REVIEW

OPEN

Recent developments in imaging of epilepsy

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Purpose of review

Imaging constitutes one of the key pillars in the diagnostic workup after a first seizure as well as for the presurgical workup in epilepsy. The role of imaging in emergency situations, mainly to support the adequate diagnosis, as well as its role in planning of noninvasive image-guided therapies is less well established. Here, we provide an overview on peri-ictal imaging findings to support differential diagnosis in emergency situations and describe recent attempts toward minimal invasive therapy in the treatment of epilepsy and its comorbidities based on a combination of imaging techniques with ultrasound.

Recent findings

Peri-ictal perfusion changes can differentiate ictal stroke mimics from acute ischemic stroke if focal areas of increased perfusion are depicted by computed tomography or MRI. Postictal perfusion patterns in patients with persisting neurological symptoms are frequently normal and do not reach enough diagnostic sensitivity to differentiate between stroke and its mimics. Noninvasive magnetic resonance-techniques as arterial spin labeling may provide a higher sensitivity, especially in combination with diffusion-weighted and susceptibility-weighted MRI. Imaging guided focused ultrasound (FUS) bears the potential to ablate epileptogenic tissue and allows suppression of epileptic activity. Imaging guided blood–brain-barrier opening with FUS offers new options for local drug administration.

Summary

MRI should be considered the method of choice in the differential diagnosis of peri-ictal imaging findings and their differential diagnosis. A combination of various MRI techniques with FUS opens new avenues for treatment of epilepsy.

Keywords

arterial spin labeling, blood–brain barrier, first seizure, focused ultrasound, peri-ictal imaging

INTRODUCTION

In their recent review, Sidhu *et al.* [1■■] provided an extensive overview of the latest advances in structural and functional imaging methods and of postprocessing methods to improve the presurgical identification of the seizure onset zone in patients with epilepsy. Here, we aim to provide a complementary review of advanced imaging methods, which focuses on (1) peri-ictal imaging and (2) new developments for imaging-based therapy. Issue 1 (RW) describes developments relating to the diagnostic workup of acute seizures. The intention is to provide an overview of recent functional imaging techniques that may help to determine the presence of ongoing ictal activity and to differentiate between focal and generalized seizures. Issue 2 (RB) will introduce new imaging-based ultrasound therapies for epilepsy and its comorbidities. The new therapies allow low-invasive ablation of dysfunctional tissue and noninvasive focal brain stimulation for deep and superficial targets. In addition, low-invasive blood–brain barrier (BBB) disruption for local drug administration is now possible.

Peri-ictal imaging

During the past decade, increased availability of advanced neuroimaging methods in emergency units has supported advances in knowledge about peri-ictal abnormalities related to transient biological processes associated with epileptic seizures. The vast majority of imaging data relate to the emergency diagnostic workup of acute ischemic stroke [2■■,3–7,8■■]. Peri-ictal

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KEY POINTS

- Susceptibility-weighted imaging, diffusion and perfusion delineate peri-ictal MRI abnormalities related to ictal and postictal conditions.
- Peri-ictal perfusion changes may aid in the differential diagnosis between ischemic stroke and epilepsy-related image abnormalities.
- Arterial spin labeling perfusion imaging identifies peri-ictal perfusion abnormalities and provides complementary information about the seizure-onset zone noninvasively.
- High intensity FUS allows low-invasive ablation of epileptogenic tissue and disruption of epileptic networks.
- Noninvasive ultrasound neuromodulation has been shown to suppress epileptic activity.

clinical symptoms may mimic those of an acute ischemic stroke, and most of the adult patients suspected of presenting with a stroke mimic have a seizure due to a remote symptomatic cause or nonconvulsive status epilepticus (NCSE) [9]. In a pediatric population, seizures that presented as stroke mimics were mainly associated with an acute neurological illness [10]. Stroke mimics can be found in 2–30% of patients admitted to a stroke unit [11], whereas peri-ictal presentations account for 20% of all stroke mimics. Transient peri-ictal abnormalities (TPA) can be depicted by computed tomography (CT), using iodinated perfusion-contrast or by MRI, using diffusion-weighted imaging (DWI), susceptibility-weighted imaging (SWI), arterial spin labeling (ASL) or gadolinium-enhanced perfusion MRI. TPA may thus encompass focal DWI restrictions, perfusion-related changes in magnetic susceptibility (SWI), or regional perfusion abnormalities. The incidence and imaging patterns of TPA are time-dependent, and may vary between heterogeneous study populations and methodologies. Imaging sequelae may partially resolve if the interval between ictus and scan acquisition is delayed. Dynamic fluctuations of the imaging parameter may occur over time, ranging from initial hyperperfusion, predominant vasogenic extracellular edema to cytotoxic edema and ictal-related neuronal loss and gliosis [12].

