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The cerebellum and epilepsy

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Abstract

Epilepsy is the fourth most common neurological disorder, but current treatment options provide limited efficacy and carry the potential for problematic side effects. There is an immense need to develop new therapeutic interventions in epilepsy, and targeting areas outside the seizure focus for neuromodulation has shown therapeutic value. While not traditionally associated with epilepsy, anatomical, clinical, and electrophysiological studies suggest the cerebellum can play a role in seizure networks, and importantly, may be a potential therapeutic target for seizure control. However, previous interventions targeting the cerebellum in both preclinical and clinical studies have produced mixed effects on seizures. These inconsistent results may be due in part to the lack of specificity inherent with open-loop electrical stimulation interventions. More recent studies, using more targeted closed-loop optogenetic approaches, suggest the possibility of robust seizure inhibition via cerebellar modulation for a range of seizure types. Therefore, while the mechanisms of cerebellar inhibition of seizures have yet to be fully elucidated, the cerebellum should be thoroughly revisited as a potential target for therapeutic intervention in epilepsy.

Keywords

Channelrhodopsin; halorhodopsin; temporal lobe epilepsy; deep brain stimulation; fastigial nucleus; thalamus

1 Introduction

Roughly one in 27 people will develop epilepsy at some point in their lifetime, yet almost half of all epilepsy patients do not experience sufficient seizure relief with current treatment options [1]. There is a clear need for the development of new therapeutic interventions in epilepsy. Many current efforts focus on deep brain and on-demand stimulation for seizure control [2–6]. While some stimulation approaches target the seizure focus directly, stimulation of brain areas outside the seizure focus has also shown promise [3, 7–10]; one such area of interest is the cerebellum [11]. There is evidence to suggest the cerebellum is

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Conflict of interest

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engaged during seizures [12–19], and cerebellar impairments have been observed in patients with epilepsy [20–23]. While early research outlines an unclear and potentially inconsistent relationship between the cerebellum and seizures, more recent work has renewed enthusiasm in the cerebellum as a promising target. In the present review, we discuss evidence for a role for the cerebellum in epilepsy and seizures, early animal work and clinical trials in which the cerebellar cortex was electrically stimulated, and recent studies using targeted optogenetic approaches in animal models of epilepsy. We argue that the increased specificity offered by on-demand optogenetic approaches in timing, direction of modulation, and cell populations engaged improves interpretability of results and may account for the more robust inhibition of seizures achieved with cerebellar modulation. While the precise mechanisms of cerebellar influence over seizures have yet to be fully elucidated, there is a clear rationale to revisit the cerebellum as a potential therapeutic target for intervention in epilepsy.

2 The cerebellum and seizure networks

2.1 Cerebellar changes associated with epilepsy

The cerebellum has not been traditionally associated with epilepsy or seizures, likely in part due to early studies conducted in the 1930s, in which electrical stimulation of the cerebellum did not readily produce seizures [24]. However, sufficient data has accumulated in the decades (nearly a century) since those original studies to firmly show that this view point needs to be updated. Recognizing a potential role for the cerebellum in epilepsy and seizures can provide a fuller understanding of seizure networks and the condition more broadly, and, importantly, ultimately provide new avenues to treatment.

Alterations in the cerebellum have been routinely noted with epilepsy, including disrupted functional and structural connectivity [25–28], changes in volume [29–37], and altered perfusion [38]. For example, atrophy of Purkinje cells (Box 1) is observed in postmortem tissue of patients with chronic epilepsy [39, 40]. Drug exposure alone cannot fully explain cerebellar alterations in epilepsy, as animal studies also reveal cerebellar alterations. A recent study examined structural alterations across the entire brain in two different rodent models of acoustically evoked seizures (the Genetically Epilepsy Prone Rat and the Wistar Audiogenic Rat models), to examine if there were any anatomical areas of overlap (i.e., any convergence in pathology) [33]. Interestingly, the cerebellum (specifically, the midline cerebellum) was the only area of structural changes unifying these two rodent models, highlighting the potential importance of the cerebellum to the observed epilepsy phenotype [33]. This data suggests that other observations of structural changes in the cerebellum in epilepsy are unlikely to be one-off or incidental findings. Rather, changes in the cerebellum may be a uniquely unifying feature across epilepsies.

