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ORIGINAL ARTICLE

Neuronal current imaging of epileptic activity: An MRI study in patients with a first unprovoked epileptic seizure

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Abstract

Objective: This study evaluates the performance of the novel MRI sequence stimulus-induced rotary saturation (SIRS) to map responses to interictal epileptic activity in the human cortex. Spin-lock pulses have been applied to indirectly detect neuronal activity through magnetic field perturbations. Following initial reports about the feasibility of the method in humans and animals with epilepsy, we aimed to investigate the diagnostic yield of spin-lock MR pulses in comparison with scalp-EEG in first seizure patients.

Methods: We employed a novel method for measurements of neuronal activity through the detection of a resonant oscillating field, stimulus-induced rotary saturation contrast (SIRS) at spin-lock frequencies of 120 and 240 Hz acquired at a single 3T MRI system. Within a prospective observational study, we conducted SIRS experiments in 55 patients within 7 days after a suspected first unprovoked epileptic seizure and 61 healthy control subjects. In this study, we report on the analysis of data from a single 3T MRI system, encompassing 35 first seizure patients and 31 controls.

Results: The SIRS method was applicable in all patients and healthy controls at frequencies of 120 and 240 Hz. We did not observe any significant age- or sex-related differences. Specificity of SIRS at 120 Hz was 90.3% and 93.5% at 240 Hz. Sensitivity was 17.1% at 120 Hz and 40.0% at 240 Hz.

Significance: SIRS targets neuronal oscillating magnetic fields in patients with epilepsy. The coupling of presaturated spins to epilepsy-related magnetic field perturbations may serve as a—at this stage experimental—diagnostic test in first seizure patients to complement EEG findings as a standard screening test.

Plain Language Summary: Routine diagnostic tests carry several limitations when applied after a suspected first seizure. SIRS is a noninvasive MRI method to enable time-sensitive diagnosis of image correlates of epileptic activity with increased sensitivity compared to routine EEG.

KEYWORDS
first seizure, high frequency oscillations, MRI

1 | INTRODUCTION

Epilepsy is a cerebral network disorder, defined by an increased risk to suffer from unprovoked seizures.[1,2] Lifetime prevalence of epilepsy is estimated to be ~5% worldwide.[3] To define the underlying epilepsy syndrome, scalp-EEG[4,5] and MRI[6] are indispensable diagnostic tools, providing measures for interictal epileptiform signals and structural epileptogenic lesions. Both are strong predictors of epilepsy after a first seizure. A recent systematic review and meta-analysis of 15 studies on first seizure patients reported a sensitivity of 17.3% and specificity of 94.7% for scalp-EEG, rendering it a screening test for the presence of epileptic activity. However, scalp-EEG is limited by low spatial resolution and restriction to superficial brain regions.[2] MRI in contrast enables the identification of abnormal cortical and subcortical tissue. It predicts a specific recurrence risk after a first seizure addressed to "remote lesions," that is, tissue damage after stroke, traumatic brain injury, or infection.[7] MRI further enables the detection of transient abnormalities related to the seizure by diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI), or perfusion imaging. However, these methods are rather sensitive to clusters of seizures or status epilepticus than to single seizures.[8] Positron emission tomography, arterial spin labeling perfusion imaging, or combined EEG-fMRI are mainly restricted to presurgical workup in patients with pharmacoresistant epilepsy. They provide information on altered brain metabolism, but are not direct measures of electrical activity.[9–11]

A recently proposed MR-based method to identify sources of altered neuronal activity in the brain is the stimulus-induced rotary saturation contrast (SIRS). SIRS aims at the direct measurement of neuronal activity through the detection of a resonant oscillating field.[12,13] Recent in silico studies and phantom experiments demonstrated that oscillating signals produce a double-resonance-based contrast.[14] In a first proof-of-concept study in humans, saturation effects were identified ipsilateral to the seizure onset zone in six of eight patients with refractory epilepsy. Patients with persistent postsurgical SIRS signals developed unfavorable outcomes.[12] In animal experiments, SIRS contrast enabled the identification of epileptic dogs with a sensitivity of 91.7% and specificity of 80% in comparison to controls.[13]

The spin-lock preparation within the SIRS sequence can be personalized to detect any frequency of the oscillating target field, encompassing gamma oscillations and high frequency oscillations (HFOs). HFOs are defined as spontaneous EEG events in the frequency range between 80 and 500 Hz, consisting of at least four oscillations that clearly stand out from the background activity. Ripples cover the range of 80–250 Hz of HFOs and fast ripples from 250 to 500 Hz.[15] In the past two decades, HFOs emerged as a more specific biomarker for the seizure onset zone, independently from interictal epileptiform discharges (IED).[16,17] Several potential pathomechanisms contribute to the expression of HFOs. Especially interneurons play a pivotal role in their generation.[18] Observations indicated them to represent the seizure-onset zone more precisely and more specifically compared to IED alone.[19,20] HFOs mirrored disease activity and treatment response, indicating their clinical relevance.[20] A prerequisite for robust analysis was the availability of invasive recordings and therefore the restriction to specific cohorts of presurgical candidates with refractory epilepsy.[21–23] Noninvasive HFOs detection is still in an experimental stage and clinical experience is mainly limited to pediatric populations.[24,25]

Here, we report on a single center investigation of the SIRS contrast within the framework of the Swiss First study,[26] a prospective observational study that aims at the characterization of EEG and MR imaging correlates acquired within 7 days after a first unprovoked epileptic seizure. We hypothesized that the SIRS contrast enables the detection of epileptic activity with a comparable sensitivity and specificity as scalp-EEG after a first seizure. Further, we considered SIRS being capable to localize epileptiform neuronal activity.

Key points

- Stimulus-induced rotary saturation is a novel MRI technique aiming to detect magnetic field perturbations induced by brain activity.
- SIRS demonstrated a comparable rate of abnormality detection compared to EEG.
- SIRS and EEG signal demonstrated concordance at the hemispheric and lobar level.