Computed tomography

The overall sensitivity of perfusion CT (PCT) to identify perfusion anomalies in patients with persisting neurological deficits is moderate and depends on the time between ictus onset and scanning. Previous studies have reported perfusion abnormalities related to peri-ictal neurological deficits in 37–78% up to 72 h [8▪▪,13–15]. Van Cauwenberge *et al.* [8▪▪] retrospectively analyzed 133 patients with postictal focal neurologic deficits or ongoing seizure within 3.25 h of admission with volume PCT. Persistent hyperperfusion was present in 59% of the patients with ongoing seizures during scanning and 38% of those admitted with a seizure. Ictal presentation on admission, age, and a history of complex partial seizures predicted hyperperfusion. The diagnostic sensitivity was low, since the majority of postictal patients presented with normal perfusion or a cortical–subcortical hypoperfusion. Cortical hyperperfusion should thus be considered a specific but insensitive finding in ictal and some postictal patients, providing diagnostic utility [8▪▪].

Strambo *et al.* [13] investigated patients with a persistent neurological deficit more than 1 h and a final diagnosis of a seizure or status epilepticus that received PCT for suspected transient ischemic attack (TIA) or acute ischemic stroke within 24 h. They detected focal hyperperfusion in 30% and focal hypoperfusion in 8% of their patients. There was a significant association between the clinical status at the time of PCT) and the imaging findings, with hypoperfusion being detected in patients with focal neurological deficit and hyperperfusion in the presence of ongoing clinical seizure activity. Austein *et al.* [4] reported hyperperfusion in 59% and hypoperfusion in 40% of patients with stroke-like symptoms that were examined with PCT and presented with persistent neurological deficits, mainly (75%) within 3 h of symptom onset. Beyond a temporal relationship between the time of onset and the presence of hyperperfusion and hypoperfusion patterns, cortical perfusion patterns favor ictal hyperperfusion, while postictal patterns frequently extend into the subcortical white matter [14]. Such studies provide evidence that TPA should alert clinicians to consider a seizure/stroke mimic in patients presenting with a focal neurological deficit or impaired consciousness. TPA can be distinguished from ischemic stroke patterns, if CT angiography is included in the protocol and other causes of symptomatic perfusion deficits (e.g. due to a migraine attack, reversible encephalopathy syndrome, metabolic or inflammatory disorders) can be excluded (Exemplary perfusion abnormalities are displayed in Fig. 1a and b, peri-ictal perfusion patterns; stroke hypoperfusion and ictal hyperperfusion patterns).

MRI

Magnetic resonance (MR)-based advanced neuroimaging in the peri-ictal period is mainly employed to enable a swift differentiation between conditions related to increased metabolic demands and associated cortical hyperperfusion and conditions where