It is important to emphasize that changes in the cerebellum are found in human patients, and that these alterations can have major implications for patient welfare. A recent study [29] found substantial gray matter loss in the cerebellum in SUDEP (sudden unexpected death in epilepsy) cases prior to the SUDEP event compared to healthy controls and low-risk patients. Additionally, these findings remained when controlling for phenytoin use, indicating that it is unlikely to simply reflect exposure to antiseizure drugs. Subjects at high

risk of SUDEP also had reduced gray matter volume, specifically in the midline cerebellum (i.e., vermis). Therefore, there are structural changes in epilepsy in the cerebellum that cannot be fully explained by drug use and, importantly, can have major consequences for the patient.

There is also evidence to suggest a relationship between seizures themselves and cerebellar activity. An increase in cerebellar blood flow during seizures has been noted in patients with temporal lobe epilepsy [41], frontal lobe epilepsy [42, 43], and other partial epilepsies [38, 44]. Experimentally, increased metabolic activity in the cerebellum has also been reported for seizures induced by administration of PTZ [45, 46], focal penicillin [47], or electrical stimulation [48, 49]. Moreover, cerebellar neuronal activity can be correlated (including phase locked spiking) with seizure activity across a range of seizure types, including spontaneous hippocampal seizures occurring in the intrahippocampal kainate model [50], electrically induced hippocampal [15, 51] or cortical [52] seizure events, spike and wave events in rodent models of absence epilepsy [13, 14], and neocortical seizures occurring after penicillin injection [16–19, 53]. Altered firing of cerebellar neurons during seizure events has been observed prior to overt motor manifestations of seizures [50], as well as during absence seizures [14], arguing against the interpretation that cerebellar engagement simply reflects motor aspects of seizures. Cerebellar engagement during seizures is also not limited to animal models. Similar results have been observed during recordings from the deep cerebellar nuclei of human patients with epilepsy, including with cerebellar engagement occurring prior to or without generalization in two patients [24]. A third patient showed synchronous spike and wave activity in the cerebral and cerebellar nuclei leads, reinforcing the idea that cerebellar engagement can occur in a range of seizure types [24].

Not only can the cerebellum participate in seizure events, there are also noted clinical cases where the seizure focus itself appears to have been within the cerebellum, typically in patients with cerebellar lesions or tumors [54–63]. Additionally, injection of ouabain (an **inhibitor of** Na/K-ATPase) into the cerebellar cortex or injection of picrotoxin (**a noncompetitive antagonist of** $GABA_A$ receptors) into the fastigial nuclei of rats has been reported to induce seizures which progress to generalized tonic-clonic seizures [64, 65]. Similarly, mice genetically prone to spike and wave discharges showed an increase in absence seizure frequency when muscimol (a $GABA_A$ agonist) was injected into the cerebellar nuclei [66], and mice with a loss of P/Q channels in the cerebellum display absence epilepsy [67, 68]. Together these data point to the cerebellum not only as a passive participant in seizures, but also as a possible driver of seizure activity, across a range of seizure phenotypes.

Clearly, there is now ample evidence for the involvement of the cerebellum not only in epilepsy, but also in seizure networks. Therefore, the classical view that the cerebellum is one of the few brain structures that does not seize needs to be updated.

2.2 Conventional cerebellar modulation and seizure control

Not only does research suggest that the cerebellum can be engaged during seizures, other work suggests that cerebellar interventions may be able to inhibit ictal activity.

At the most crude level, the effects of cerebellectomy or cerebellar cortical lesions on seizures have been investigated. This work, perhaps unsurprisingly given the nature of the intervention, has produced mixed results. Some studies, examining the impact of cerebellectomy on penicillin-induced seizures, report an increase in the frequency of seizures [69, 70]. This finding can be interpreted as reflecting a native seizure-suppressive role of the cerebellum [24, 71]. However, other studies found no effect of cerebellectomy on epileptiform activity induced by penicillin [72] or electrical stimulation [73]. Additionally, lesions to either dorsal or ventral aspects of the cerebellar dentate nucleus have also been reported to *decrease* seizures in human [74]. These conflicting results are difficult to interpret. Experiments with more refined intervention methods are likely to provide greater insights.