2 | MATERIALS AND METHODS

2.1 | Patient and control cohort

The recruitment of the Swiss First study was closed in December 2022 after enrollment of 636 patients. The goal of this observational study was to identify the presence of potential epileptogenic lesions and peri-ictal imaging abnormalities using MRI as well as clinical follow-ups for 24 months to determine new onset epilepsy.[26] In our center, 245 patients with a suspected first unprovoked epileptic seizure were enrolled into the study and received MRI examination and routine EEG (10–20 electrode placement, acquisition time 20 min in wake state) within 7 days after the suspected first seizure. For the study at hand, we analyzed a subgroup of 55 patients who were eligible for extended imaging acquisitions within the routinely scheduled workflows. The eligibility required an extended imaging acquisition slot beyond 45 min. For all patients, the final diagnosis of epilepsy after a first seizure followed the evidence-based guidelines for management of an unprovoked first seizure in adults of the International League Against Epilepsy (ILAE) and American Academy of Neurology (AAN).[1,4] Following this definition, we categorized epileptic seizures as the "...transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain..."[1]

The healthy controls encompassed 61 subjects above 18 years of age without a history of neurological or psychiatric comorbidities, who were recruited via institutional advertisement. Subjects with a structural findings suspicious for an epileptogenic lesion[6] were excluded from this study.

2.2 | MRI acquisition

Imaging data from 27 healthy controls (14 males, 13 females, mean age 37.4 ± 10.8 years) and 39 patients (22 male, 17 female, mean age 50.6 ± 19.5 years) was acquired on a Siemens Magnetom Vida 3T MRI scanner, Siemens, Erlangen, Germany. The MRI protocol for patients and healthy controls followed the Swiss First study protocol (Figure S1).[26] MRI protocol for patients followed the HARNESS recommendations after a first seizure with an additional DWI, SWI, perfusion, and SIRS sequence.[27] Healthy controls received the identical MRI protocol as patients, with exception of no applied contrast agent and hence no available perfusion imaging study. Only SIRS acquisitions from the Siemens Magnetom Vida scanner were included in the final analysis.

The SIRS studies with patients and healthy controls were also conducted on a Siemens Magnetom Skyra Fit. Due to hardware constraints, the preadjustment of the desired target frequency resulted in imprecise adjustments of 60/120 Hz instead of 120/240 Hz. This led to the exclusion of 13/55 patients and 33/61 healthy controls from the analysis. Three patients were additionally examined on a Siemens Prisma Fit system at 120/240 Hz. However, since no healthy control data were acquired from this scanner, we also excluded these scans from the analysis (Figure 1). Patient allocation to the respective MRI scanner was determined by the availability in clinical setting.

A board-certified neuroradiologist performed visual assessment of all available MRI sequences for structural epileptogenic abnormalities and transient peri-ictal abnormalities (TPMA).[6,8,28]

2.3 | EEG analysis

EEGs were reviewed by expert neurophysiologists for slow activity and IED based on the criteria defined by the International Federation of Clinical Neurophysiology (IFCN). Slow activity and IED were either classified as focal or generalized.[29]

2.4 | Stimulus-induced rotary saturation (SIRS) as a new contrast to detect neuronal currents

The SIRS sequence used in this study encompassed successive and alternating spin-lock on (SL_{on}) and spin-lock off (SL_{off}) prepared measurements as used in the previous comparable studies in dogs and epilepsy surgery patients.[12,13] The SL preparation lowered the effective oscillation frequency of the magnetization to a predetermined target frequency. This allowed the magnetization to resonate with oscillating magnetic fields induced by neuronal activity with the target frequency ω_{NC} in a range of ±10 Hz.[30] After each preparation, 12 slices were acquired using 2D echo planar imaging (EPI) readout for image formation. A measured contrast between successive SL_{on} and SL_{off} indicated the presence of electrophysiological activity with ω_{NC} during SL_{on} measurement.[31]

For this study, we used a nonselective rotary echo SL preparation formed by four radio frequency (RF) pulses. A first $\pi/2$ hard pulse brought the magnetization to the transversal plane where two long RF pulses with opposite phase lock the magnetization inducing the target frequency ω_{SL} (see Figure S1B). The opposite phase of the two pulses made the preparation robust against errors in

