Review

Toward new paradigms of seizure detection

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ABSTRACT

Great effort has been made toward defining and characterizing the pre-ictal state. Many studies have pursued the idea that there are recognizable electrographic (EEG-based) features which occur before overt clinical seizure activity. However, development of reliable EEG-based seizure detection and prediction algorithms has been difficult. In this review, we discuss the concepts of seizure detection *vs.* prediction and the pre-ictal "clinical milieu" and "EEG milieu". We proceed to discuss novel concepts of seizure detection based on the pre-ictal "physiological milieu"; in particular, we indicate some early evidence for the hypothesis that pre-ictal cell swelling/extracellular space constriction can be detected with novel optical methods. Development and validation of optical seizure detection technology could provide an entirely new translational approach for the many patients with intractable epilepsy.

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1. Introduction: clinical importance of seizure detection/prediction

Epilepsy, affecting approximately 2% of the population [1], comprises a group of disorders of the brain characterized by the periodic and unpredictable occurrence of seizures. As seizures are intermittent in patients with epilepsy, prediction or early detection of seizures before they occur would be revolutionary in both warning patients and also developing "closed-loop" seizure detection and termination paradigms. Indeed, the NIH Curing Epilepsy 2000 and Curing Epilepsy 2007 conferences have designated the creation of an effective closed-loop seizure detection/termination device as a critical benchmark in epilepsy research. The most important application would be to detect a focal seizure before it can generalize or spread through the brain and to couple this detection to any of a variety of seizure termination methods.

Seizure prediction and early detection methods based on electroencephalographic and clinical features have been extensively reviewed [2–5], and these are discussed briefly below. Herein, we present other novel approaches to identify the pre-ictal state, with a focus on physiologic examinations of the pre-ictal cellular milieu and, in particular, optical imaging prior to electrographic seizure onset.

2. Prediction *vs.* detection

Although there is a large literature concerning the pre-ictal or early ictal state, the terminology is not uniform. The terms prediction and detection are often used interchangeably but actually describe different brain states. Seizure "prediction" implies that an impending seizure is predicted prior to some measure of ictal manifestation, while seizure "detection" suggests that the seizure is being identified at the earliest ictal manifestation. Certainly, this distinction is not always clear, for example, some changes in intracranial EEG may represent a true "pre-ictal" state or may be more accurately considered to be the earliest EEG manifestation of the seizure.

We propose a conceptual system that will translate into different intervention strategies. Seizure "prediction" takes place during the true pre-ictal period, at a time when either the clinical, electrographic and/or physiological milieu represents an "at risk" state where the likelihood of progression to seizure is high. Interventions at this phase would be considered pre-emptive. In contrast, seizure "detection" takes place during the earliest physiological detection of an ictal state. This may be well before either a clinical or EEG manifestation is evident. Interventions at this phase would be abortive.

3. "Clinical milieu" of the pre-ictal state

The search for a clinical pre-ictal state has largely focused on constellations of symptoms and/or the presence of precipitants that indicate a high likelihood of impending seizure. Many patients report

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awareness of an impending seizure hours or days prior to the event. However, the challenges implicit in a rigorous investigation of this phenomenon are many, including the fact that these combinations of symptoms and precipitants may be specific for individuals and the reality that this type of data is subject to recall bias. Thus, the optimal study might include a large cohort, with subjects having frequent seizures and data collection consisting of time-stamped prospective data collected for long periods of time. There have been an increasing number of studies focused on this area, although no published study meets those criteria.

To date, the most widely studied feature of a clinical pre-ictal "milieu" is the presence of prodromal or premonitory symptoms. Both questionnaire studies and prospective diary studies have identified symptoms such as irritable mood, headache, dizziness, visual changes and concentration difficulties, to name a few, as being reliably prodromal [6–11]. However, not all studies confirm this finding [12], including a recent electronic diary study [13], and in fact, this topic was recently debated at a seizure prediction workshop [14].