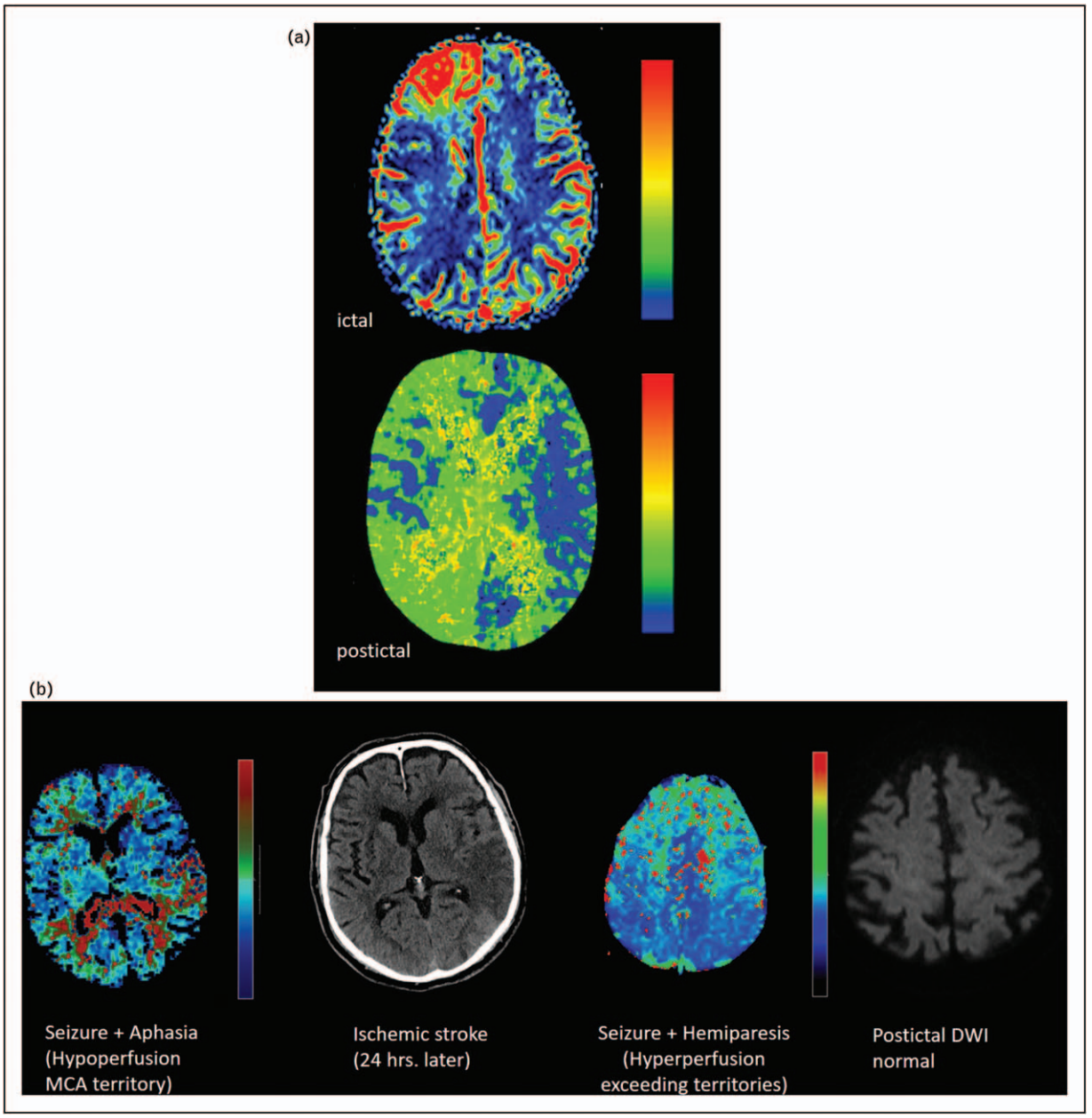

FIGURE 1. (a) Exemplary perfusion maps for ictal hyperperfusion (cerebral blood flow map, upper row) and hypoperfusion (time to peak map, lower row). Ictal hyperperfusion is restricted to the cortex, while the areas of hypoperfusion encompass the white matter and exceed the vascular territories. (b) Different perfusion imaging patterns in a patient who presented with an ischemic stroke and witnessed seizure with postictal aphasia (left) and a patient who presented with aphasia and motor hemiparesis suspected for an ischemic stroke (right). The perfusion patterns reflect hypoperfusion within a segmental artery (cerebral blood flow, left) characteristic for an ischemic stroke vs. multisegmental hyperperfusion (TTP, right) characteristic for peri-ictal abnormalities.

