**Review**

**Optogenetic Study of Networks in Epilepsy**

ManKin Choy, 1 Ben A. Duffy, 1 and Jin Hyung Lee1,2,3,4,*

1Department of Neurology and Neurological Sciences, Stanford University, Stanford, California
2Department of Bioengineering, Stanford University, Stanford, California
3Department of Neurosurgery, Stanford University, Stanford, California
4Department of Electrical Engineering, Stanford University, Stanford, California

Abstract: Currently, approximately 30% of patients with epilepsy do not have adequate seizure control. A greater understanding of the underlying mechanisms by which seizures start or propagate could lead to new therapeutic strategies. The recent development of optogenetics, because of its unprecedented precision for controlling activity within distinct neuronal populations, has revolutionized neuroscience, including epilepsy research. This Review discusses recent breakthroughs made with optogenetics in epilepsy research. These breakthroughs include new insights into the key roles that different cell types play in mediating seizures as well as in the development of epilepsy. Subsequently, we discuss how targeting different brain regions and cell populations has opened up the possibility of highly specific therapies that can stop seizures on demand. Finally, we illustrate how combining newly available neuroscience tools with whole-brain imaging techniques will allow researchers to understand better the spread of seizures on a network level.

Key words: optogenetics; epilepsy; seizures

Epileptic seizures are characterized by transient bursts of pathological activity permeating brain networks. Since the middle of the 20th century, epilepsy researchers have used electrical and pharmacological tools to probe epileptic networks, leading to considerable improvements in treatments for epilepsy (Putnam and Merritt, 1937; Spiegel, 1937; Goddard et al., 1969; for excellent historical reviews of epilepsy drug development, see Shorvon, 2009a,b; Brodie, 2010). However, approximately 30% of patients with epilepsy do not respond to antiepileptic medications, and at this time we do not fully understand the conditions required for seizures to start, propagate, or stop. The recent development of optogenetics, because of its unprecedented precision, has revolutionized neuroscience, including epilepsy research; it has allowed us to target specific cell types and to switch them on or off with exquisite temporal control, revealing the details of seizure circuits like never before. Although the use of optogenetics in epilepsy research is still in its infancy, exciting work has already emerged, including new insights into the key roles of certain cell types in mediating seizures and epileptogenesis. Optogenetics has also revealed the potential of very specific targeted interventions that could allow on-demand seizure interventions. Combining these new research tools with imaging technologies such as functional magnetic resonance imaging (fMRI) will allow us to have a better understanding of seizure circuits over the whole brain. This Review

SIGNIFICANCE

Optogenetics is a relatively new technique that allows researchers to control brain cells and neural circuits by genetically engineering them to respond to light. Using optogenetic tools, epilepsy researchers have made breakthroughs in our understanding of seizures and the development of epilepsy. Recent studies have also highlighted a potential new therapeutic avenue. Furthermore, by combining optogenetics with whole-brain imaging, seizure circuits can now be monitored in their entirety and manipulated with cell type specificity.

Contract grant sponsor: National Institute of Biomedical Imaging and Bioengineering; Contract grant number: R00EB008738; Contract grant sponsor: Okawa Foundation Research Grant Award; Contract grant sponsor: National Institutes of Health Director’s New Innovator Award; Contract grant number: DP2OD007265; Contract grant sponsor: National Science Foundation Career Award; Contract grant number: R01NS087159; R01NS091461; Contract grant sponsor: Stanford Bio-X Interdisciplinary Initiatives Seed Grant Program; Contract grant sponsor: National Institute of Neurological Disorders and Stroke; Contract grant numbers: R01NS087159; R01NS091461; Contract grant sponsor: National Institute on Aging; Contract grant number: R1AG047666

*Correspondence to: Jin Hyung Lee, PhD, 1201 Welch Road, P206, Stanford, CA 94305. E-mail: ljinhly@stanford.edu

Received 23 February 2016; Revised 27 April 2016; Accepted 28 April 2016

Published online 14 July 2016 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/jnr.23767

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discusses some of the most recent breakthroughs in the field of optogenetics and epilepsy research. First, we discuss how optogenetics has been used to further our understanding of seizure circuits, and then we consider the future potential of this technique to aid both our understanding and the treatment of epilepsy.