Precipitating factors are likely essential features of the clinical pre-ictal milieu, by contributing to the creation of a time period where the risk of a seizure is increased. Such precipitants as derived from both questionnaire and prospective studies appear to reliably include increased stress, decreased sleep, and menstrual status [11,15–20]. It is likely that the reported ability of a subset of patients to self-report their seizures [21,22] is related to awareness of precipitants and prodromal features.

While intriguing, clinical investigations of the clinical pre-ictal milieu have not resulted yet in prediction with adequate sensitivity and specificity for a pre-emptive pharmacologic trial. However, the importance of studying this area is clear: if the period of time preceding a seizure is characterized by specific prodromal or predictive symptoms, identifying this "at risk" period clinically may enhance other methodologies for identifying the pre-ictal state and suggest clinical interventions.

4. "EEG milieu" of the pre-ictal state

The concept of the pre-ictal state has existed since the early 1970s [23]. To date, seizure prediction and early detection algorithms have been solely based on analysis of either surface or intracranial electroencephalography (EEG). More recent studies have used a variety of computational algorithms to attempt to define characteristics of the pre-ictal state with EEG modalities [2,24–26].

Recent efforts in optimizing EEG-based seizure detection have generally followed two distinct strategies: improving seizure detection algorithms *vs.* improving EEG spatial and temporal resolution. Seizure detection algorithms aim to recognize specific patterns that occur in the EEG which represent impending or early seizure activity and produce a "trigger" that alerts the clinician to the seizure. Using various mathematical methods, investigators have evaluated EEG trends that occur prior to seizures in the attempt to predict seizure onset [3,24,26,27]. However, despite over a decade of research on this topic, no seizure prediction/detection algorithm has been proven prospectively to perform better than chance [3,4,26].

The second strategy, methodology development, is largely based on improved spatial and temporal EEG sampling through engineering advancements and new monitoring/analysis protocols [4]. Increased spatial sampling has been obtained with recent advances in electrode design, which has led to the discovery of "microseizures" detectable by individual microelectrodes [28–31]. Increased temporal sampling has led to the finding that high-frequency oscillations (HFOs) have a close relationship with the seizure-onset zone [28,31–34].

It is likely that further technological advancements in EEG and analysis algorithms will continue to yield important clues toward the physiology of seizure generation and propagation in the brain. However, current EEG modalities still have several drawbacks. First, most clinical EEG systems have low spatial resolution, too low to detect "microseizures" generated in localized cortical regions requiring invasive electrodes. Second, the temporal resolution of most clinical EEG systems is too low to detect HFOs. Third, for high spatial and temporal resolution EEG data, analysis algorithms and automated signal processing techniques are still in development. Fourth, current paradigms require off-line, retrospective analysis to achieve reliable prediction [27,35]. Initial human trials with implanted recording electrodes had inconsistent detection rates and high rates of false positive triggering events [36,37].

We would like to suggest that a more important conceptual problem is that the synchronized neuronal discharges which EEG measures are the end result of a preceding physiologic cascade, making early seizure detection or seizure prediction difficult with EEG modalities. While great efforts are underway, there are currently no real-time methods of EEG analysis capable of reliably and reproducibly predicting seizure onset [4,38].

5. "Physiological milieu" of the pre-ictal state

Since patients ultimately desire a seizure prediction device with high sensitivity and specificity [39], is there any approach distinct from EEG that may give us clues to the pre-ictal state? Our hypothesis is that physiological changes which occur during the pre-ictal state may lead us to novel approaches of early seizure detection and prediction.

A wealth of research in animal models has led to many insights regarding the neurochemical, histological, and behavioral characteristics of acquired epilepsy (epileptogenesis) [2]. However, most of these studies are not *directly* relevant to the exact physiological changes occurring in the brain just prior to a seizure.