neuronal activity is downregulated due to metabolic exhaustion or compensated by activity of inhibitory interneurons. Transient peri-ictal MRI abnormalities (TPMA) include a variety of reversible brain lesions that encompass signal abnormalities on conventional T2w and FLAIR sequences, vasogenic and cytotoxic edema on DWI, diamagnetic and paramagnetic susceptibility changes and, similar to PCT, perfusion abnormalities. Most peri-ictal MRI studies have either focused on DWI or perfusion MRI. A recent systematic review of 96 articles with 575 case descriptions with ictal induced MRI changes identified the mesial temporal structures and neocortex as the most vulnerable cortical locations and the thalamus and pulvinar as the most frequent subcortical grey matter locations. The frequency of MRI abnormalities varied between 0.007% after a single seizure or seizure cluster and 29.4% after a status epilepticus. MRI findings

encompassed restricted diffusion, reduced apparent diffusion coefficient values, and hyperintense area on FLAIR or T2w images [16▪▪]. From a clinical perspective, the development of periodic lateralized epileptiform discharges concordant with ictal imaging change was associated with worse clinical prognosis and patients with symptomatic origin of their seizure were more likely to develop related imaging abnormalities. Contrast-enhanced perfusion studies resemble the patterns of PCT, with hyperperfusion occurring mainly during ongoing seizure activity or immediately postictal or hypoperfusion in the postictal phase. Perfusion asymmetries have been reported in 22% of patients with migraine associated with aura, lasting up to 24 h after symptom onset [17]. In contrast to TPMA, DWI restrictions in patients with migraine are exceptional and cortical oligemia is predominantly observed in the parieto-occipital cortex, reflecting predominantly language and sensory symptoms in patients with perfusion abnormalities [17]. Mitochondrial myopathy, encephalopathy, lactic acidosis, and a stroke-like episode may present with atypical combinations of focal hypoperfusion and hyperperfusion with cytotoxic and vasogenic edema and clinically manifest headache and/or seizures and should be considered as a rare stroke-mimic, migraine-mimic and/or epilepsy-mimic. TPMA abnormalities can also be depicted without gadolinium injection. Pseudo-narrowing of cortical veins has been demonstrated in association with focal perfusion increase in patients with NCSE, indicating an association between lower deoxyhemoglobin levels in cortical veins and increased focal cerebral perfusion [18]. In contrast, pseudo-prominent cortical veins have been described during the postictal state while regional perfusion is decreased [19] (Fig. 2, predilection areas of DWI restriction).

Compared to contrast-enhanced PCT and MRI, ASL offers advantages when slowly varying changes in brain function are investigated. ASL can be performed with reproducible results during routine MRI examination and has a potential use for the comparison of within-subject and between-subject differences associated with epilepsy-induced state changes and baseline differences in regional cerebral blood flow (CBF) [5]. ASL outperforms DWI as a surrogate marker of TPMA; however, TPMA are an inconsistent finding in ASL perfusion studies [20,21,22▪▪]. Some retrospective studies reported prolonged hyperperfusion exceeding the period of postictal neurological deficits without ongoing seizure activity in EEG [20,21] for several days. These findings may be partially explained by the inclusion of epileptogenic lesions that may favor sustained hyperperfusion themselves, local tissue pressure, carbon dioxide level or persisting epileptic activity not detectable by surface EEG. Patients with idiopathic generalized epilepsy, that were investigated with multidelay, multiparametric ASL perfusion MRI, showed hypoperfusion when compared to healthy controls or healthy volunteers [23]. Recent ASL studies revealed consistent downregulation of CBF, localized to brain areas involved in seizure generation and propagation in the early postictal period (average 65 min, 45–116). This has been shown in patients with drug-resistant epilepsy when compared to interictal epochs and seizure freedom [22▪▪]. Gaxiola *et al.* reported postictal perfusion decrease in 71.4% and a partial to complete overlap with the presumed seizure onset zone in 80% of cases with overt hypoperfusion. Postictal hypoperfusion was also positively correlated with seizure duration, while interictal hypoperfusion in periods

