as in remote cortical or subcortical areas generally believed to represent regions involved by ictal activity at the network level (eg, the thalamus and ipsilateral pulvinar).<sup>12,18,19</sup> Moreover, lateralized periodic discharges (LPDs) *plus* seizures seem to be associated with the development of acute/subacute DWI alterations.<sup>25</sup>

These MRI changes can be completely reversible, although their exact appearance or disappearance timing is unknown<sup>20</sup> and is variable among different patients.<sup>12</sup> The changes can even persist and be followed by permanent alterations such as cortical laminar necrosis, mesial temporal sclerosis,<sup>10,26</sup> and focal brain atrophy.<sup>9,13</sup>

## 2 | PURPOSE

The MRI changes associated with SE have been described, but the reports in the literature are scarce and based mainly on small selected populations. There are only a few studies correlating MRI changes with electroclinical patterns in SE. Therefore, we aimed to identify and stratify the patterns of PMA associated with SE and to correlate them with electroclinical features of SE in a large series of adult patients.

## 3 | METHODS

### 3.1 | Inclusion criteria and adopted definitions

This is a retrospective monocentric study on an adult SE population studied with a brain MRI in the ictal/postictal period of SE.

Status epilepticus (or SE) was defined as a continuous seizure or 2 or more discrete seizures between which there is no complete recovery of consciousness, that lasts  $\geq 5$  minute for convulsive SE (CSE) and more than 10 minutes in nonconvulsive status epilepticus (NCSE).<sup>1</sup>

The inclusion criteria were the following: (1) an electro-clinical diagnosis of SE, (2) an MRI that included all sequences of the hospital SE protocol, and (3) MRI performed within 30 days of the beginning of SE.

### 3.2 | Enrollment strategies

We searched the clinical and EEG database of the Department Neurology, Christian Doppler Klinik, Paracelsus Medical University, Salzburg, Austria, between 01.01.2011 and 31.12.2015 (see Figure 1).

### 3.3 | MRI study protocol and analysis

All included patients underwent high-resolution MRI (3-Tesla; Philips Achieva Stream, Andover, Massachusetts) using the standard protocol for SE patients routinely used at our institution. MRI sequences included T1-weighted 3-dimensional isovoxel ( $1 \times 1 \times 1$  mm) turbo field echo images with (when needed) and without intravenous contrast application, axial and coronal T2-weighted turbo spin echo, T2-weighted FLAIR, and DWI sequences. Coronal T2-weighted (2 mm) and FLAIR slices were 2.35 mm thick and were acquired at 90 degrees perpendicular to the long axis of hippocampus.

The acute/subacute MRI scans were reviewed independently by 2 raters who judged for the presence/absence of MRI's alterations related to SE. Whenever there was any discordance, a third rater was consulted. Finally, for the patients with PMAs, we searched for and analyzed the follow-up MRIs whenever present.