UNDERSTANDING SEIZURE CIRCUITS

Epilepsy research has a long history of using electrical stimulation of brain regions to drive seizure-like afterdischarges, and this technique is widely used in animal models (Goddard et al., 1969; Racine, 1972; Pinel and Rovner, 1978; Leung, 1987; Nissinen et al., 2000; Englot et al., 2008). However, electrical stimulation is nonspecific, exciting all types of neurons as well as nonneuronal cells, thus making it difficult to elucidate the role played by individual cell types during the generation of seizures (Pitkänen et al., 2006). The optogenetics toolbox has helped to disentangle these roles and, in this way, has aided our understanding of the conditions that allow seizures to emerge.

Optogenetics uses light at different wavelengths to excite or inhibit the activity of opsin-expressing cells with millisecond control (Boyd et al., 2005; Deisseroth, 2015). The nonselective cation channel channelrhodopsin-2 (Chr2) and its variants are used for depolarizing cells, and halorhodopsin-3, a chloride pump, archeorhodopsin-3, a proton pump, or their variants are commonly used for inhibition or hyperpolarization. By tying the expression of these genes to specific promoters and delivering light onto targeted regions, the activity of particular cell populations can be rapidly modulated in a given circuit.

The emergence of seizures has classically been attributed to a shift in the balance between excitation and inhibition neuronal activity toward excitation. The mechanisms that underlie this transition to seizure are not well understood, but evidence suggests that there is significant interplay between pyramidal cells and interneurons in the emergence of epileptic phenomena. For example, in vitro hippocampal slices from rats, simultaneous whole-cell recordings from pyramidal cells and interneurons have revealed that both types of cells are active at different times during the course of a seizure; interneurons are more active at onset of epileptiform discharges but then undergo a period of depolarization block, during which there is an increase in pyramidal cell firing (Ziburkus et al., 2006). Toyoda and colleagues (2015) found a similar response in vivo using unit recordings in the postpilocarpine epileptic rat. Most interneurons recorded in the hippocampus (most notably in the subiculum) increased in firing rate up to 4 min prior to the onset of spontaneous seizures. During this time, a smaller population of interneurons decreased in firing rate. After seizure onset, many of the examined interneurons briefly stopped firing before resuming activity. The mechanism of this pause is not known, but Toyoda and colleagues (2015) speculated that it could be due to depolarization block resulting from elevated extracellular potassium ion concentrations.

The preictal change in interneuronal firing rate could indicate a possible role for them in the initiation of spontaneous seizures. With respect to evoked seizures, remarkably, blocking GABAergic synapses with bicuculline in hippocampal slices enhances the generation of short-duration interictal bursts but prevents electrically induced afterdischarges altogether (Higashima et al., 1996). Studying epileptic tissue from the human hippocampus, Huberfeld and colleagues (2011) found that the transition to seizure is preceded by pyramidal cell firing and dependent on glutamatergic signaling, whereas interictal epileptiform activity is preceded by interneuron firing and involves both glutamatergic and GABAergic mechanisms. Nevertheless, because of complex interdependencies, it has been difficult to disentangle the precise role of individual cell populations. The development of optogenetics has afforded researchers the possibility of driving specific cell populations, with the aim of investigating their roles in seizure mechanisms.

Osawa and colleagues (2013) found that repetitive optogenetic stimulation of hippocampal neurons at 10 or 20 Hz efficiently evokes seizure-like afterdischarges in rats anesthetized under ketamine and xylazine. Furthermore, selective stimulation of the excitatory hippocampal pyramidal cell population via the Ca$^{2+}$/calmodulin-dependent protein kinase IIa (CamKII) promoter (Weitz et al., 2015) also evokes seizure-like afterdischarges in awake and anesthetized rats, confirming the hypothesis that excessive tetanic stimulation of excitatory neurons can result in seizures. Alongside the benefits of inducing epileptic activity from specific cell types with temporal precision, another key advantage of optogenetic seizure initiation is that simultaneous electrophysiology remains uncontaminated by electrical stimulation artefacts during the stimulation period so that the dynamics of the stimulation period may be investigated. However, artefacts on electrophysiology can occur if the light delivered for stimulation hits the recording electrode, inducing a photovoltaic effect. These artefacts may be reduced or eliminated by moving the electrode away from light contamination (Cardin et al., 2010). Stimulating rat dorsal hippocampal neurons (expressing ChR2 under the Thy1.2 promoter) in vivo, Osawa and colleagues (2013) noted that, at the start of stimulation, evoked potentials were time locked to the light pulses, but, eventually, abnormal spontaneous activity emerged in addition to the evoked potentials that persisted beyond the end of the stimulation period. A Granger causality analysis on the local field potential (LFP) traces recorded from the septal and temporal hippocampus suggested that the direction of causal influence shifts during the development of afterdischarges from initially being greater in the septotemporal direction at onset to being greater in the temporal-septal direction toward the end. Using fMRI during selective stimulation of CamKII hippocampal neurons allowed the visualization of distinct frequency-dependent networks, which depended on the location along the septal-temporal axis at which the stimulation was applied (Weitz et al., 2015). For example, dorsal stimulations resulted in activity...
restricted to limbic regions, whereas intermediate stimulations led to widespread brain activity, including recruitment of the cortical and subcortical regions. Awake-behavioral experiments also suggested a more severe phenotype after stimulation of the intermediate compared with the dorsal hippocampus.