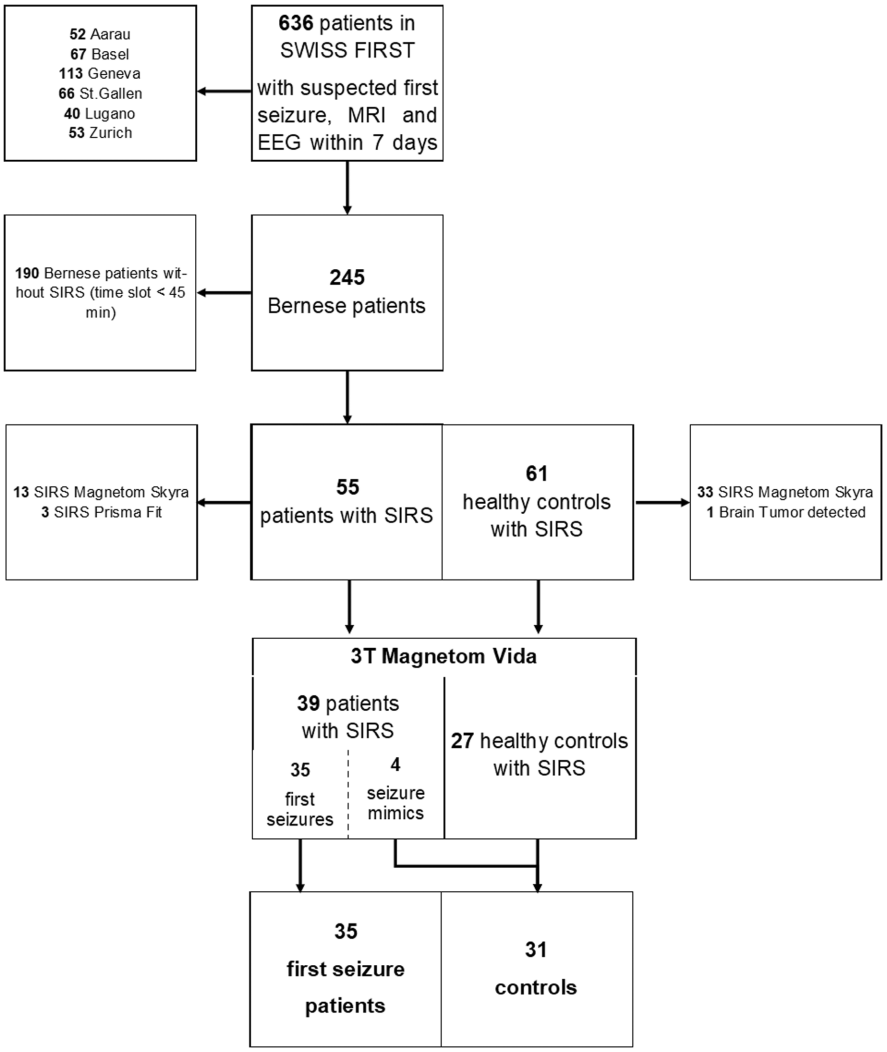

FIGURE 1 Flowchart of the SWISS FIRST study and acquisition of SIRS in patients and healthy controls. Only patients and healthy controls whose MRI with epilepsy protocol was performed on a Siemens Magnetom Vida scanner were included in the final analysis. SIRS measurements were performed on 120 and 240 Hz.

the transmit field B_1.[32] We heuristically targeted frequencies associated with fast oscillations in the epileptogenic zone based on previous literature as in the previous experiments. Specifically, we targeted frequencies at 120 Hz and 240 Hz, falling within the ripples and fast ripples range.[12,13,33] During the SL period ($T_{SL} = 70$ msec), the resonance effect between the target neuronal field with frequency ω_{NC} and the induced SL frequency ω_{SL} was expected to decrease the local MR contrast, if ω_{SL} was equal to ω_{NC}. The last nonselective $\pi/2$ pulse returned the magnetization back to the longitudinal plane, from where selective excitation and readout followed.

The consecutive measurement of SL_{on} and SL_{off} acquisition separated effects encoded by the common echo-planar imaging readout (i.e., BOLD effect) in both acquisitions. Image parameters common to both acquisitions were number of slices = 12, matrix size = 64 × 64, slice thickness = 5 mm, BW = 1950 Hz/px, and TR = 1675 msec. The full acquisition period for two preselected target frequencies resulted in 500 s (8 min and 20 s), comprising 250 s of acquisitions at 120 Hz and 250 s at 240 Hz.

2.5 | Image analysis

We intended to obtain a metric capable of reliably detecting paroxysmal occurring signals, such as neuronal currents in high frequency range. Therefore, we required a measure of signal variability that highlighted sporadic high variance while effectively filtering out constant noise.[12]

A SIRS contrast map was computed for each patient through the following procedure: At first, we calculated the normalized subtraction NS (t) between SL_{on} and SL_{off} measurements for each voxel at each time point t as

$$NS(t) = SL_{on}(t) - \frac{SL_{off}(t)\, SL_{on}(0)}{SL_{off}(0)}$$

The normalized subtractions of each voxel varied over time, filtering out the variance arising from the common EPI readout that was encoded in the same manner in both SL_{on} and SL_{off}.[12] Then, the zscore-contrast was quantified for each voxel as the absolute mean of the zscore of NS (t).

If a paroxysmal high variation occurred, such as expected during neuronal activity, the normalized subtraction will deviate largely from the mean variation, generating a lower zscore-contrast. We then calculated the final SIRS contrast map by transposing the zscore-contrast maps to highlight the activated regions:

$$\text{SIRS contrast} = \max(z\text{ score contrast}) - z\text{ score contrast}$$

We then normalized the SIRS contrast value across the entire map to a scale up to 1000. Noise was expected to correspond to low SIRS contrast values, where SL_{on} measurements varied in the same extent as SL_{off} measurements. High amplitude paroxysmal occurring signals were expected to yield high SIRS contrast values, reflecting sporadic variations of SL_{on} measurements absent in the SL_{off} measurements. Finally, the SIRS maps containing SIRS contrast value were co-registered with high-resolution T1-weighted anatomical images from each patient.

The SIRS overlay maps were visually analyzed for the peak SIRS contrast within a predefined cluster of voxels. To reduce the probability of false positives (type I error), assuming that neural activity exceeded single voxels and will manifest in spatially restricted neighbored voxels, only brain regions containing a cluster of minimum 20 adjacent voxels were reported. Using cluster voxel analysis instead of single voxel analysis, the likelihood of encountering false positive findings (noise) decreased, and statistical power increased by allowing a reduction of the minimal SIRS contrast value for a significant signal of the whole cluster. The probability of a whole cluster containing 20 adjacent voxels being false positive decreased to 0.0029, assuming the false positive detection probability of each voxel was 0.05.[34]

All post-processing and analysis steps were performed using an in-house developed MATLAB script (version MATLAB R2022b).

Outlier voxel clusters were rejected as artifacts, if the voxel cluster of the SIRS contrast maps (i) expanded into nonneural tissue (e.g., expansion into the tentorium cerebelli, falx cerebri, and bone), (ii) was composed of voxels with identical SIRS contrast value or (iii) presented with nonphysiological distributions and shapes (ring and line artifacts) (Figure S3A). SIRS contrast signals that passed the artifact rejection were analyzed according to their variations in the SL_{on} and SL_{off} signal acquisition. If a SL_{off} baseline condition was unstable due to unrelated magnetic field inhomogeneities,[30] SL_{off} became unreliable and normalized subtraction would cause false contrasts (Figure S3B). If peak contrasts were identified as artificial and required rejection, the clusters with the subsequently highest contrast were reanalyzed. If a SL_{off} condition remained stable, and intermittent fluctuations were present during SL_{on}, we classified them as causal effects of oscillations (Figure S3C). After preprocessing, the SIRS contrast overlays were visually analyzed and localized via case-by-case comparisons between patients versus control subjects. Finally, presence of structural imaging abnormalities and TPMA were reviewed by a board-certified neuroradiologist and compared to the SIRS findings.[6,8,28]

The values of each subject, as well as EEG findings of patients, are listed in the Supporting Information.