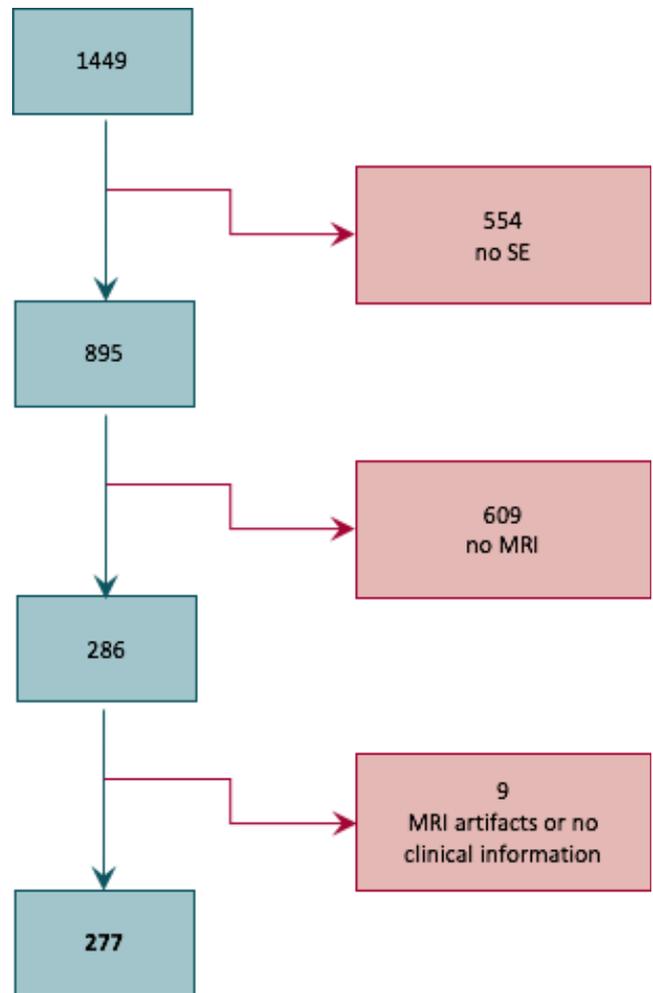
### 3.4 | EEG study details and clinical data collection

Using informatics databases, for each included SE episode we collected clinical information such as age, gender, and type of treatment. Each SE episode was classified in relation to etiology, duration, clinical manifestations, response to treatment, and EEG characteristics too.

The EEGs were acquired using the international 10-20 system. Each EEG recording lasted for at least 20 minutes and was assessed by board-certified neurophysiologists.

### 3.5 | Statistical analysis

Statistical analysis was performed using SPSS Statistics 23.0 (2015; IBM Corporation, Armonk, New York).



**FIGURE 1** Selection process flowchart. We initially identified 1449 patients with either suspected or definite diagnosis of SE. Medical records of each patient were thereafter meticulously analyzed. We excluded 554 patients because, despite the initial suspicion, these patients did not have SE. Of the 895 selected SE cases, 286 (32%) underwent brain MRI scan in the first 30 days from the beginning of SE, and thus they were included in the study. For each included patient we reviewed brain MRI results, EEG recordings, and medical records: 2 patients were thereafter excluded because of lack of clinical information and 7 patients were excluded due to either presence of MRI artifacts that interfered with the analysis or because they received an incomplete MRI study. At the end of the search 277 patients fulfilled the criteria and were included in the study

Descriptive statistics were used to analyze and compare clinical and demographic variables in the whole population and in subgroups divided according to the presence/absence of PMAs.

Categorical data were analyzed by means of  $2 \times 2$   $\chi^2$  test with Yates correction. Two-by-two comparisons were performed by means of the Mann-Whitney test. Inter-rater agreement for identifying SE-associated MRI alterations was assessed using Cohen's kappa coefficient ( $\kappa$ ).

Univariate logistic regression analysis was conducted to identify significant associations of each clinical variable with the presence of PMAs. The statistical significance cut-off was set at .05.

## 4 | RESULTS

### 4.1 | Population's demographic characteristics

In the studied population ( $n = 277$ ), 58% were male with a mean age of 63 years (ranging from 13 to 90 years). Thirty-two of them (12%) showed PMAs related to SE (see Table 1).

### 4.2 | SE clinical characteristics

The demographic and clinical characteristics of the patients are shown in Table 1. In the whole population, the most common SE etiologies were brain tumors (21%), SE in a previously diagnosed epilepsy (16%), and chronic cerebrovascular disease (11%). Only inflammatory/autoimmune etiology (odds ratio [OR] 4.23, confidence interval [CI] 1.20-14.96) and sepsis (OR 8.1, CI 1.1-59.63) were associated with PMAs.

The majority of patients (73%) presented with NCSE, either as the evolution form from previous motor manifestations or as the only semiology of the SE episode. Generalized convulsive status epilepticus (GCSE) evolving into NCSE with coma was associated with the presence of PMAs (OR 5.00, CI 1.83-13.68).