Several studies have directly addressed physiological changes occurring in the brain immediately prior to seizure activity. In 1989, Traynelis and Dingledine performed a series of *in vitro* studies using the high-K^+ model in the CA1 region of rat hippocampal slices. Among other findings, they noted that "a slight (approximately 2%) but significant increase in electrical resistance gradually occurred over the 20 s immediately preceding seizure generation. The observed increase in tissue resistance suggests extracellular space is decreased during these events" [40]. These results suggested for the first time that brain extracellular space (ECS) may be decreased just prior to seizure activity. In a separate group of studies, Dudek's group found that reduction of ECS size with hypoosmolar treatment powerfully induced epileptiform bursting in rat hippocampal slices, an effect that was reversed by mannitol [41].

Does pre-ictal ECS constriction occur *in vivo*? Early pioneering studies of ECS parameters using the iontophoretic TMA^+ method demonstrated significant constriction of the ECS during seizure activity *in vivo* [42–44], but the temporal onset of ECS constriction relative to seizure onset remained unclear. To address this question, Binder et al. developed a novel technique termed cortical fluorescence recovery after photobleaching (cFRAP) to determine real-time extracellular space diffusion parameters *in vivo* and applied this technique in the PTZ model of generalized seizure [45]. The cFRAP technique involves *in vivo* loading of fluorescein-dextrans into the extracellular space (ECS) of intact brain, followed by laser-induced spot photobleaching and measurement of fluorescence recovery using confocal optics (Fig. 1). Like cytotoxic edema produced by water intoxication, seizure activity slowed diffusion and created dead-space microdomains in which free diffusion was prevented. Critically, slowed ECS diffusion preceded electroencephalographic seizure activity (Fig. 1, *bottom*). These experiments established proof-of-principle for the idea of seizure detection by detection of water movement/ECS constriction prior to seizure onset [45].

Similar to Traynelis and Dingledine's 1989 measurements of tissue electrical resistance before seizure activity *in vitro*, Willoughby's group has performed studies *in vivo* with electrical impedance monitoring combined with EEG [46,47]. In these studies [46,47], animals
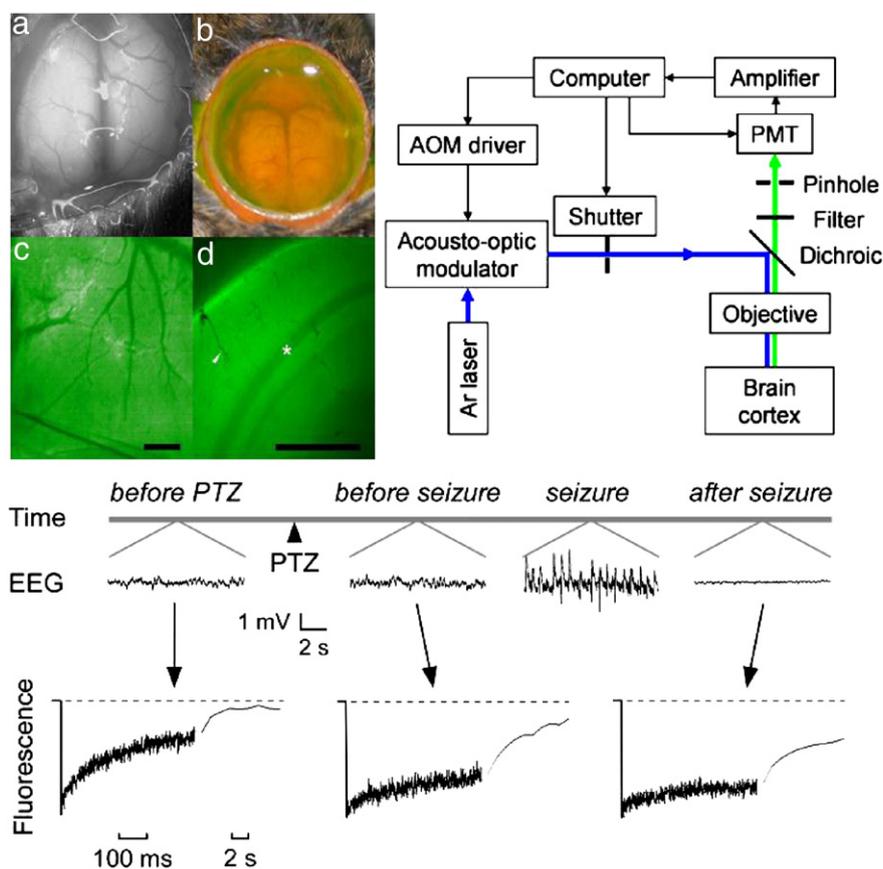
Fig. 1. *In vivo* cortical surface photobleaching detects pre-ictal ECS constriction. *Top left. In vivo* loading of brain ECS by fluorescein-dextrans. a. Brain surface exposure following craniectomy showing cortical blood vessels and intact dura. b. Transdural loading of brain ECS with ACSF solution of fluorescein-dextran. c. Fluorescence image of cortical surface after dye loading (scale bar, 1 mm). d. Coronal 300-μm brain slice obtained *ex vivo* following loading demonstrates fluorescence loading of cortex (scale bar, 1 mm). Arrowhead, cortical blood vessel; asterisk, white matter. *Top right.* Photobleaching apparatus. A laser beam is modulated by an acousto-optic modulator and directed onto the surface of the cortex using a dichroic mirror and objective lens. Emitted fluorescence is focused through a pinhole and detected by a gated photomultiplier (PMT). *Bottom.* Upper traces: Electroencephalographic recordings before and after intraperitoneal injection of PTZ (100 mg/kg). Lower traces: Fluorescence recovery curves for 70-kD fluorescein-dextran before PTZ administration, after PTZ but prior to electroencephalographic seizure activity, and following seizure activity. Note the change in fluorescence recovery signal prior to EEG seizure onset, suggesting ECS constriction prior to seizure onset and providing the potential for seizure detection. Modified from [45].