Several early studies dating back to the 1950s electrically targeted the cerebellum in animal models of epilepsy to assess whether cerebellar stimulation could disrupt seizure events (Table 1). Here too, however, experimental data is rife with conflicting results. For example, in some studies, seizures induced by cobalt application [75–77], penicillin [70, 78, 79], PTZ [80], or electrical stimulation of the hippocampus, amygdala, or cortex [81–85] were suppressed by stimulation of either the midline cerebellar cortex [76, 77, 82–84] or deep cerebellar nuclei [75, 84, 86]. However, others found that cerebellar stimulation instead had no effect or actually evoked seizures or prolonged seizure duration for cobalt [75, 86, 87], alumina-gel [88, 89], penicillin [79, 90], PTZ [90], hyperbaric oxygen [91], or electrically evoked seizures [83, 92–94]. The widespread nature of these conflicting results suggest that differences in the model or type of seizure were unlikely to underlie differences in results. However, methodological differences may have been key -- a range of stimulation parameters, locations, and electrode configurations were used. The broad range and combinations of these variables, and the unfortunate situation that these variables were not consistently reported, make it difficult to glean insight by comparing results across studies. Additionally, all of these studies examining the impact of electrical stimulation of the cerebellum on seizures were done in an open-loop, rather than on-demand, manner, which creates another important experimental caveat.

Even when the work utilized the same models and was reported by the same authors in the same publication, mixed results could occur. In some cases, however, these divergent results begin to provide some potential insight into the mixed results in the literature. For example, Maiti and colleagues reported that electrically induced seizures could be inhibited by stimulation of the cerebellar cortex, but were exacerbated by stimulation targeting the downstream deep cerebellar nucleus [34]. Similarly, Godlevski and colleagues report that high frequency stimulation of the cerebellar cortex could inhibit ictal events while low frequency stimulation of the same area facilitated ictal discharges [95]. This suggests that successful interventions may be a complex interaction between stimulation protocol (e.g. high versus low frequency stimulation) and intervention location (e.g. cerebellar cortex versus nuclei).

Electrical stimulation of the cerebellum for epilepsy treatment has also been examined in human clinical trials (Table 2). As with the animal work, electrical stimulation of the cerebellum in humans has been done entirely with open-loop approaches, where stimulation

occurred without regard for ictal or interictal state. Also as seen with animal work, electrical stimulation for seizure suppression in human patients has been done with a variety of methods, and produced very mixed results. Offering hope, in one study, a majority of patients (71%) were seizure free after >10 years of cerebellar cortical stimulation [96]. Another study showed cerebellar cortical stimulation produced a greater than 50% reduction in seizure frequency in over half of patients tested [97]. Similarly, a different study reported stimulation of the anterior lobules and cerebellar hemispheres resulted in a significant decrease in seizure frequency in 5 out of 6 patients tested [98], other studies reported that targeting the dentate nuclei was also effective at reducing seizure frequency [99, 100], and separate studies examining chronic cerebellar stimulation reported seizure freedom in at least half of patients [101, 102].

While these successful studies suggest promise of targeting the cerebellum in epilepsy, other studies produced more mixed effects, with some patients showing no change or even increased seizure frequency with stimulation of the cerebellar cortex [101, 103–105] (Table 2). Double blind clinical trials in patients with both partial and generalized seizures showed no significant effect of electrical stimulation of the superior cerebellar cortex on the frequency of behavioral seizures [106, 107], seizure severity [107] or patient EEG [106]. Therefore, moving forward, it will be important to have a clearer picture of the source(s) of the disparate findings, to allow successful, robust inhibition of seizures in the future.

3 Potential contributions to heterogeneous effects of electrical stimulation

Why might these initial animal and clinical studies have produced such mixed effects? We focus on four sources of complexity in interpreting the results of studies using cerebellar stimulation to inhibit seizures: 1) lack of cell-type specificity and 2) lack of direction of modulation specificity, combined with 3) disparate experimental/intervention variables, and finally, 4) lack of temporal specificity.