Finally, the duration of the SE itself was the strongest observed association with the appearance of PMAs. Indeed, patients with SE-related MRI alterations, had a SE mean duration of 6 days (mean duration of refractory status epilepticus/super-refractory status epilepticus (RSE/SRSE): 9.2 days; mean duration of RSE: 5.4 days), whereas patients without PMAs had a mean SE duration of 2 days (mean duration of RSE/SRSE: 7.5 days; mean duration of responsive SE: 1.2 days) ( $P = .011$ ). Only 27% of patients without MRI alterations had a SE lasting  $\geq 48$  hours compared to 59% with MRI alterations ( $P = .0003$ ).

### 4.3 | EEG characteristics

In patients with PMA, focal EEG patterns were more often ( $P = .00003$ , OR 21.25, CI 2.85-158.22) than diffuse ictal EEG ones ( $P = .0002$ , OR 0.06, CI 0.008-0.44).

Lateralized periodic discharges (or LPDs) were present in 47% of patients with PMAs vs 13% of patients in whom MRI changes were not seen ( $P < .0001$ , OR 5.76, CI 2.62-12.67).

In the whole population, 97 patients received MRI during SE. Among them, 24 had LPD activity and 73 did not. Nine patients of 73 without LPD activity (12%), showed PMAs, whereas 11 of 24 with LPD activity (46%) had PMAs ( $P < .001$ ).

Conversely, 172 patients were imaged after the end of SE. Among them 149 did not have LPD activity on the previous EEG, whereas 23 had LPDs in any of the EEG recorded during the SE. Eight of 149 patients without LPDs (6%) had PMA, whereas 4 of 23 with LPDs (17%) showed PMA ( $P < .035$ ).

Notably, the presence of LPDs and SE duration showed a “synergistic” effect on PMAs. Indeed, the median duration of SE in patients with LPDs and PMA was 11 days, whereas SE duration in patients with LPDs but without PMAs was 1 day.

### 4.4 | Timing of MRI study

In the majority (63%), MRI was performed after SE has ended. Among patients with SE-related MRI alterations, 20 of 32 patients (63%) had the investigation while SE was still ongoing, whereas only 78 of 245 patients (32%) without SE-related MRI alterations underwent MRI during the SE ( $P = .001$ ).

### 4.5 | Classification of SE-related MRI changes

Inter-rater agreement for identifying SE-associated MRI alterations was very high (Cohen's kappa .818). An increased signal in DWI and ADC with or without correspondent hyperintensities in T2/FLAIR sequences was seen in 11 patients (34%); 14 patients (44%) presented with an increased signal in DWI and a correspondent decreased ADC value with or without hyperintensities in T2/FLAIR sequences; the remaining 7 patients presented an increased signal on DWI, but for them the ADC map was not available (see Table 2).

Either unilateral (23 patients, 72%) or bilateral (9 patients, 28%) changes could be seen on MRI. In 19 patients (59%), alterations were observed in multiple brain structures either affected alone or as part of a more extensive circuit: (1) mesiotemporal structures (17 patients, 53%); (2) pulvinar nucleus of the thalamus (16 patients, 50%); (3) neocortex (15 patients, 47%): frontal and temporal cortices in 6 cases each, parietal cortex—in 5 cases and occipital cortex—in 1 case; and (4) insula (7 patients, 22%). Sixteen patients (50%) showed alterations involving the neocortex or mesiotemporal structures alone. In 13 patients (41%), cortical and deep structures (thalamus) were involved. In 3 patients (9%), MRI changes were found only in the thalamus.