were treated with picrotoxin, kainic acid or fluorocitrate. Epileptiform discharges were preceded by small increases in electrical tissue impedance. Interestingly, increases in baseline impedance were correlated with increases in power of non-ictal high-frequency EEG activity. This may suggest that pre-ictal HFOs may be associated with detectable tissue impedance and ECS changes.

The finding of pre-ictal ECS constriction leads naturally to the question of what is the mechanism of ECS constriction before and during seizure activity. It is noteworthy that McBain, Traynelis, and Dingledine used the identical hippocampal slice preparation and the high-K^+ model to demonstrate marked (30%) ictal reductions in ECS volume fraction in the hippocampus [48]. Presumably, ECS constriction is related to cell swelling. However, the cell type responsible for swelling in these early studies is unclear. Recently, it has become clear that astrocytes but not neurons express aquaporin water channels which allow rapid facilitated water transport and swelling in response to osmotic gradients [49,50]. In addition, astrocytes but not neurons have been shown to swell after osmotic stimulation [51]. It remains unresolved whether astrocytes or neurons swell before and during seizure activity. However, it is clear that astrocytes but not neurons express aquaporin-4 water channels abundantly in the hippocampus [52]. Using two-photon imaging, Tian et al. demonstrated consistent pre-ictal calcium signaling in cortical astrocytes [53], suggesting that astrocytes may be activated during the pre-ictal period and may be responsible for pre-ictal swelling and ECS constriction.

6. New optical approaches to seizure detection

The above findings suggesting pre-ictal cell swelling and ECS constriction together with our experience in sensitive optical detection of cellular swelling [54] lead us to our new unifying hypothesis that *pre-ictal ECS constriction can be detected with optical methods*.

The optical properties of brain tissue during neuronal activity have been under investigation for decades [55,56]. Changes in the intrinsic optical signal (IOS), a measure of cortical diffuse reflectance, have been observed during focal cortical seizures in animal models [57] and during intraoperative mapping in patients with neocortical epilepsy [58]. Intrinsic optical signal changes are believed to result primarily from increased light absorption by hemoglobin during increased tissue perfusion due to neurovascular coupling. As such, these absorption-derived optical changes typically occur at or slightly after the onset of electrographic seizure, limiting the potential of this modality in seizure prediction.