Modulating excitatory neurons is not the only means for driving seizures optogenetically; other research has suggested that activity within the inhibitory system also plays a critical role in this shift toward excitation. When postsynaptic intracellular chloride concentrations significantly increase, which occurs during seizure discharges, GABA<sub>A</sub> receptors become depolarizing instead of hyperpolarizing, and inhibitory interneurons effectively become excitatory; this mechanism is thought to induce or facilitate seizures (Staley et al., 1995; Bernard et al., 2000; Lillis et al., 2012; Trevoryan et al., 2015). In line with this hypothesis, under certain conditions, epileptiform discharges can be initiated in entorhinal cortex slices by selective optogenetic activation of individual classes of interneurons, including parvalbumin (PV)- and somatostatin (SOM)-expressing neurons (Shiri et al., 2015; Yekhlef et al., 2015). For example, in the 4-aminopyridine (4AP) in vitro slice model, stimulating PV-expressing cells rapidly evokes epileptiform activity with a distinct low-voltage fast-onset pattern resembling those that occur spontaneously in the same model (Shiri et al., 2015). Similarly, Yekhlef and colleagues (2015) demonstrated that stimulating either PV- or SOM-expressing neurons in medial entorhinal cortical slices perfused in 4AP triggers interictal and preictal spikes that rapidly lead to seizure-like events. Furthermore, these stimulations were accompanied by a rapid and transient accumulation of extracellular potassium, an effect also found in spontaneous events, before the emergence of epileptiform activity. Such an accumulation in itself can contribute to these discharges and is consistent with the hypothesis that intense interneuronal activation can result in an excitatory drive resulting from elevated intracellular chloride and a consequent increased extracellular potassium mediated by the K<sup>+</sup>–Cl<sup>-</sup> cotransporter KCC2 (Kaila et al., 1997; Vittamnen et al., 2010; Yekhlef et al., 2015).

The role of inhibitory interneurons is likely to be nuanced, and researchers have suggested that their effect is apparent only when there is a background of pathological activity (Ellender et al., 2014; Sessolo et al., 2015; Yekhlef et al., 2015). Activating PV interneurons in vitro generated epileptiform discharges only in areas with concomitant localized hyperactivity (Sessolo et al., 2015). Furthermore, directly increasing the GABA reversal potential by loading hippocampal pyramidal cells with chloride using halorhodopsin was not enough on its own to induce epileptiform discharges; although overall network activity was affected, discharges emerged only after a low dose of 4AP was added to increase background activity (Alfonsa et al., 2015). These findings suggest that the preictal environment is crucial in determining the role played by different cell types in seizure onset. Also highlighting the importance of the preictal state, in an in vivo model of absence seizures generated by optogenetic stimulation of excitatory neocortical neurons, Wagner and colleagues (2015) found that the average LFP power before optogenetic stimulation appears to be significantly lower in trials that led to induced seizures compared with those that did not. Likewise, the influence of different cell types may change or wax and wane over the course of a seizure. For example, Ellender and colleagues (2014) found in their in vitro preparation that, although PV interneurons are inhibitory during the early stages of epileptiform discharges, during the later clonic stages they not only excite pyramidal cells because of high intracellular chloride levels but also directly act to synchronize pyramidal cells across the network, thereby potentiating and maintaining epileptiform discharges (Ellender et al., 2014).