3.1 Lack of cell type specificity

One major limitation of electrical stimulation is that it is often unclear which cell types are being modulated and how. Electrical stimulation can alter activity in local excitatory or inhibitory cells, efferent axons, afferent inputs, or combinations of these depending in part on stimulation parameters used. The effects of the electrical stimulation utilized in previous studies on cerebellar activity are thus highly difficult to interpret. In the case of electrical stimulation applied to the cerebellar cortex, the activity of Purkinje cells can be directly modulated, as can the activity of inhibitory stellate, basket, golgi, and lugaro cells (Box 1provides a brief overview of cerebellar anatomy). Additionally, parallel fibers, climbing fibers, and even mossy fibers can be impacted. Similarly, both excitatory and inhibitory input from cerebellar nuclei to the cortex can be altered, as could axons from neuromodulatory regions such as the locus coeruleus or raphe nuclei. Antidromic spiking can therefore also produce changes in nuclear neurons (directly), brain regions like the locus coeruleus or raphe which could produce neuromodulatory changes in other brain regions, the inferior olives (which provide climbing fiber inputs to the cerebellar cortex), and pontine neurons providing mossy fiber inputs to the cerebellum. To further complicate matters,

climbing fiber inputs to Purkinje cells produce complex spikes, which can have longer term consequences due to synaptic plasticity and other potential mechanisms (for review, see [108]). Additionally, both inferior olive input and mossy fibers have collaterals to the cerebellar nuclei, providing an additional potential route for influence over cerebellar output that would need to be considered when electrically stimulating the cerebellar cortex.

Similar heterogeneous effects are possible when targeting the deep cerebellar nuclei, which contain several cell types, including excitatory projection neurons, inhibitory projection neurons, excitatory and inhibitory interneurons, as well as mossy fiber, climbing fiber, neuromodulatory, and Purkinje cell inputs, all of which might be affected by electrical stimulation (Box 1, Panel C&D). Increasing the specificity of intervention can improve the interpretability of results, and has the potential to provide needed insights into when or how cerebellar modulation can be an effective strategy for seizure control.

3.2 Direction of modulation

Electrical stimulation often produces mixed effects on excitability, in part due to the lack of cell-type specificity discussed above. Without a clear picture of the effects of stimulation, results are difficult to interpret, and the direction of modulation of cerebellar neurons may be critical for effective intervention. In the case of cerebellar cortical stimulation, differences in electrode position, orientation, or stimulation parameters can have differing effects on Purkinje cell firing [109]. For example, a study found that Purkinje cell responses to electrical stimulation at a variety of frequencies and train durations can be excitatory, inhibitory, or more complex alternating patterns of activation and suppression based on the distance from the stimulating electrode and Purkinje cell recorded [110, 111]. Interestingly, 0.5 Hz surface stimulation failed to produce pure activation in any Purkinje cells recorded [111]. Similar mixed effects are also likely when targeting the deep cerebellar nuclei, especially given the more heterogeneous cytoarchitecture as compared to the cerebellar cortex (See Box 1). The complexity of responses to electrical stimulations likely contributes to the observations that different stimulation parameters can inhibit or exacerbate seizures in the same animal models [95, 112]. For example, while 0.5 Hz stimulation of the cerebellar cortex can produce a mix of suppression and more complex changes in firing, 10 Hz stimulation produces suppression in almost all Purkinje cells recorded [111]. In this view, the mixed results of cerebellar stimulation in both animal models and human patients could be due to heterogeneous effects of electrical stimulation on activity. Increasing the specificity of intervention to evoke either pure excitation or inhibition (in the desired cell populations), for example with techniques such as optogenetics, may not only provide greater insight, it may also allow consistent seizure inhibition. Despite the challenges of electrical stimulation, however, it may be possible to find appropriate settings to also allow consistent seizure inhibition with electrical stimulation. This would provide a more immediate translational opportunity than optogenetic techniques.

3.3 Disparate experimental variables

As discussed above, electrical stimulation can cause varied responses depending on the location, stimulation parameters (including amplitude, pulse width, and frequency of stimulation), and other experimental variables. In considering the disparate findings as to the

effectiveness of cerebellar stimulation for seizure suppression, it is therefore certainly worth noting the large range of methods used in previous literature (Tables 1 and 2). Theoretically, some insight might be gleaned by comparing across studies. However, this is hampered by two large factors. 1) There is inconsistent reporting of key variables. Sometimes relevant information is not reported at all (Tables 1 and 2), and sometimes ranges are given that are so large as to significantly hamper interpretability (e.g., 4–100 Hz [93]). 2) There are a large number of dimensions to explore. This may be the largest hurdle. Without a systematic study, disentangling the effects of any one parameter on outcomes becomes extremely difficult. For example, if study X differs from study Y in regard to location, pulse width, and frequency, how does one decide which variable is the key variable? This is especially difficult as variables may interact with one another.