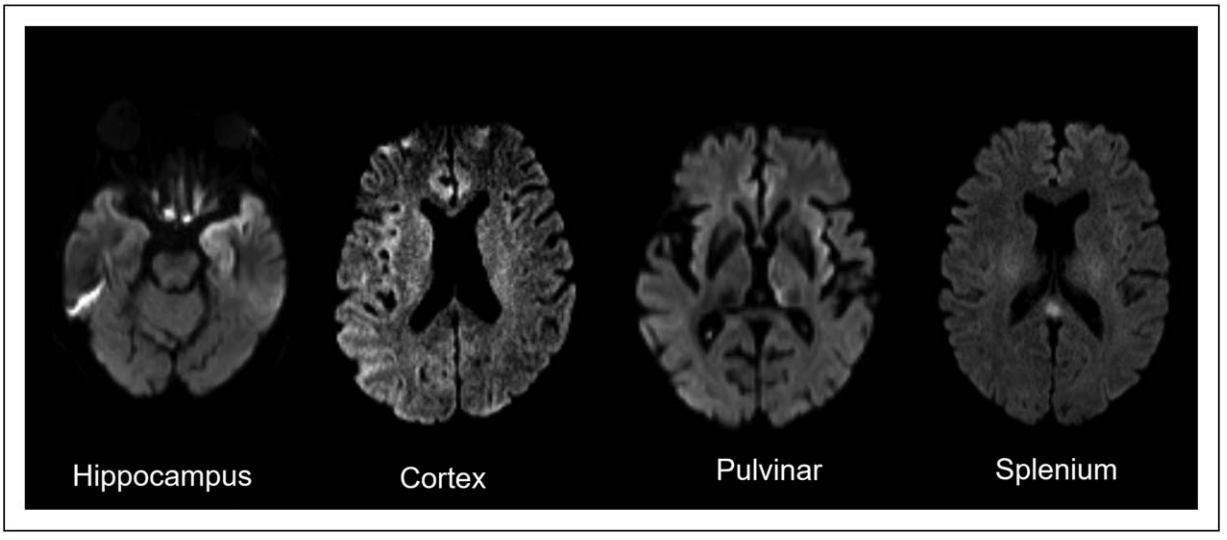

FIGURE 2. Diffusion-weighted imaging maps ($b = 1000\,\text{mms/s}^2$) of typical peri-ictal patterns of restricted diffusion in the hippocampus, neocortex, pulvinar of the thalamus and the splenium of the corpus callosum.

of seizure freedom was a rare finding. The study confirmed previous investigations that observed high agreement (18/20 pts) between hypometabolism of FDG-PET and hypoperfusion in ASL-MRI in the affected hemisphere. In the assessment, expert-based hypotheses encompassing clinical history, neuropsychological assessment and electrophysiological findings were considered in 12/20 cases. Although most perfusion abnormalities during postictal conditions reflected hypoperfusion, exceptional cases of hyperperfusion have been reported* [23,24]. These findings indicate, similar to peri-ictal imaging in emergency situations, the clinical uncertainty or lack of knowledge about precise termination of seizure and persistence of ongoing epileptic activity in the absence of clinical signs.

Transient peri-ictal MRI abnormalities after a first seizure

Several studies showed that the presence of vascular, postinfectious and posttraumatic brain damage increases the risk of a subsequent seizure up to 70% if there is no specific treatment [25,26]. MRI has become the method of choice to detect structural epileptogenic lesions that predispose patients to develop epilepsy after a first seizure. Factors like temporal or frontal lobe epilepsy, focal EEG discharges, and focal lesion signs on brain imaging increase the risk of seizure recurrence [26]. According to the International LEague against Epilepsy, 50–99% of MRIs and up to 70% of scalp EEGs may be negative, despite an underlying epileptic disorder which hampers proper diagnosis at the first event [27]. Differential diagnosis encompasses a variety of seizure mimics in all age groups, including dissociative events, TIAs, migraine, vegetative and cardiac disorders. Here, detection of TPMA after a first unprovoked seizure points to its epileptic cause and, thus, supports definite diagnosis. Hübers *et al.* [28] identified DWI restrictions in 19% of patients with SE/seizure series and in 3% of patients after single focal and 2.5% after single generalized seizures that underwent MRI within 24 h after seizure onset*. Kim *et al.* retrospectively investigated 69 patients who presented with a first seizure or status epilepticus within 24 h after seizure onset* [20]. Abnormal hyperintensities on DWI and FLAIR images were noted in 16%, affecting predominantly the neocortex, hippocampal structures and thalamus, confirming the predilection areas detected in previous studies in patients with status epilepticus or after single seizures [29–33].