**EPILEPTOGENESIS**

Epileptogenesis is the process in which neural circuit reorganization leads to epilepsy. Understanding how the circuit reorganizes and understanding the conditions required for the emergence of seizures remain critical, unsolved goals for epilepsy research (Buckmaster and Dudek, 1997; Kelley et al., 2009). One of the challenges to achieving these goals is that weeks or even years can pass between an epilepsy-inducing brain injury and the onset of seizures, and during this time the insult will have induced a myriad of processes, including inflammation, neurogenesis, cell death, and gliosis (Mathern et al., 1995; Lukasiuk et al., 2003; Duffy et al., 2012; Choy et al., 2014a,b). The degree of neuronal activity during development may play an important role by setting homeostatic limits that can influence subsequent seizure expression. In a genetic *Drosophila* model of epilepsy, researchers were able to prevent the emergence of the seizure phenotype by reducing neuronal activity with halorhodopsin during a critical period in embryonic development (Giachello and Baines, 2015). Conversely, using ChR to increase activity during this period, they were able to induce the seizure phenotype in wild-type flies. If this property is conserved across species, identifying such a critical developmental window may have profound consequences for genetic epilepsies and could also inform our understanding and treatment of acquired epilepsies, in which significant neurogenesis is known to occur.

Even after epilepsy emerges, however, it is unclear which features of an epileptic circuit make it hyperexcitable and inherently prone to seizures. Epilepsy is often associated with widespread circuit changes, but it is difficult to separate epileptogenic changes from those that are compensatory or mere epiphenomena. In temporal lobe epilepsy, common structural changes include mossy fiber sprouting, granule cell dispersion, loss of pyramidal cells in CA1, and changes to inhibitory neurons (Thom and Bertram, 2012), but we do not yet know which of these changes, if any, makes the region prone to seizures. Directly manipulating individual cell populations will
help to characterize epileptic circuits further and to reveal
the roles of those cells (Buckmaster and Lew, 2011; Peng
et al., 2013). For example, in rats with epilepsy induced
by status epilepticus, there is substantial axonal reorganiza-
tion in the hippocampus, including in dentate granule
cells and in PV- and SOM-expressing interneurons (Peng
et al., 2013). By targeting SOM-expressing CA1 neurons
and using optogenetic stimulation in slices taken from
these epileptic rats, Peng and colleagues (2013) demon-
strated that these interneurons increase their functional
territories in the reorganized circuit, extending their
influence from the CA1 into the dentate gyrus. Recently,
three separate studies have shown that hippocampal grafts
of GABAergic interneurons reduce seizure frequency in
chronic epilepsy (Hunt et al., 2013; Cunningham et al.,
2014; Henderson et al., 2014). First, Hunt and colleagues
(2013) showed that implanting inhibitory neurons into
the mouse hippocampus dramatically reduced spontane-
ous seizures, whereas grafting these cells into the amygdala
did not affect seizure frequency. Cunningham and col-
leagues (2014) transplanted ChR2-expressing human-
derived maturing GABAergic interneurons into the hip-
locampus of epileptic mice and discovered extensive
migration and integration with host circuitry. Channelrhodopsin-2 stimulation led to robust postsynap-
tic responses in host hippocampal neurons. Similarly,
Henderson and colleagues (2014) transplanted ChR2-
expressing fetal medial ganglionic eminence GABAergic
progenitor cells into the mouse hippocampus 2 weeks after
pilocarpine-induced status epilepticus and found reduced
seizure frequency between 61 and 80 days after the initial
injury. These cells became functionally integrated into
the network, and stimulating ChR2-expressing cells from
hippocampal slices collected during this period yielded
responses in host granule cells, innervated by these trans-
planted interneurons. Histology indicated that the grafts
differentiated into interneuron subtypes, including neuro-
peptide Y-, PV-, and SOM-expressing cells. Additional
functional mapping of these grafts may reveal the connec-
tivity changes that reduce seizure activity and also help
assess potential cell therapies for epilepsy.

OPTOGENETIC SEIZURE CONTROL
Controlling seizures, ideally without side effects, is still an
unattained goal; approximately 30% of patients with epi-
lepsy do not respond to conventional therapies. However,
it has been shown that optogenetics can be used to ameli-
orate seizures and that this can be achieved with only a
brief targeted intervention at the beginning of the seizure
(Krook-Magnuson et al., 2013; Paz et al., 2013).