Our work has focused on a different approach—optical detection of physiologic changes that occur prior to EEG seizure onset. Seizures are associated with depolarization of neurons and glial cells and concomitant ion flux and water movement from the extracellular (ECS) to the intracellular space (ICS). This depolarization of small neuronal populations putatively occurs prior to recruitment of enough neurons to generate a true "clinical" seizure detectable by standard EEG.

The importance of cell swelling (and reduction of the extracellular space) to the generation of seizure activity *in vitro* has been appreciated
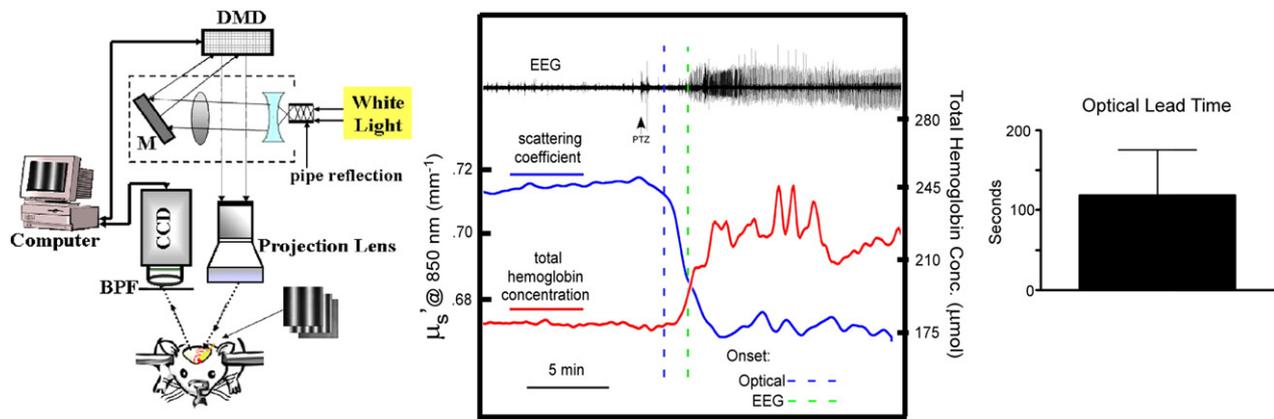
Fig. 2. Spatial frequency domain imaging (SFDI) detects pre-ictal reduction in optical scattering. *Left*: SFDI system. BPF, bandpass filter. CCD, charge-cooled device. DMD, digital micromirror device. M, mirror. *Middle*: Optical scattering coefficient (blue) and simultaneous EEG demonstrate a reduction in optical scattering coefficient (at 850 nm) (dashed blue line, 2 S.D. reduction in scattering coefficient) following convulsant administration (PTZ) but prior to electrographic seizure onset (dashed green line, 2 S.D. increase in EEG power). Spatial frequency domain imaging-derived total hemoglobin concentration (red) demonstrates cortical hyperperfusion following seizure onset. *Right*: optical lead time defined as time at optical "trigger" (2 S.D. change in optical scattering from baseline) to time of EEG seizure onset (analyzed blindly and by power analysis of EEG epochs). Mean optical lead time was 118 s (n = 5).
Courtesy of Owen et al.

for some time [40,59] but not well studied *in vivo*. We hypothesize that during the pre-ictal period, hyperactivity induces glial (in particular astrocyte) activation [53] and swelling resulting from ion and water fluxes during uncontrolled neuronal firing, which leads to the observed pre-seizure ECS constriction [45]. Extracellular space constriction is predicted to decrease optical back-scattering of near-infrared light back to the surface of the brain [60]. This decreased back-scattering, thus, manifests itself as an optical dip from the baseline. This suggests the possibility that a correctly configured optical apparatus could indeed provide reliable detection in the pre-ictal period as ECS constriction should alter photon propagation. We hypothesized that quantitative measurements of brain optical scattering coefficient, an optical property largely ignored in previous IOS studies, would provide a correlate to the ECS constriction and associated glial swelling preceding seizure onset.