ASL perfusion revealed areas of focal hyperperfusion that corresponded to the presumed seizure onset zone in newborns [34] and in children who presented with a first seizure and normal MRI [35▪]. Perfusion changes were detected in 58% of children (focal in 36 and generalized in seven patients) with an overlapping area between the TPMA and the suspected seizure onset zone in 76%. A promising approach beyond imaging of TPMA is to investigate large-scale network differences between patients with new onset epilepsy and healthy controls. Reduced functional connectivity between regions within the fronto-parietal attention network and other areas of the brain has recently been demonstrated in patients with newly diagnosed epilepsy and normal brain MRI [36▪]. These findings open a potential new window for imaging, since they provide preliminary evidence that functional brain abnormalities are not necessarily a consequence of secondary effects of chronic epilepsy rather than being present at the onset of epilepsy.

Neuronal current imaging

Although perfusion MRI and DWI are indirect methods, which focus on imaging correlates of hypersynchronous discharges and postictal exhaustion, alternative attempts have focused on fMRI methods that can detect neural magnetic fields directly [37]. A new MRI method using a spin-lock pulse has attracted attention because of its potential for detecting small oscillating magnetic fields. Experimental studies have suggested that MRI could detect oscillating magnetic fields directly by using the spin-lock technique. Spin-locking experiments enable the investigation of contrasts in populations of labile protons with a Larmor frequency that is different from water. If synchronized magnetic fields are generated by neuronal signaling during epileptic discharges, they interact with the externally applied oscillating magnetic field and attenuate local MR signal intensity. Detection of the neuronal current-induced MR signal attenuation requires a temporal synchronization between the synchronized magnetic field and the image acquisition. A detection of neuronal activity can eventually be achieved by lowering the Larmor frequency toward frequencies in the high and ultra-high frequency domain by interactions with the Spin-locking mechanism. A first technical report of effects on magnetic field perturbations in a small series of patients that underwent presurgical phase II workup reported a hemispheric concordance in seven of eight patients. Notably, the effects of the spin-lock experiment were absent after successful epilepsy surgery (Engel Class I), but remained detectable in cases of less favorable outcome [38]. Clinical studies are mandatory to validate this experimental technique in patients, for example after a first seizure (Fig. 3, schematic overview: neuronal current imaging).