2.6 | Statistical analysis

Statistical analysis was performed with RStudio (version 2022.07.2 Build 576). To group similar data points together and discover underlying patterns, we employed k-means clustering, an unsupervised machine learning algorithm. The number of centroids in the dataset was set to 2 (for positive and negative), where each centroid represents the center of the cluster and the data points were assigned to the nearest cluster by minimalizing the in-cluster sum of squares. We employed k-means clustering 25 times for the covariates SIRS contrast value, age, and sex. The threshold for positive finding was determined by the average of both centroids for each frequency separately. SIRS clusters with contrast values above the threshold were regarded as positive findings.

The comparison of SIRS contrast values between epileptic seizure patients and the control group was performed with a one-sided *t*-test.

3 | RESULTS

Image acquisition was performed at the day of admission in 17 patients, and EEG in nine patients. In all other patients, EEG and MRI were performed within 1 week after the event. Mean delay between event and MRI was 1 day, and between event and EEG 2 days. Twenty patients received MRI ahead of the EEG, eight patients received EEG at first. Eleven patients performed EEG and MRI the same day (Figure S3A–C).

Thirty-five of 39 patients were diagnosed with an unprovoked epileptic seizure. Three patients presented with a generalized seizure, 11 with a focal seizure. The seizure semiology could not be definitely determined in 21 patients. Four patients presented with a seizure mimic. Seizure mimics and healthy controls were used as comparators ($n = 31$).

3.1 | Age- and sex-related findings

We used age and sex as covariates in the SIRS analysis (Figure 2A–D). For healthy controls, the linear regression

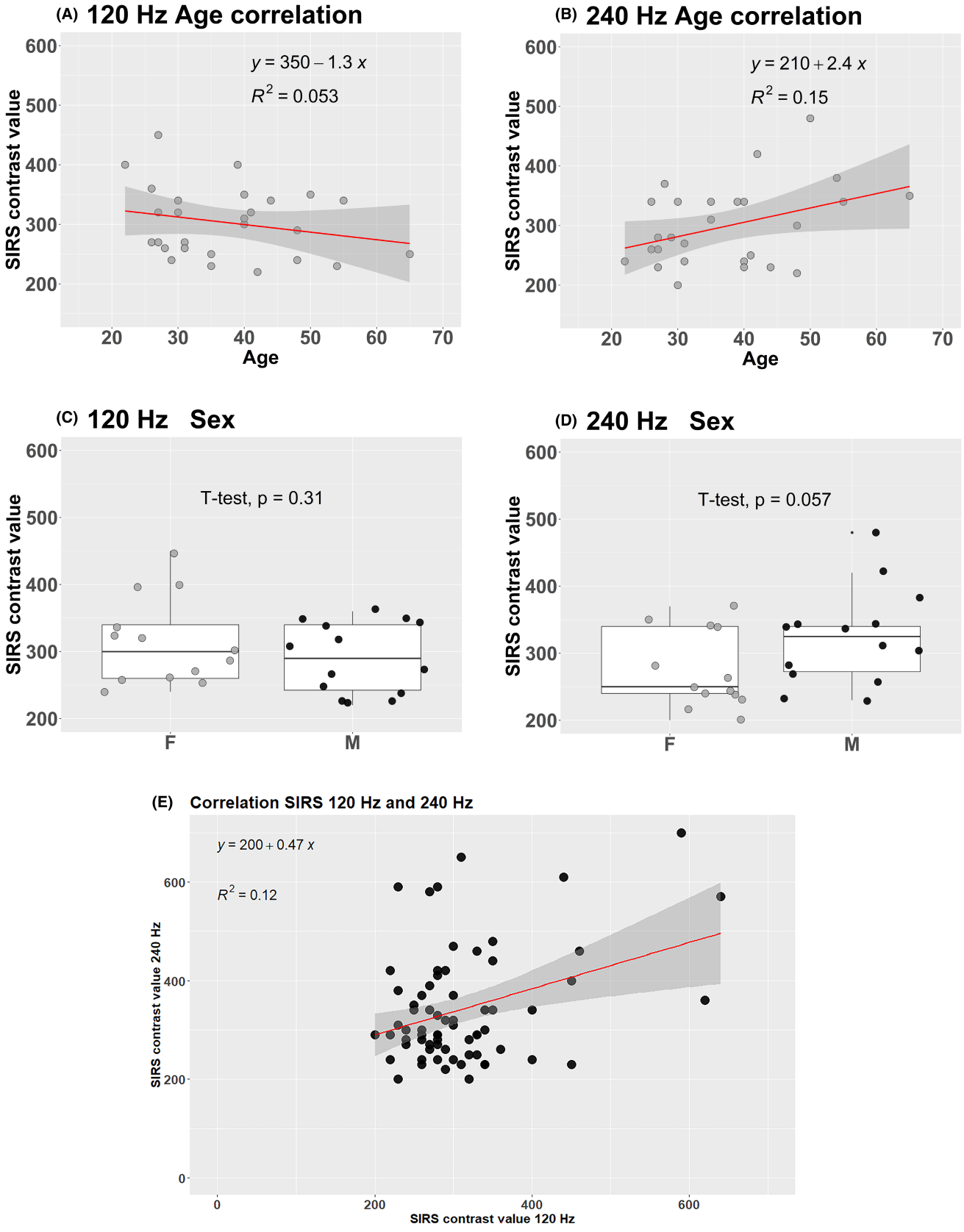

FIGURE 2 Measurements with healthy controls only with the highest remaining SIRS contrast value of clusters with a minimum of 20 adjacent voxels after exclusion of artifacts. (A) Age correlation at 120 Hz. (B) Age correlation at 240 Hz. (C) Sex differences at 120 Hz. (D) Sex differences at 240 Hz. (E) Correlation between SIRS measurements at 120 and 240 Hz. For A, B, and E, R^2 corresponds to the coefficient of determination.

analysis of SIRS contrast and age identified no correlation (R^2 for 120 Hz = 0.053, R^2 for 240 Hz = 0.150). No statistical differences were observed between male and female control subjects ($p = 0.31$ at 120 Hz, $p = 0.06$ at 240 Hz). Comparison between SIRS contrast values for each healthy control at 120 Hz and 240 Hz showed no correlation between both measured frequencies ($R^2 = 0.059$; Figure 2E).