Even without taking into account potential effects of epilepsy type or model on outcomes, the number of dimensions with regard to stimulation parameters to explore results in a *huge* parameter space, which is simply too sparsely sampled by the current literature. As noted above, studies in which a given parameter was varied within the study, to explore the impact of that parameter, provide some level of insight and hope for clarification. However, these studies are few and far between, and explore a very limited subset of the parameter space. What would be most beneficial in this regard would be a much larger undertaking – one that explored the impact of changing *combinations* of stimulation parameters in a systematic and thorough way, covering a large swath of the parameter space, in the same study. This would allow researchers to identify which parameters are critical and which combination of parameters allows for robust, consistent, seizure suppression. Effective settings may also be epilepsy type, or perhaps even individual, specific. There are strategies that provide a mechanism to do a thorough, rationale, and data driven search of the parameter space to identify which combinations of settings do, and do not, work [6, 113]. In some circumstances, such approaches can even be applied at an individual subject level. Experiments providing a large coverage of the parameter space, allowing direct comparisons of important experimental variables, will provide needed insight into this complex, but very relevant issue.

3.4 Closed versus open loop modulation

Previous work examining the effects of electrical stimulation of the cerebellum on seizures relied on open-loop stimulation protocols, in which electrical stimulation was applied on a regular basis irrespective of ongoing seizure activity. This can result in a misalignment of the intervention, limiting efficacy. It may also result in ‘over-stimulation’, with intervention occurring during interictal or other periods not needing intervention. Such continuous stimulation has the potential to carry negative side effects such as mal-adaptive plasticity, which may reduce the efficacy of electrical stimulation or even result in a kindling-like phenomenon. One alternative is to implement closed-loop on-demand interventions in which stimulation is applied only in an ‘as-needed’ basis, i.e., only during or immediately prior to seizure events (Figure 1). In addition to limiting potential mal-adaptive plasticity or other negative side-effects of stimulation, the improved temporal alignment of closed-loop approaches may simply be more effective [114, 115]. Therefore, on-demand interventions may not only allow more interpretable results, but may also have significant clinical benefits.

Closed-loop on-demand interventions are now used both clinically [2, 116] and experimentally [50, 66, 114, 115, 117–119].

4 Renewed interest with more targeted approaches

As outlined above, the complex effects of electrical stimulation on both the populations of neurons recruited as well as the direction of modulation of cells may contribute to the inconsistency of cerebellar electrical stimulation in the attenuation of seizures. Improvement of the specificity of interventions in i) cell populations engaged, ii) direction of modulation, and iii) temporal alignment relative to seizure events may therefore improve efficacy of cerebellar modulation, and, importantly, interpretability of results. Optogenetics allows for the targeting of specific cell populations for either direct excitation or inhibition using transgenic and/or viral approaches [120]. When combined with on-demand light delivery, optogenetics also provides temporal specificity, and therefore overcomes many of the challenges in interpretability discussed above. The development and implementation of these techniques to increase the specificity and targeting of neuronal populations has led to renewed interest in the cerebellum as a target for therapeutic intervention in epilepsy. In the following subsections, we describe findings obtained using optogenetic techniques to modulate the cerebellum in mouse models of temporal lobe and absence epilepsy. A summary of findings from these studies is also provided in Table 3.

4.1 On-demand optogenetic modulation of cerebellar neurons in a mouse model of temporal lobe epilepsy

Using closed-loop optogenetic approaches, Krook-Magnuson et al selectively modulated cerebellar Purkinje cells in an on-demand fashion in the intrahippocampal kainate mouse model of chronic temporal lobe epilepsy [50] (Figure 2). On-demand optogenetic excitation of Purkinje cells in lobules IV/V of vermis (midline) or the simplex (either ipsilateral or contralateral to the presumed seizure focus) robustly inhibited spontaneous seizures recorded from the hippocampus (Fig. 2B) [50]. This showed that optogenetic excitation of Purkinje cells could be an effective strategy to inhibit seizures. These findings also suggested that, when optogenetically manipulating Purkinje neurons, multiple locations of intervention can be effective. Moreover, inhibition of seizures was achieved with short or long light pulses, indicating that a specific frequency of light delivery was not key to success with this optogenetic approach.