**TABLE 1** Demographic and clinical variables of the patients

Clinical characteristics of included patients							
n	All included patients		Patients without PMAs		Patients with PMAs		P
	n	(n, %)	n	(n, %)	n	(n, %)	
Gender (M)	160	58%	143	58%	17	53%	.572
Average age (years)	62.5		63.0		59.3		.233
Type of SE							
NCSE	168	61%	150	61%	18	56%	.588
GCSE—NCSE	20	7%	13	5%	7	22%	<b>.001</b>
FMSE—NCSE	8	3%	7	3%	1	3%	.932
GCSE	43	16%	40	16%	3	9%	.307
FMSE	30	11%	27	11%	3	9%	.778
MSE	8	3%	8	3%	0	0%	.3
SE duration							
Average (days)	2		2		6		<b>.011</b>
≥48 h	85	31%	66	27%	19	59%	<b>&lt;.001</b>
Etiology							
Acute CVD	25	9%	23	9%	2	6%	.56
Chronic CVD	30	11%	26	11%	4	13%	.747
Alcohol related	2	1%	2	1%	0	0%	.608
Anoxia	27	10%	27	11%	0	0%	.05
Brain trauma	10	4%	9	4%	1	3%	.876
Inflammatory/autoimmune	12	4%	8	3%	4	13%	<b>.016</b>
Dementia	3	1%	3	1%	0	0%	.529
Hydrocephalus	2	1%	2	1%	0	0%	.608
Metabolic alterations	24	9%	18	7%	6	19%	.11
Infectious encephalitis	12	4%	11	4%	1	3%	.721
Sepsis	4	1%	2	1%	2	6%	<b>.015</b>
Brain neoplasm	58	21%	54	22%	4	13%	.212
Perinatal injuries	7	3%	7	3%	0	0%	.333
Epilepsy related	45	16%	41	17%	4	13%	.541
Cryptogenic	16	6%	12	5%	4	13%	.104
Treatment response							
Responsive SE	229	83%	204	83%	25	78%	.47
RSE	18	6%	16	7%	2	6%	.952
SRSE	30	11%	25	10%	5	16%	.353

Bold values are statistically significant ( $P < .05$ ). CVD, cerebrovascular disease; FMSE, focal motor status epilepticus; GCSE, generalized convulsive status epilepticus; MSE, myoclonic status epilepticus; NCSE, nonconvulsive status epilepticus; RSE, refractory status epilepticus; SRSE, super-refractory status epilepticus.

**TABLE 2** MRI characteristics of the cohort

Patient no.	DWI	ADC	T2	Flair	Post-contrast	F-UP
1	↑	N/A	↑	↑	N	D
2	↑	↑	↑	↑	N/D	D
3	↑	↓	N	N	N	N/D
4	↑	↑	N/A	N/A	N	D
5	↑	N/A	N/A	N/A	N/D	N/D
6	↑	↑	N/A	N/A	N/D	N/D
7	↑	↓	N	N	N/D	N/D
8	↑	↓	N/A	↑	N/D	D
9	↑	↓	↑	↑	N	N/D
10	↑	N/A	↑	↑	N/D	D
11	↑	N/A	N	N	N/D	D
12	↑	↑	N/A	N	N	N/D
13	↑	↓	↑	↑	N/D	N/D
14	↑	↓	N	N	N	N/D
15	↑	↑	N	N	N	N/D
16	↑	↓	N/A	N/A	N/D	N/D
17	N/A	N/A	↑	↑	N	A
18	↑	N/A	N/A	N/A	N/D	N/D
19	↑	N/A	N	N	N/D	N/D
20	↑	↓	↑	↑	N	D
21	↑	↑	↑	↑	N	D
22	↑	↓	↑	↑	N/D	N/D
23	↑	↓	↑	↑	N/D	A
24	↑	↓	N/A	↑	N/D	N/D
25	↑	↓	N/A	↑	N/D	D
26	↑	↑	↑	↑	N/D	A
27	↑	↓	↑	↑	N/D	N/D
28	↑	↑	N	N	N	N/D
29	↑	↑	↑	↑	N/D	N/D
30	↑	↑	↑	↑	N	N/D
31	↑	↓	N/A	N	N/D	A
32	↑	↑	↑	↑	N	D

↑, increased signal; ↓, reduced signal; A, attenuated; D, disappeared; N, normal; NA, not accessible due to motion artifacts; ND, not done; Pt, patient.