3.2 | SIRS at 120 Hz

Direct comparison of the SIRS contrast at 120 Hz of epileptic seizure patients (mean = 321 ± 103) and controls (mean = 302 ± 59) resulted in no statistical significant difference between the two of them with $p = 0.37$. At 120 Hz, clustering determined a threshold of k = 389.8 (centroids 494.4 for positive, 285.1 for negative), which resulted in a sensitivity of 17.1% (6/35) at a specificity of 90.3% (28/31). In this observational study design, the SIRS contrast value and delay between seizure (in the epileptic seizure group) and scan did not show any correlation ($R^2 = 5 \times 10^{-4}$). Measurements with high signal intensities were also detectable up to 5 days after seizure (see Figure S3D), with the restriction of four patients scanned beyond 3 days after seizure.

3.3 | SIRS at 240 Hz

The SIRS contrast at 240 Hz differed significantly between epileptic seizure patients (mean = 377 ± 131) and controls (mean = 299 ± 68) with $p = 0.003$. At 240 Hz, the clustering threshold was set to k = 403.9 (centroids 516.9 for positive, 290.8 for negative), resulting in a specificity of 93.5% (29/31) at a sensitivity of 40.0% (14/35). No relevant correlation between SIRS contrast value and time from seizure to scanning was observed at the preadjusted frequency of 240 Hz ($R^2 = 0.017$) (Figure 3).

3.4 | Electroencephalography, perfusion, diffusion-weighted imaging, susceptibility-weighted imaging and potentially epileptogenic lesions

3.4.1 | Diagnostic yield of EEG

EEG findings were extracted from clinical reports. IED were identified in four of 35 first seizure patients (sensitivity$_{IED}$ 11.4%). Seizure mimics ($n = 4$) displayed no IED (specificity$_{IED}$ 100%). Fourteen EEGs of epileptic seizure patients indicated abnormal slowing (sensitivity$_{slowing}$ 39.6%), and two seizure mimics expressed also abnormal slowing (specificity$_{slowing}$ 50.0%). The overall sensitivity taking IED and slowing into account was 48.6%.

3.4.2 | Diagnostic yield of structural and advanced MRI

Twenty-five out of 35 patients were investigated with DSC perfusion imaging with sufficient image quality. Three patients presented with perfusion abnormalities, two patients with focal hypoperfusion, and one with focal hyperperfusion (sensitivity$_{perfusion}$ 11.4%). One seizure mimic presented with a perfusion abnormality accounting as TPMA (specificity$_{perfusion}$ 75.0%).

All patients were investigated with diffusion-weighted imaging (DWI). Focal DWI restrictions as TPMA were identified in four patients. Thirty-one patients with an unprovoked seizure and all seizure mimics showed no diffusion abnormalities (sensitivity$_{DWI}$ 11.4%, specificity$_{DWI}$ 100%).

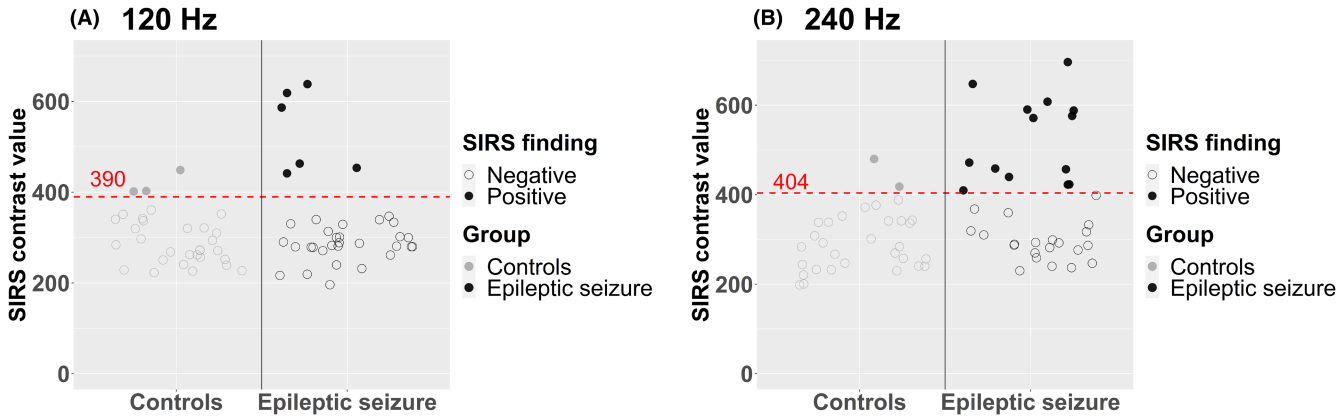

FIGURE 3 Jitter plots with the highest remaining SIRS contrast value of clusters with a minimum of 20 adjacent voxels after exclusion of artifacts. Red: Segregation line. (A) 120 Hz: Segregation at threshold = 390 (centers of clusters are 494.4 and 285.1). (B) 240 Hz: Segregation at threshold = 404 (centers of clusters are 516.9 and 290.8).