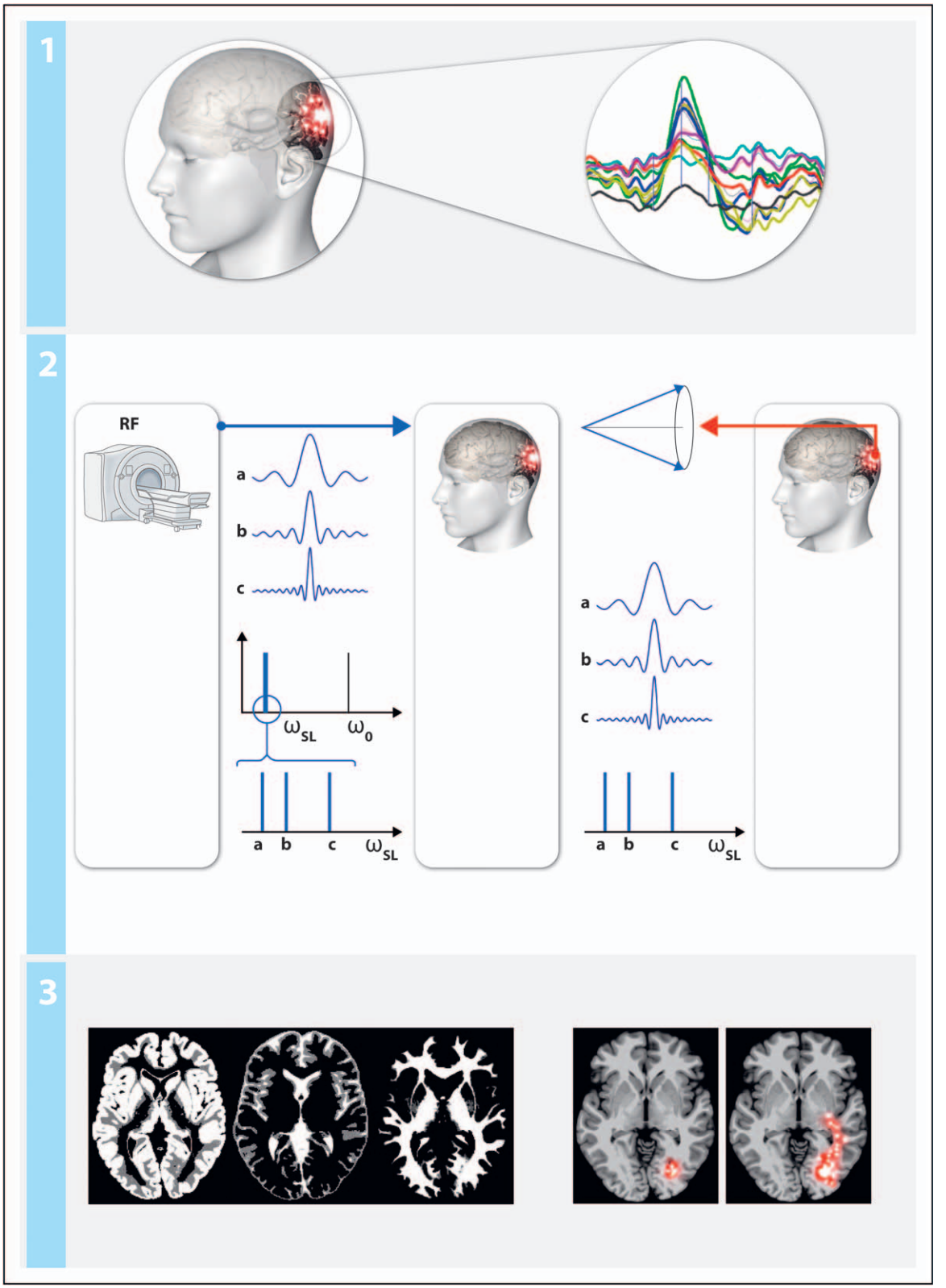

FIGURE 3. Schematic description of the spin-locking experiment: local neuronal currents produce weak transient magnetic fields that attenuate focal magnetic resonance signal intensity. The key approach of the proposed method is nonhemodynamic resonant saturation effect, whereby epilepsy-related oscillations in the high and ultrahigh frequency domain (80–600 Hz) are overlaid with processing spins in the magnetic field of the magnetic resonance scanner. The spins synchronize with oscillations in preselected frequency domain, which – if present – generate a weak signal attenuation in the magnetic field. The method

New developments in imaging-based therapy

In recent years, groundbreaking research has focused on imaging-based ultrasound techniques which allow new low-invasive or noninvasive therapies for brain diseases. These methods use ultrasound for low-invasive and highly focal ablation of dysfunctional tissue, noninvasive focal and exactly targeted neuromodulation, and low-invasive and exactly targeted opening of the blood brain barrier (BBB). The major new technique for focal ablation are high-intensity focused ultrasound (HIFUS). Focal neuromodulation uses low-intensity ultrasound. BBB disruption also uses low energy but is combined with intravenous microbubble administration.

Tissue ablation with high-intensity-focused ultrasound

The current state of the art for HIFUS ablation are FDA-approved hemispherical transducers with 1024 channels, which are mounted on the MRI table [39▪▪,40,41]. They operate either at 650 kHz for thermal ablation, or at 220 kHz for thermal ablation and histotripsy (i.e. mechanical destructions due to oscillating gas bubbles which are inherent in the target tissue). Clinical FDA approval has been granted for refractory essential tremor [42], but current investigations include a wide variety of diseases [39▪▪]. A typical ablation session for the ventral intermediate nucleus of the thalamus (essential tremor therapy) lasts 2–4 h with 10–15 sonications. Imaging is an essential part of the new therapies. Diffusion tensor imaging helps to define the exact neuroanatomical localization of the targets for ablation. Functional MRI can be used to monitor the ablation effect either online or via longitudinal functional monitoring post ablation. The significance of HIFUS for epileptic disorders relates to the possibility of ablating the epileptogenic zone or disrupting epileptic networks with low invasiveness [41,43]. Clinical trials are investigating FUS ablation for lesional epilepsy (including dysplasia) and for removing cortical seizure foci. A further trial concerns prevention of secondary generalization with partial-onset refractory epilepsy by targeting the anterior thalamic nucleus [39▪▪].