#### 4.6 | Correlation of EEG and MRI features

PMAs were well co-localized with focal EEG ictal discharges in 16 patients (50%). Twelve patients (38%) had focal ictal activity on EEG, and MRI changes involving local structures corresponding to the site of the highest EEG activity plus subcortical structures (unilateral or bilateral changes in the pulvinar nucleus of the thalamus).

Only 3 patients (9%) presented focal ictal activity on EEG and isolated deep homolateral thalamus involvement

on the MRI without cortical alterations. On the other hand, the only patient with a diffuse ictal pattern on EEG presented a diffuse bilateral involvement of insular cortex and thalamus.

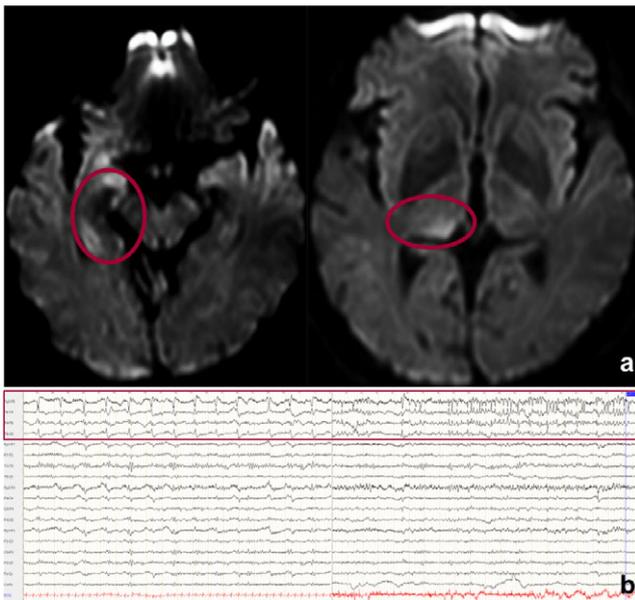
Among patients with LPDs, 6 (40%) presented with isolated local MRI changes corresponding to the focus of LPDs activity; 6 (40%) showed focal MRI changes together with deep homolateral involvement of the pulvinar; 3 patients (20%) had isolated homolateral pulvinar involvement (Figures 2-5).

#### 4.7 | Follow-up MRI evaluations

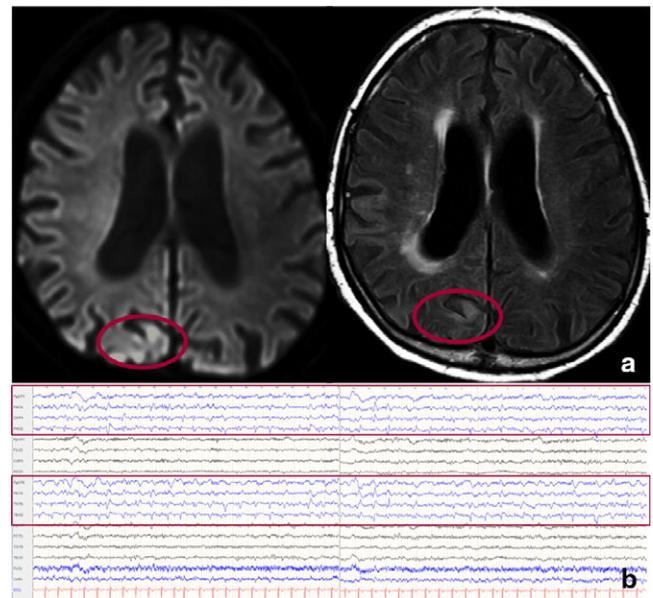
A follow-up MRI was performed (9 days to 3.6 years after the SE) in 14 of 32 patients (44%). MRI changes completely disappeared in 10 of 14 patients (71%), whereas in the remaining 4 of 14 (29%), signal alterations were attenuated but not completely resolved. No patients had unchanged alterations.