All patients received susceptibility-weighted imaging (SWI). The seizure mimic patients and 34 first seizure patients had normal and symmetric SWI patterns (specificity$_{SWI}$ 100%). One patient with an epileptic seizure presented with asymmetric cortical veins, indicating focal postictal hypoperfusion (sensitivity$_{SWI}$ 2.9%).

All investigated patients received MRI protocols dedicated to detect potential structural causes for epilepsy, including high-resolution T1 sequences (native and with contrast agent), FLAIR all with 1 mm slice thickness and two T2 sequences (aligned to the hippocampal axis and sagittal) both with 3 mm slice thickness. One seizure mimic patient had a structural lesion not associated with epilepsy (acute meningitis), the remaining three were normal (specificity$_{structural}$ 75.0%). In five patients with first epileptic seizure a structural, epileptogenic lesion was detected (sensitivity$_{structural}$ 14.3%). Twenty-four seizure patients had unspecific MRI abnormalities, six patients had a normal MRI.

The sensitivity and specificity of EEG and MRI are summarized in Table 1.

3.5 | SIRS in relation to EEG findings

Overall, seven patients with abnormal EEG (including IED and slowing) revealed positive SIRS findings (one at both 120 Hz and 240 Hz, six at 240 Hz only). Focal IED were hemispherically concordant with SIRS findings at 240 Hz in one patient (Pat249). One EEG displayed widespread/generalized IED, whereas SIRS abnormalities at 240 Hz were restricted to the left frontal lobe (Pat015).

TABLE 1 Sensitivity and specificity of SIRS, EEG, and other MRI modalities in the Swiss First patients and healthy control cohort.

	Sensitivity epileptic seizure	Specificity seizure mimic	Specificity control group
$SIRS_{120Hz}$	17.1% (6/35)		90.3% (28/31)
$SIRS_{240\ Hz}$	40.0% (14/35)		93.5% (29/31)
$SIRS_{combined}$	45.7% (16/35)		83.9% (26/31)
EEG_{IED}	11.4% (4/35)	100% (4/4)	
$EEG_{Slowing}$	39.6% (14/35)	50.0% (2/4)	
$EEG_{combined}$	48.6% (17/35)	50.0% (2/4)	
Perfusion	8.6% (3/25[a])	75.0% (3/4)	
Diffusion-weighted imaging	11.4% (4/35)	100% (4/4)	
Susceptibility-weighted imaging	2.9% (1/35)	100% (4/4)	
$TPMA_{combined}$	17.1% (6/35[a])	75.0% (3/4)	
Structural potential epileptogenic lesions	14.3% (5/35)	75.0% (3/4)	

Abbreviations: Sensitivity, true positive/epileptic seizure patients; specificity, true negative/seizure mimic and control group; TPMA, transient peri-ictal MRI abnormalities including perfusion, DWI and SWI.

[a]Not all epileptic seizure patients received all modalities.

TABLE 2 Patients with positive EEG (slowing and IED included) and positive SIRS finding.

Code	EEG slowing	EEG IED	EEG localization	SIRS frequency (Hz)	SIRS contrast	SIRS localization
EpiCH1st_CH_BE_Insel_Pat015_M_28	None	Generalized		240	410	L frontal
EpiCH1st_CH_BE_Insel_Pat029_F_80	Focal	None	L predominant frontal	240	470	L temporal
EpiCH1st_CH_BE_Insel_Pat063_F_71	Focal	None	L frontotemporal	240	460	L frontal
EpiCH1st_CH_BE_Insel_Pat066_F_20	Focal	None	R predominant temporal	240	650	R temporal
EpiCH1st_CH_BE_Insel_Pat146_M_72	Focal	None	R temporal	240	420	R frontal
EpiCH1st_CH_BE_Insel_Pat202_F_47	Focal	None	R + L temporal	120	590	R temporal
				240	700	R temporal
EpiCH1st_CH_BE_Insel_Pat249_M_78	None	Focal	L frontal	240	580	L parietal

Note: Code is generated generically. EpiCH1st_CH_BE_Insel = Swiss First, Inselspital. Pat = Patient. Subject ID. M = Male, F = Female. Age. L—Left. R—Right.

Five EEGs showed focal slowing, with spatially concordant SIRS findings at the hemispheric level in four patients (Pat029, Pat063, Pat066, and Pat146). Four SIRS localizations corresponded to EEG slowing localization on lobar level (Pat063 and Pat066 at 240 Hz, Pat202 in both frequencies). The individual findings are indicated in Table 2, and an example with concordant SIRS and EEG is depicted in Figure 4A.