Noninvasive neuromodulation of deep and superficial targets

Recent technical developments enable exactly targeted focal neuronal stimulation through the skull and to any area of the brain using ultrasound and imaging [44,45]. Despite impressive neuromodulation data previously obtained with electromagnetic techniques like transcranial magnetic stimulation or transcranial direct current stimulation, these methods did not allow focal deep brain stimulation and secure targeting within pathological brains [46▪]. FUS beams typically operate at a frequency less than 0.7 MHz, apply energy levels less than 100 W/cm^2 in a pulsed mode, and have lateral and axial resolutions around 5 and 20 mm. The highest spatial resolution reported is 90 μm [47]. Possible mechanisms of action center on direct effects on the cell membrane via mechanosensitive ion channels, alteration of membrane potentials and pore formation [48]. These may result in increased levels of serotonin, dopamine, and various neurotrophic factors, as well as cell proliferation and glial activation. Several studies showed modulation of superficial and deep human brain activity with effects on evoked potentials, motor behavior and cognition [44,45]. The first patient study by Lohse-Busch *et al.* [49▪▪] used a transcranial pulse stimulation technique with a nonnavigated global stimulation approach. Potential clinical applications include all diseases that have already been studied by electromagnetic techniques, but for the first time noninvasive deep brain area stimulation is possible. For epilepsy, efficient suppression of epileptic activity has been shown in an animal study via thalamus stimulation [50▪]. Therapeutic applications may therefore focus on seizure suppression, epileptic network modulation, and cognitive rehabilitation [51].

Opening of the blood–brain barrier with focused ultrasound

A new therapeutic option for a wide variety of brain diseases is offered by localized opening of the BBB. This technique combines intravenous administration of microbubbles with low-energy FUS [52,53]. In the sonicated areas, oscillating microbubbles broaden the endothelial cell junctions of the BBB and collapsing microbubbles may induce blood-tissue permeation. Several commercial sonication techniques and FDA-approved microbubble types currently exist. The artificial BBB leaks allow focal administration of drugs (about 98% of drug compounds are usually blocked by the BBB). They also

uses nonhemodynamic resonant saturation effects to detect magnetic field oscillations induced by large rhythmic electrical activity in epileptic neural tissue (1). The spins are sensitized to neuronal magnetic fields oscillating at different frequencies (here exemplarily displayed for frequencies between 120 and 480 Hz) that colocalize with epileptic activity. If epileptic activity is present, the oscillations induce weak distortions of the magnetic field (2). The spin-lock on and spin-lock off acquisition related images are subtracted, deconvolved and postprocessed using gray matter/white matter segmentation and adaptive filtering (3) and the effects can be *z*-transformed and displayed on anatomical images.

allow focal gene delivery for long-term expression of therapeutic proteins via viral vectors, liposomes or nanobubbles (about 200 nm in diameter). Furthermore, BBB opening generates immunogenic responses (e.g. activation of microglia and neuroglia) and stimulates neurogenesis. It may also modulate local neuronal activity, including cognitive enhancement [54]. The feasibility of nonthermal tissue ablation and focal disconnection of brain network components has also been shown in animal studies [55,56]. These mechanisms are being investigated in clinical trials on brain tumors, Alzheimer's disease, Parkinson's disease (PD), dementia and amyotrophic lateral sclerosis. The importance of imaging tools relates to the definition of BBB targets, brain temperature control by magnetic resonance thermometry and control of BBB opening via Gd-DTPA MRI. Functional consequences can be monitored via functional MRI [57]. Although no specific studies on epilepsy have yet been published, therapeutically applicable mechanisms may include local administration of high dosages of antiepileptic drugs, alternative ablation of epileptogenic tissue, alternative epileptic network disruptions, cognitive enhancement and benefits from stimulation of neurogenesis.

CONCLUSION

Seizures can induce TPA that can be depicted by structural and functional imaging techniques. TPA may alert clinicians to consider a seizure or a NCSE in the differential diagnosis of focal neurological deficits in emergency situations. Although patterns of regionally or global cortically increased perfusion are predominantly observed during an ictus or in the immediate postictal period, postictal patterns are less consistent and observed during postictal deficits or prolonged seizures. Yet, it remains unclear which individuals do develop TPA and which do not. Beyond new technological developments to leverage decision making after a first seizure and during peri-ictal periods, new developments also concern new imaging-based therapies. Combinations of various MRI techniques with focused ultrasound open new avenues for innovative treatment of epilepsy.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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