Recently, we have employed neurophotonic technology including spatial frequency domain imaging (SFDI), near-infrared (NIR) fiber-optic probes, and optical coherence tomography (OCT) to interrogate brain tissue *in vivo* prior to and during seizure activity. Our 850-nm NIR dual-fiber-optic probe system demonstrated a reduction in NIR reflectance during early cell swelling and cerebral edema in the water intoxication model [54]. Spatial frequency domain imaging (SFDI) is capable of generating quantitative absorption and scattering maps of tissue while simultaneously imaging across multiple wavelengths of light (Fig. 2) [61]. Our optical results in the PTZ model of acute cortical seizure activity with SFDI indeed indicate that a

decrease in NIR optical scattering occurs several seconds to minutes prior to electrographic seizure onset (Fig. 2). Scattering returns to baseline levels after seizure termination. We obtained similar results with fiber-optic NIR probes (data not shown). Interestingly, fiber-optic NIR probes can be stereotactically implanted in deep brain structures important for epilepsy (*e.g.* the hippocampus), potentially providing a solution to optical seizure detection in deep brain structures.

Optical coherence tomography can be thought of as an optical analog of ultrasound imaging, in which the intensity and time delay of reflected light are used to generate cross-sectional images of tissue microstructure with micron-level resolution [62]. Optical scattering and reflectivity coefficients can be extracted from OCT images accurately and with high spatiotemporal resolution [63,64]. These findings make OCT attractive for development as a real-time structural and functional brain imaging modality for use in neuroscience. While OCT has already been employed clinically in retinal and vascular imaging and diagnosis [65,66], it remains to be developed and applied for neurological diagnosis. Our working hypothesis is that OCT, an imaging modality sensitive to NIR scattering changes, will be able to detect, with high temporal and spatial resolution, the changes in NIR scattering that occur prior to seizure activity. Recently, we have developed the ability of our OCT imaging system to reliably image the adult mouse cerebral cortex. In preliminary experiments, we have prepared anesthetized mice with atraumatic cranial windows as previously described [45,54] and also with thinned-skull preparations (Fig. 3)
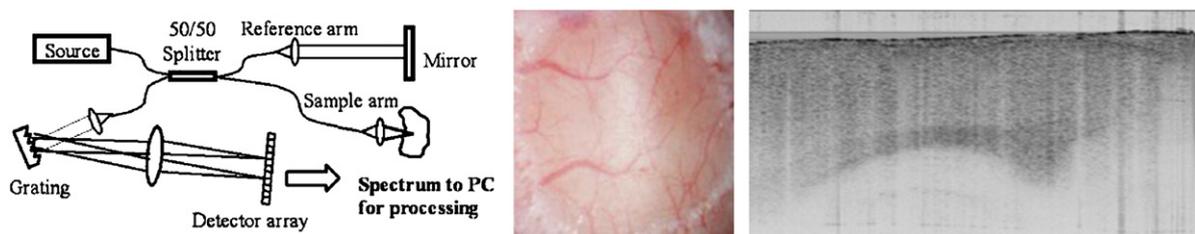