Since the first study, in 2009, that reported halorho-
dopsin could be used to control hippocampal epileptiform
activity in vitro (Tonnesen et al., 2009), progress has been
rapid, and in vivo studies have quickly followed (Wykes
et al., 2012; Krook-Magnuson et al., 2013; Paz et al.,
2013; Sukhотовsky et al., 2013). Optogenetics has now
been shown to be effective for ameliorating seizures in
vivo across a spectrum of epilepsy models, including neo-
cortical, temporal lobe, poststroke, and absence epilepsies
as well as status epilepticus (see Table I). For example,
several studies have shown that halorhodopsin, expressed
in excitatory neurons, can be used to stop seizures. Inhibi-
ting neocortical CamKII-expressing neurons with halor-
hodopsin reduced epileptiform activity in the tetanus rat
model of neocortical epilepsy (Wykes et al., 2012), and
suppressing hippocampal activity was effective in a mouse
model of temporal lobe epilepsy (Krook-Magnuson et al.,
2013). After photothrombotic cortical stroke in rats, using
halorhodopsin to inhibit CamKII-expressing neurons in
the ventrobasal thalamus halted thalamocortical seizures
(Paz et al., 2013), and, in the lithium-pilocarpine rat
model of status epilepticus, inhibiting hippocampal
CamKII-expressing neurons with halorhodopsin delayed
seizure onset (Sukhотовsky et al., 2013).

Another approach for suppressing seizures in vivo is to
activate interneurons selectively with ChR2 (Krook-
Magnuson et al., 2013; Lu et al., 2016). For example,
Krook-Magnuson and colleagues (2013) reported that
selectively stimulating PV interneurons reduced seizure
duration by 43% compared with within-animal nonsti-
mulated control. However, stimulating larger populations
of interneurons in vivo may further improve efficacy as
suggested by Ledri and colleagues (2014); stimulating glu-
tamate decarboxylase (Gad)-2-ChR2 neurons, which
include PV, SOM, neuropeptide Y, and cholecystokinin
interneuronal subpopulations, was more effective for sup-
pressing epileptiform activity in slice preparations than
either PV or SOM interneurons alone. Although a direct
comparison between targeting mixed and specific inter-
neuron populations for in vivo seizure control has yet to
be performed, stimulating mixed interneuron cell types in
vivo has been shown to be effective for controlling intra-
hippocampal KA-induced acute seizures (Lu et al., 2016).
Also, both halorhodopsin and ChR may be less effective
at the later stages of seizures because of the accumulation
of intracellular chloride (Huberfeld et al., 2007; Ellender
et al., 2014; Alfonso et al., 2015; Soper et al., 2015). One
potential means of suppressing activity without directly
modulating intracellular chloride is the opsin archaeorho-
dopsin, an outward proton pump (Raimondo et al., 2012;
Pavlov et al., 2013; Alfonso et al., 2015). However,
although archaeorhodopsin has been effective for stopping
epileptiform activity in vitro, there are no published
reports of its effects on seizures in vivo at the time of
writing.