## 5 | DISCUSSION

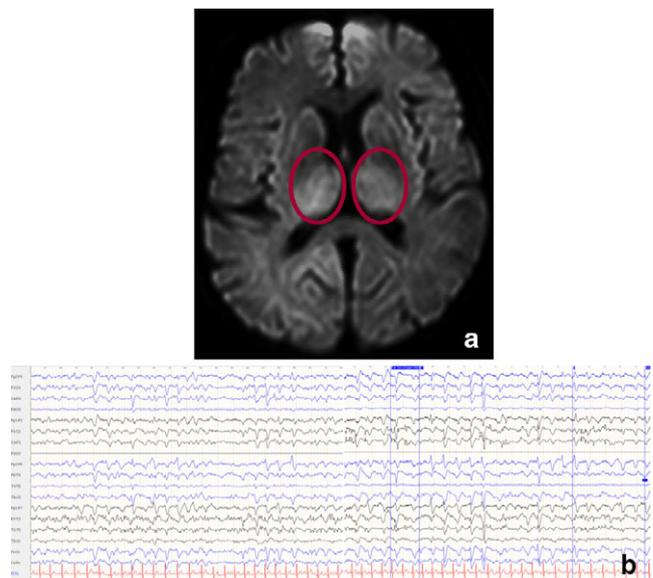
In this retrospective study on a large single-center cohort, we identified 32 patients (12%) with MRI changes related to SE. The duration of the SE episode was the factor with the highest significant association with the appearance of PMAs. In addition, LPDs were strongly associated with SE-related MRI changes.



**FIGURE 2** A, DWI signal hyperintensity in the pulvinar of thalamus on the right and in the right hippocampus. B, Continuous quasi-periodic spike and waves at frequency of 0.7-1 Hz showing an evolving pattern into a poly-spikes at 4-5 Hz on the right frontotemporal leads

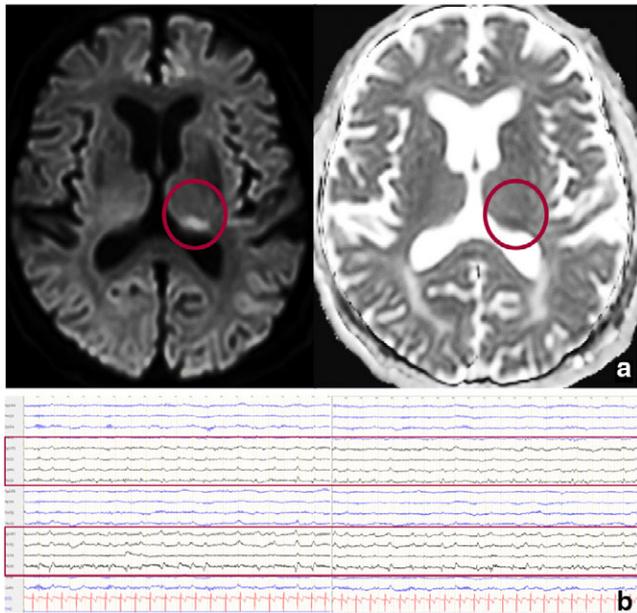


**FIGURE 3** A, DWI and FLAIR signal hyperintensity in the right parietal cortex. B, Continuous quasi-periodic sharp waves at frequency of 1 Hz on the right temporoparietal leads



**FIGURE 4** A, Bilateral thalamic DWI hyperintensity. B, Diffuse triphasic sharp waves at frequency of 1 Hz

Incidence of SE-related MRI signal alterations in retrospective series varies between 11.6% and 50%.<sup>18,27</sup> In our population, acute/subacute MRI changes were present in only 12% of the patients studied with MRI during or after an episode of SE. This low proportion is related mostly to the fact that only 35% of the patients received an MRI study during SE and most investigations were performed after cessation of the study. Because these MRI changes are supposedly caused by continuous or repetitive epileptic activity, a higher proportion of patients with PMAs can be