Fig. 3. Spectral domain OCT setup for *in vivo* OCT imaging of mouse brain. *Left*: schematic of SD-OCT setup. The light source, super luminescent diodes centered at 1310 nm, is split between the sample and the reference arm. The reflected light from these arms recombines in the detector arm, and the resulting spectrum is imaged onto the detector array. A Fourier transform of the spectrum generates the depth profile information. *Middle*: OCT imaging of mouse cortex can be done through a thinned-skull preparation and does not require craniectomy. *Right*: sample sagittal OCT image of mouse cortex (image dimension: 3 × 2 mm). The entire depth of the cerebral cortex and some subcortical structures lie within the optical interrogation volume and can be observed serially for reflectance intensity changes *in vivo*.
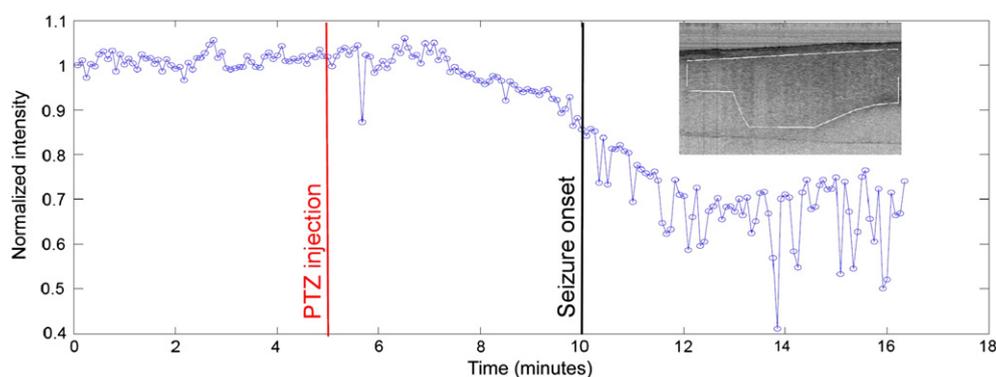Courtesy of Eberle et al.

Fig. 4. Reduction in OCT scattering signal prior to seizure onset. Stable baseline OCT images were obtained for 5 min prior to administration of PTZ (*red line*). *Inset* shows region of interest (ROI) in brain cortex OCT image in which near-infrared (NIR) backscatter intensity was analyzed at every time point (every 5 s or 0.2 Hz) indicated by the *blue circles*. Approximately 10% reduction in intensity was observed prior to generalized seizure onset at 10 min (*black line*). These data provide proof-of-principle for real-time OCT-based seizure detection with excellent optical stability, sensitivity and temporal resolution.
Courtesy of Eberle et al. (unpublished data).

[67] and performed *in vivo* OCT imaging [68]. Preliminary data from these experiments indicate that our OCT imaging system demonstrates a stable optical baseline and a reduction in OCT-derived scattering intensity of NIR light following PTZ injection but prior to clinical seizure onset (Fig. 4). These results provide proof-of-principle for optical detection of the pre-ictal state on a clinically relevant timescale. One important advantage of OCT is its noninvasive nature relative to approaches requiring implanted fiber optics. Clearly, further studies with careful simultaneous electrophysiological and optical recordings are necessary to further delineate the spatiotemporal dynamics of pre-ictal optical signal changes and validate these optical signal changes as reliable biomarkers of seizures.

7. Summary and conclusions

Detection of impending seizures prior to clinical manifestation would be groundbreaking in the treatment of epilepsy. Based on previous results demonstrating pre-ictal constriction of the extracellular space (ECS), we hypothesized that optical detection systems configured to detect changes in scattering of near-infrared (NIR) light can be developed for early seizure detection. Early results using fiber-optic NIR probes, SFDI, and OCT appear consistent with this hypothesis. Future directions include the following: (1) comparison of optical changes with new higher temporal resolution EEG modalities that detect high-frequency oscillations or "HFOs" in the seizure-onset zone [31,32,34,69]; (2) testing the spatial resolution of OCT to determine seizure-onset location in focal seizure models; and (3) developing a real-time predictive algorithm for early warning of seizure onset based on pre-ictal NIR scattering changes. A predictive algorithm would incorporate online interaction with the optical system, instantaneous computational analysis of optical reflectance and scattering, and real-time EEG analysis to alert of optical changes indicative of impending seizure.

Ultimately, a real-time seizure detector could, in principle, be integrated into existing closed-loop methods for seizure termination. Optical detection of seizure activity could be coupled to focal drug injection, deep brain stimulation, cortical cooling, or other seizure termination methods [70–74] to provide "closed-loop" control of seizures. Recently, described optical methods of seizure termination could provide an all-optical solution [75,76]. In summary, development and validation of optical seizure detection technology could provide an entirely new translational technology for the many patients with intractable epilepsy.

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