For each form of epilepsy, multiple regions may be
good targets for seizure control, and it is important to
understand which are the most effective with the fewest
side effects. For example, with a mouse model of tempo-
ral lobe epilepsy, Krook-Magnuson and colleagues (2014)
reported that spontaneous seizures could be controlled in
regions including the ipsilateral and contralateral hippo-
campus, ipsilateral dentate gyrus, and the cerebellum.
However, targeting PV neurons in the vermis of the cere-
bellum not only successfully stopped seizures on demand
but also increased the time between seizures. Further-
more, targeting the cerebellum may also be effective for
| Target region                  | Promoter | Cell type            | Opsin   | Model                               | Effect                                      | Reference                      |
|-------------------------------|----------|----------------------|---------|-------------------------------------|---------------------------------------------|----------------------------------|
| Motor cortex                  | CamKII   | Glutamatergic        | NpHR    | Intracortical tetanus toxin         | Reduced frequency of epileptiform events    | Wykes et al., 2012              |
| Ventrobasal thalamus          | CamKII   | Glutamatergic        | NpHR    | Phototrombotic stroke               | Reduces power of epileptic events           | Paz et al., 2013                |
| Hippocampus                   | CamKII   | Glutamatergic        | NpHR    | Systemic pilocarpine-induced SE     | Delayed SE onset by 5 min                   | Sukhotinsky et al., 2013       |
| Ipsilateral hippocampus CA1   | PV       | GABAergic            | ChR2    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration                   | Krook-Magnuson et al., 2013    |
| Contralateral hippocampus CA1 | PV       | GABAergic            | ChR2    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration                   | Krook-Magnuson et al., 2013    |
| Ipsilateral hippocampus CA1   | CamKII   | Glutamatergic        | NpHR    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration                   | Krook-Magnuson et al., 2013    |
| Ipsilateral cerebellum        | PV       | GABAergic            | ChR2    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration                   | Krook-Magnuson et al., 2014    |
| Contralateral cerebellum      | PV       | GABAergic            | ChR2    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration                   | Krook-Magnuson et al., 2014    |
| Ipsilateral cerebellum        | PV       | GABAergic            | NpHR    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration                   | Krook-Magnuson et al., 2014    |
| Contralateral cerebellum      | PV       | GABAergic            | NpHR    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration                   | Krook-Magnuson et al., 2014    |
| Midline cerebellum (vermis)   | PV       | GABAergic            | ChR2    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration and increase time to next seizure | Krook-Magnuson et al., 2014    |
| Midline cerebellum (vermis)   | PV       | GABAergic            | NpHR    | Intrahippocampal KA spontaneous seizures | No effect on time to next seizure         | Krook-Magnuson et al., 2014    |
| Hippocampus                   | PV       | GABAergic            | NpHR    | Intrahippocampal KA spontaneous seizures | No effect                                  | Krook-Magnuson et al., 2014    |
| Deep cerebellar nuclei        | PV       | GABAergic            | ChR2    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration and increase time to next seizure | Krook-Magnuson et al., 2014    |
| Purkinje neurons in ipsilateral cerebellum | Pcp2 | Purkinje (GABAergic) | ChR2    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration                   | Krook-Magnuson et al., 2014    |
| Hippocampus                   | Thy1     | Panneuronal          | ChR2    | 4-AP intrahippocampal               | Seizure activity (signal power) during stimulation reduced by 80% but does not stop events | Chiang et al., 2014            |
| Hippocampus                   | hSyn     | Panneuronal          | NpHR    | Intrahippocampal Bicuculline Penicillin in somatosensory cortex | Reduced bursting frequency                | Berglind et al., 2014          |
| Ventrobasal thalamus          | CamKII   | Glutamatergic        | NpHR    | Intrahippocampal KA spontaneous seizures | No effect                                  | Han et al., 2015                |
| Ipsilateral dentate gyrus     | Pome     | Granule cell         | NpHR    | Intrahippocampal KA spontaneous seizures | Reduces seizure duration                   | Krook-Magnuson et al., 2015    |
| Contralateral dentate gyrus   | Pome     | Granule cell         | NpHR    | Intrahippocampal KA spontaneous seizures | No effect                                  | Krook-Magnuson et al., 2015    |
controlling absence seizures (Kros et al., 2015). Whether the cerebellum or other regions, such as the superior colliculus (Soper et al., 2015), can generally alleviate seizure activity clinically remains to be seen, but identifying regions with general antiseizure properties would be particularly useful for treating refractory epilepsies, such as multifocal epilepsies, in which surgery is not an option (Chen et al., 2015; West et al., 2015). Optogenetic seizure control has exciting potential for epilepsy therapy, but it is important to note that optogenetics is still in its infancy, and there will be significant hurdles before translation to the clinic becomes a reality. In contrast, deep brain stimulation (DBS) has a longer clinical history and has been recently approved for seizure control in the clinic (Morrell, 2011; Fisher and Velasco, 2014; Bergey et al., 2015). Although the mechanisms that underlie DBS are not well understood, studies suggest that the regions chosen for stimulation and the choice of

**TABLE I. Continued**

| Target region                  | Promoter | Cell type         | Opsin | Model                          | Effect                                          | Reference                        |
|--------------------------------|----------|-------------------|-------|--------------------------------|------------------------------------------------|----------------------------------|
| Ipsilateral dentate gyrus      | Pomc     | Granule cell      | ChR2  | Intrahippocampal KA spontaneous seizures | Increased seizure severity               | Krook-Magnuson et al., 2015 |
| Superior colliculus            | hSyn     | Panneuronal       | ChR2  | Systemic PTZ                   | Reduced seizure severity                  | Soper et al., 2015             |
| Superior colliculus            | hSyn     | Panneuronal       | ChR2  | Bicuculline in area tempestus  | Reduced seizure severity and frequency    | Soper et al., 2015             |
| Superior colliculus            | hSyn     | Panneuronal       | ChR2  | GEPR-3s (audio-genic seizure)  | Reduced seizure severity and increased latency to onset | Soper et al., 2015             |
| Superior colliculus            | hSyn     | Panneuronal       | ChR2  | Systemic $\gamma$-butyrolactone (absence seizures) | Reduced seizure frequency and duration | Soper et al., 2015             |
| Hippocampus                    | Thy1     | Panneuronal       | ChR2  | 4-AP intrahippocampal          | Seizure activity (signal power) during stimulation reduced but does not stop events | Ladas et al., 2015             |
| Cerebellar nuclei              | hSyn     | Panneuronal       | ChR2  | Tg mice spontaneous SWDs       | Reduced number of SWD events               | Kros et al., 2015              |
| Cerebellar nuclei              | hSyn     | Panneuronal       | ChR2  | C3H/HeOuJ mice spontaneous SWDs | Reduced number of SWD events               | Kros et al., 2015              |
| Dentate gyrus                  | Vgat     | Interneurons      | ChR2  | KA intrahippocampal SE         | Reduced seizure frequency post-KA and stopped seizure propagation to MEC and motor cortex | Lu et al., 2016                |
| MEC                            | Vgat     | Interneurons      | ChR2  | KA intrahippocampal SE         | Stopped seizure activity in MEC but did not stop seizure activity in dentate gyrus and M1 | Lu et al., 2016                |
| Dentate gyrus                  | Gad      | Interneurons      | ChR2  | KA intrahippocampal SE         | Reduced seizure frequency post-KA and stopped seizure propagation to MEC and motor cortex | Lu et al., 2016                |
| Dentate gyrus                  | Gad      | Interneurons      | NpHR  | KA intrahippocampal SE         | No effect on seizures                     | Lu et al., 2016                |