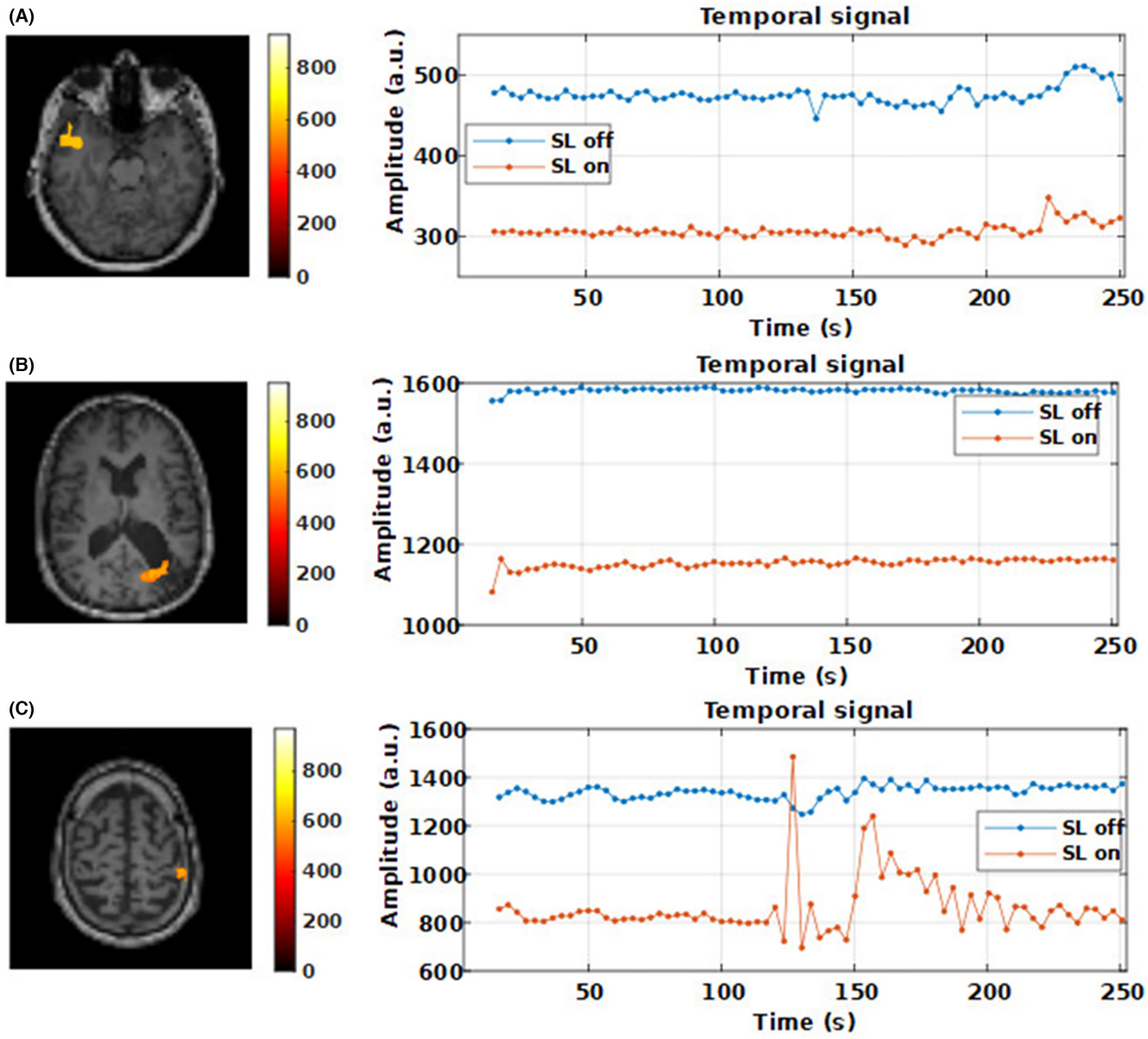

FIGURE 4 Minimal cluster size: 20 adjacent voxels; Left: T1 image with colored SIRS contrast overlay on a T1 image and its colored legend. Right: SL_{off} (blue) and SL_{on} (red) measurement (y axis) at its respective time point (x axis) of the SIRS overlay left. Normalized subtraction of SL-off/on measured are transposed to the colored SIRS overlay left. (A) EpiCH1st_CH_BE_Insel_Pat202_F_47: A 47-year-old female epilepsy patient with SIRS measurement at 120 Hz. The resolution at the signal in the right temporal lobe shows a large peak at second 220 s, what we account as a positive signal. The higher amplitude between 230 and 250 s do not necessarily account as SL-effect, because also in SL_{off} condition we measure a more intense signal. EEG shows bitemporal slowing, but no interictal epileptiform discharges. The patient is suffering from an epilepsy caused by limbic encephalitis, with most probably seizure-onset zone in the temporal lobe with unclear lateralization. (B) EpiCH1st_CH_BE_Insel_Pat024_M_46: A 46-year-old male epilepsy patient with SIRS measurement at 240 Hz. We can see a small peak in SL_{on} at 10 s. The patient had an ischemic stroke in the vascular territory of left medial cerebral artery 8 years before first seizure. This signal is located in proximity of the postischemic lesion. EEG was normal. The patient was diagnosed with epilepsy with remote structural lesion. (C) EpiCH1st_CH_BE_Insel_Pat249_M_78: A 78-year-old male epilepsy patient with SIRS measurement at 240 Hz. A high peak in SL_{on} condition is visible after 130 s and again at 160 s. EEG localizes IED in the left frontal lobe. The etiology of the epilepsy of this patient is unknown.

The two remaining patients with IED in EEG showed no positive SIRS contrast.

EEG (IED only) and SIRS (both measured frequencies) independently revealed abnormalities in 18 of the 35 epileptic patients ($sensitivity_{IED+SIRS} = 51.4\%$). IED were present in four epileptic seizure patients, SIRS contrast in 16 patients at 120 Hz and/or 240 Hz. Twenty-six out of 31 healthy controls and seizure mimics had normal SIRS at both frequencies ($specificity_{SIRS} = 83.9\%$).

4 | DISCUSSION

In this study, we conducted a prospective investigation of diagnostic performance of SIRS contrast in patients who had experienced their first epileptic seizure compared to those with seizure mimics and healthy control subjects. We contrasted our findings with established screening tests for epileptic activity, such as scalp-EEG, transient periictal MRI abnormalities, and structural MRI. As a main finding, we observed that SIRS contrast at 240 Hz discriminated seizure patients from seizure mimics and healthy controls with high specificity. Further, SIRS contrast exhibited a remarkable sensitivity relative to existing screening tests, maintaining its high specificity. Structural and advanced MRI, as well as EEG demonstrated a limited sensitivity in the emergency setting in first seizure patients. The newly proposed SIRS contrast should therefore be further investigated as an independent diagnostic test during the emergency workup.

In cases with SIRS activations within neural tissue, a substantial agreement between EEG and SIRS was observed both at the hemispheric as well as the lobar level. Although it was not possible to record EEG and SIRS simultaneously, our findings suggest a common source of origin of SIRS-related magnetic field perturbations and the electrical sources of the EEG signal.