**FIGURE 5** A, DWI increased signal and correspondent ADC restriction located in the left thalamus. B, Continuous quasi-periodic left hemispheric sharp waves at frequency of 0.8-1 Hz

expected if MRI is performed during the SE instead of after its cessation.<sup>24,28</sup> Nevertheless, it is still possible to find these alterations for some time after the end of SE; the duration could depend on two factors: patient characteristics (eg, age, comorbidities), or seizure characteristics (type and duration of ictal activity).

Among all investigated clinical parameters, we identified a crucial role of SE duration: the longer the duration of SE, the higher the probability of finding SE-related MRI alterations.<sup>24,29</sup> Moreover, these alterations were mostly associated with the presence of LPDs. Thus, long-lasting SE with LPD activity is most frequently associated with the presence of PMAs.<sup>25,30</sup> LPDs were present in patients with SE of various etiologies, such as cerebrovascular, autoimmune, or infectious. In 4 patients, PMAs were observed in the context of autoimmune encephalitis. In these cases, the observed MRI alterations can represent abnormalities related to the underlying etiology not representing a consequence of the ictal activity per se.

Our results indicate that PMAs well co-localize with either the epileptic focus or remote areas presumably involved in the epileptic network,<sup>15</sup> such as the cortical connections to the pulvinar of the thalamus.<sup>19</sup> Even if there is a certain degree of susceptibility among different individuals<sup>12</sup> (variability in mitochondrial reserve in stress situations) and in the same individual among the different cerebral areas, we confirmed that the mesiotemporal structures are highly susceptible to ictal damage, thus they were most frequently involved.<sup>10,31</sup>

In the majority of our patients, PMA alterations were transient,<sup>16</sup> but because only a minority of our patients had a follow-up MRI we cannot draw any firm conclusion about their role as a possible biomarker of permanent functional and structural damage.

## 6 | STUDY LIMITATIONS AND CONCLUSIONS

The most important limitations of the present study are its retrospective nature and the low number of patients with MRI acquired during SE itself. The number of follow-up MRI studies was also low and as it would be expected in a retrospective study, the MRI were not performed at fixed intervals but at highly different time points in the course of SE or after its cessation. These limitations do not allow us to attribute observed MRI alterations to SE per se. MRI changes might be caused by the nature of the possible underlying lesion such as limbic encephalitis or stroke. It is challenging to disentangle the role of the underlying structural lesion, and we did not address this issue in the current study, which could be better tackled in the prospective design.

A prospective study with MRI performed during the SE and at regular follow-ups would also better define the relationship between the electroclinical characteristics and MRI alteration patterns and the role of MRI in the early prediction of long-term consequences after SE.

In summary, in this retrospective study, PMAs were observed mainly in association with prolonged SE and lateralized epileptiform discharges on EEG. MRI alterations affected different brain structures, involving mesiotemporal in more than half of cases.

## DISCLOSURE OF CONFLICT OF INTEREST

Prof. Trinka has acted as a paid consultant to Eisai, Ever Neuropharma, Biogen, Sunovion, Bial, and UCB, has received speakers' honoraria from Bial, Eisai, GL Pharma, GlaxoSmithKline, Boehringer, Viropharma, Actavis, Newbridge, Sunovion, Novartis, Takeda, and UCB. Dr. Trinka has received research funding from UCB Pharma, Biogen, Red Bull, Merck, the European Union, FWF Österreichischer Fond zur Wissenschaftsförderung, Bundesministerium für Wissenschaft und Forschung, and Jubiläumsfond der Österreichischen Nationalbank.

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Kuchukhidze, and Dr McCoy have no disclosures. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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