*GEPR, genetically epilepsy-prone rat; hSYN, human synapsin; KA, kainic acid; NpHR, halorhodopsin; Pcp2, purkinje cell protein 2; Pomc, proopiomelanocortin; PTZ, pentylenetetrazol; PV, parvalbumin; SE, status epilepticus; SWD, spike-wave discharge; Thy1, thymocyte differentiation antigen 1; Vgat, vesicular GABA transporter.
stimulation parameters determine its efficacy (Lozano and Lipsman, 2013). Thus, in the short-term, one promising application of optogenetics research may be to inform the location and stimulation parameters that will be most effective for seizure control with DBS (Chiang et al., 2014; Fisher and Velasco, 2014; Bergey et al., 2015; Ladas et al., 2015).

**IMAGING SEIZURE NETWORKS**

Optogenetic control of seizures holds much promise as a potential therapy, but little is known about the consequences that these focal interventions may have on seizure networks and underlying brain function. Evaluating seizure activity and its effects across the whole brain in vivo will help optimize treatments and limit potential off-target effects (Faingold and Blumenfeld, 2015). Combining optogenetics with imaging tools such as fMRI (Lee et al., 2010; Desai et al., 2011; Kahn et al., 2011; Duffy et al., 2015; Liu et al., 2015; Weitz et al., 2015) or positron emission tomography (Kolodziej et al., 2014) has significant potential as a means of understanding these seizure networks in greater detail.

Visualizing activity over the whole brain can be achieved with fMRI as a readout and optogenetic stimulation to modulate activity (Lee et al., 2010; Duffy et al., 2015; Weitz et al., 2015). For example, stimulating the intermediate and dorsal hippocampus has been shown to evoke activity in distinct networks (Weitz et al., 2015). Although intermediate hippocampal stimulation resulted in widespread activity that included cortical and subcortical regions, stimulating the dorsal hippocampus resulted in activity restricted to the limbic system. Notably, dorsal hippocampal stimulation resulted in decreased fMRI signal in the contralateral dentate gyrus. This response may indicate the presence of seizure modulating activity attributed to the dentate gyrus. Because seizures are often detected and classified with physiology, simultaneous measurement of electrophysiological signatures allow confirmation of seizures by using well-accepted measures (Logothetis, 2002; Kim and Ogawa, 2012). By developing MRI-compatible optrodes for simultaneous LFP and fMRI in rats sedated with dexmedetomidine, we were able to show that stimulating hippocampal CamKII-expressing neurons with ChR2 (using a subseizure threshold light intensity) results in activity restricted to the ipsilateral hippocampus and septum. However, when the light intensity delivered to the brain was increased, seizure-like afterdischarges were generated and were confirmed with fMRI and electrophysiology together. The fMRI time series results in a prolonged hemodynamic response during afterdischarges, and simultaneously acquired LFP measurements allow a more informed analysis of the fMRI data. During afterdischarges, the activated network extended to the contralateral hemisphere, recruiting the hippocampus, septum and cerebellum as well as discrete cortical and thalamic regions (Duffy et al., 2015; see Fig. 1). These networks are similar but distinct from those reported following electrical hippocampal stimulation (Englot et al., 2009). During electrically induced afterdischarges, fMRI signal changes are observed in the hippocampus and septal nuclei, whereas reduced neuronal activity results in the cingulate, retrosplenial, and orbital frontal cortices. Genetically targeting only neuronal cells has the advantage of being able to evoke a hemodynamic response that is more physiological and less affected by stimulation of nonneuronal cells. Notably, despite seizures being evoked under a nonepileptogenic background, the activated regions encompass those that have been shown to be effective targets for controlling temporal lobe seizures (Krook-Magnuson et al., 2013, 2014, 2015), demonstrating the potential that imaging seizure networks may have for identifying regions for seizure control. Nevertheless, the aforementioned studies imaged evoked seizures in a normal nonepileptogenic network. Because epilepsy is defined by significant alterations in the underlying networks, imaging seizures in a pathological setting may identify additional changes that may not be apparent in seizures evoked in a naive brain.