We aimed to reproduce previous experiments as described in a technical report,[12] an animal study in dogs suffering from epilepsy and human presurgical epilepsy patients.[12,13] Following these studies, we employed two preselected frequencies at different frequency bands centered at 120 Hz and 240 Hz. Hardware constraints in one of our scanners led to deviating frequency bands in all subjects examined in this scanner. This resulted in an exclusion of 13 patients and 33 healthy controls. We excluded three SIRS acquisitions measured at 120 Hz and 240 Hz acquired from a further scanner due to missing healthy controls as comparator.

SIRS detects a narrow frequency band centered around the preadjusted SL frequency (approximately ±10 Hz). It must be noted that these frequencies represent a restricted sample within a variety of neuronal activity. Deviations from the preadjusted frequencies may have hindered detection in cases with differing frequency bands.

We have also included a healthy control population to determine if the SIRS contrast is associated with physiological activity unrelated to epilepsy. Only at 240 Hz a significant difference of the SIRS contrast values between epileptic seizure patients and the control group was present. The experiments with healthy controls revealed no significant correlation between measurements at 120 Hz and 240 Hz, as well as with age and sex. However, we observed an insignificant preponderance toward higher SIRS contrast values in male subjects compared to females ($p = 0.057$). Due to the limited number of subjects, these effects may be explained as individual variances in healthy subjects. Previous EEG studies did not report sex-related differences of HFOs expression.[35]

Previous studies have indicated the presence of physiologic HFOs at frequencies between 76 and 121 Hz.[24,36,37] In contrast, HFOs in epilepsy patients are predominantly recorded above 130 Hz.[37] This aligns with our observations of higher detection rates in epilepsy patients at the upper frequency used in this study. At 240 Hz, we maintained a high specificity due to the measurement in fast ripple range, while achieving a substantial increase in sensitivity of 40%. Fewer patients exceeded the threshold level with SIRS preadjusted to 120 Hz, where physiologic HFOs might have contaminated the signal. Our findings challenge the results of previous studies and suggest to adapt the frequency band to variant acquisitions between 80 Hz and 500 Hz in future studies. Additionally, future work will focus on the implementation of more robust sequence designs.[30,38]

We have applied the method in an emergency setting where patients presented with a first unprovoked epileptic seizure. Our objective was not to classify an epilepsy syndrome or determine the localization of the seizure onset zone, but rather to depict imaging correlates of epileptic activity. We considered EEG and SIRS as co-localizing if spatial concordance was achieved at the hemispheric or lobar level. In two out of four patients with IED, SIRS remained negative. Conversely, SIRS contrast at 120 Hz and 240 Hz was visible in 14 cases where EEG failed to record IED. The overall low prevalence of IED on EEG highlights a potential use case for SIRS, which needs to be further investigated complementary to routine EEG acquisitions.

In an emergency setting, early and reliable diagnosis is mandatory. Advanced MRI (DWI, SWI and perfusion studies) was of limited value to identify TPMA. Seventeen percent of the first seizure patients had peri-ictal diffusion restriction, SWI or perfusion abnormality. Only 14% presented with a structural lesion, although MRI was performed with the HARNESS protocol. These findings emphasize the need for more robust imaging methods applicable after a first seizure in emergency setting.

5 | LIMITATIONS

This study had several limitations. While this study was targeted to investigate imaging correlates of a first seizure by the SIRS method, the numbers of patients with seizure mimics remained considerably low. This may be explained by the triage in the emergency setting that focused on patients with an urgent suspicion of an epileptic seizure. Only these patients were further admitted to specific epilepsy imaging. A further limitation is the relatively low rate of IED in our cohort compared to previous studies that reported a sensitivity of up to 52% when EEGs were acquired within the first 16 h.[39] In our study, EEGs were performed up to 7 days after the event due to logistic reasons, which explains the difference in the EEG sensitivity. Our findings were in keeping with previous studies underpinning the low sensitivity of routine EEG in later stages. A previous study reported a similar detection rate of 11% in patients who have been investigated within 2 months after first seizure.[40] A recent study by Ménétré et al. highlighted the increased diagnostic yield if first seizure patients were diagnosed with MRI and long-term EEG in the acute stage after the seizure.[41] Further, if treatment was started within 48 h after the first seizure, the risk of recurrence was reduced by 24%.[42] Therefore, new and accurate imaging biomarkers that complement EEG and are available at a 24/7 basis are of relevance to enable diagnosis of epilepsy early in the emergency setting.

SIRS as an imaging technology being still at its early stage of development and application was a further limitation. To improve the robustness of this sequence, we are currently working on adaptations to make it more resilient against magnetic field inhomogeneities and hardware constraints.[30] Since we can only measure neuronal currents appearing during spin-lock preparation ($T_{SL} = 70$ msec), a shorter repetition time is expected to enhance its detection sensitivity. Sequence adaptations would allow to depict a broader range of oscillations with this novel technique. This would lead to improved sensitivity for SIRS as a search test.

6 | CONCLUSION

Using SIRS as a MR based contrast, we observed an improved sensitivity in comparison to existing screening tests, albeit with a trade-off of reduced specificity in first seizure patients. When used in combination with scalp-EEG, these methods yield a sensitivity comparable to long-term EEG recordings at the cost of lower specificity.

Since MRI can be acquired in emergency settings, SIRS may influence decisions about new onset epilepsy at an early stage and add converging evidence to the diagnosis. Further optimization of the sequence is necessary to enhance its robustness against magnetic field inhomogeneities. Further studies may benefit from a priori information about the target frequencies for the oscillating contrast, as, for example, during presurgical phase II studies and from longitudinal monitoring of patients with established epilepsy.

AUTHOR CONTRIBUTIONS

Concept of study: RW, CK, and KS. Data collection: BJ. Data postprocessing: MC, AF, CK, and UA. Statistical analysis: BJ, RW. Manuscript draft: BJ, MC, and RW.

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CONFLICT OF INTEREST STATEMENT

The authors have nothing to disclose.

DATA AVAILABILITY STATEMENT

All data were collected within the Swiss First study.[15] Data are available upon request after approval by the Swiss First consortium and the local ethical committee.

ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this article is consistent with those guidelines.

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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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