Although many regions may be activated during a seizure, it is unlikely that all of these regions are equally efficacious for seizure control (see Table I). As a seizure starts and spreads through a network, targeting regions early in the propagation pathway may be more effective for abolishing the seizure than regions recruited later. Using a focal hippocampally evoked seizure mouse model and multiregional electrophysiological recordings, Lu and colleagues (2016) showed that seizures propagated from dentate gyrus to medial entorhinal cortex (MEC). When interneurons (by targeting vesicular GABA transporter or Gad2) in the dentate gyrus were stimulated, seizure activity in dentate gyrus, MEC, and motor cortex stopped. However, when interneurons in the MEC were stimulated, seizure activity was abolished in that region but persisted in the dentate gyrus and the motor cortex, demonstrating that successfully controlling seizure activity within a region does not necessarily indicate effective seizure control. Therefore imaging seizure networks and their interactions with proposed seizure control interventions can help identify critical nodes that are effective for completely stopping seizures.

Imaging seizure networks has also allowed researchers to identify a signature pattern in fMRI and electrophysiological recordings that is thought to be associated with the impaired consciousness that occurs during seizures (Blumenfeld, 2012; Motelow et al., 2015) or during stimulations that regulate arousal (Liu et al., 2015). Impaired consciousness during seizures is known to be associated with prominent frontoparietal slow-wave activity on electrophysiological recordings in humans (Englot et al., 2010). Using fMRI in rats has allowed researchers to investigate the underlying circuit mechanisms of this phenomenon (Englot et al., 2009; Motelow et al., 2015). These data indicate a possible role for the lateral septum and anterior hypothalamus, which are activated during fMRI acquisitions and are known to have inhibitory connections with subcortical arousal systems. Using mice
anesthetized with ketamine and xylazine, Furman and colleagues (2015) reduced this cortical slow-wave activity during electrically evoked hippocampal seizures by optogenetically stimulating cholinergic brainstem neurons, suggesting that targeting these circuits may be effective for restoring consciousness. Thus, imaging seizure networks is important for allowing epilepsy researchers to go beyond stopping seizures to identifying regions that may not directly form part of the seizure network but have pathological implications for brain function.

**SUMMARY**

Optogenetics has proved to be a useful set of tools for epilepsy research, with powerful potential applications in the clinic. However, many questions remain. For example,
little is known about many aspects of epilepsy circuits, including the role of subclasses of interneurons, glia, and G-protein–coupled receptors such as metabotropic glutamate or GABA\textsubscript{B} receptors (Craig and McBain, 2014; Kubota, 2014; Roux et al., 2014). The breadth of optogenetic tools continues to expand rapidly, including opsins that can be excited with different wavelengths and that have improved kinetics or that can be switched on for extended periods with a single light pulse and switched off with another (Mattis et al., 2012). Furthermore, engineered opsins now come as inhibitory chloride channels or G-protein–coupled receptors and can even directly modulate gene expression and epigenetic processes (Konermann et al., 2013; Levitz et al., 2013; Berndt et al., 2014). Targeting specific cell populations with optogenetics can help us to understand the generation and propagation of seizures as well as the development of epilepsy. Modulation of circuits to interrupt seizure activity has exposed the possibility of highly specific antiepileptic strategies. Finally, these new techniques can be combined with whole-brain imaging methods to observe seizure dynamics over the whole brain and during modulation of distinct neural circuits. Such imaging approaches can be used to identify specific nodes in networks as well as time points that might be crucial for seizure propagation or even the development of epilepsy. Optogenetics, in combination with the many other new technologies being developed, likely will pave the way for significant strides in our understanding and treatment of epilepsy in the near future.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

ROLE OF AUTHORS

MC, BAD, and JHL equally researched, wrote, and edited the Review.

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