On-demand optogenetic inhibition of Purkinje cells, in the same cerebellar regions, was also tested [50]. Surprisingly, a reduction in seizure duration was also observed when Purkinje cells were inhibited rather than excited (Fig. 2A). This suggests that, when optogenetically manipulating Purkinje neurons, the direction of modulation is also not a critical factor for aborting hippocampal seizures. How could both excitation and inhibition of Purkinje cells be effective? Notably, it has been shown that optogenetic excitation of Purkinje cells can be followed by brief pauses in Purkinje cell firing, and, conversely, that optogenetic inhibition of Purkinje cells can be followed by brief periods of increased firing after light offset [50, 121]. The ability of both optogenetic excitation and inhibition of Purkinje cells to stop seizures may be a consequence of this phenomenon. However, optogenetic excitation and

inhibition of Purkinje cells are not uniformly equivalent. This is evident when considering seizure frequency. In addition to truncating on-going hippocampal seizures, optogenetic excitation, but not inhibition, of the vermis produced a unique increase in time to next seizure, which, though brief, far outlasted the duration of the light intervention [50]. This finding highlights that the direction of modulation of Purkinje cells can, in certain circumstances, have functionally important consequences. It further indicates that that the midline cerebellar cortex can not only cause immediate changes (truncating ongoing seizures), but can also have longer lasting impacts which influence ictogenicity.

Recently, we used similar on-demand optogenetic methods to instead target the downstream fastigial nucleus. The fastigial nucleus gets inhibitory input from Purkinje cells, and contains a large variety of neuronal types (Box 1). Among these nuclear neuron types are glutamatergic projection neurons, which project to areas including the thalamus, superior colliculus, and brainstem nuclei including the reticular formation. In contrast to findings targeting Purkinje neurons described above, optogenetic inhibition of glutamatergic nuclear neurons had no effect on seizures (Fig. 2C). However, optogenetic *excitation* of glutamatergic nuclear neurons produced robust inhibition of seizures (Fig. 2D). This inhibition of seizures was sufficiently strong and immediate that a single 50 ms pulse of light was able to significantly shorten seizures (Fig. 2D, **inset**). These findings provide important additional insight into how cerebellar modulation may be inhibiting hippocampal seizures. Specifically, they indicate that excitation, but not inhibition, of nuclear neurons is able to inhibit seizures. Therefore, the direction of modulation of the nuclear neurons may be a critical factor in successful interventions when targeting the cerebellum. When targeting the cerebellar cortex, the brief pauses in Purkinje cell firing after optogenetic excitation may allow for disinhibition in the nuclei [121–123], and thereby successful seizure inhibition.

These experiments further illustrate how *combinations* of experimental factors can be especially relevant, in this case location and direction of modulation – when optogenetically targeting the cerebellar cortex, the direction of modulation was not a critical factor in reducing seizure duration; when targeting the nuclei, it was absolutely critical. It also provides a potential explanation for why previous electrical stimulation studies could have produced such mixed results: stimulation parameters that ultimately failed to excite nuclear neurons were unlikely to have been successful.

An additional important point is illustrated in our work using optogenetics to target the fastigial nucleus. **Using viral approaches, we were able to either target the fastigial nucleus broadly, without cell type specificity, or specifically target glutamatergic neurons** (Figure 3A–B). **While both methods were able to successfully terminate hippocampal seizures** (Figure 3C–D), we found that optogenetic excitation of glutamatergic nuclear neurons selectively provided greater seizure inhibition than optogenetic excitation of nuclear neurons broadly (Figure 3E–F, **66% versus 39% reduction, respectively**). This highlights an important benefit optogenetic approaches can provide over electrical stimulation or many pharmacological approaches. Cell-type specificity of intervention improves interpretability of findings, and, as seen here, can improve outcomes.

4.2 Optogenetic and pharmacological cerebellar modulation in models of absence epilepsy

As discussed in previous sections, cerebellar modulation with electrical stimulation has been applied to a wide range of seizure types. Similarly, on-demand optogenetic approaches have not only been applied in the intrahippocampal mouse model of temporal lobe epilepsy, but also in mouse models of absence epilepsy. Kros and colleagues [66] found that on-demand optogenetic activation of cerebellar nuclear neurons was effective at attenuating generalized spike and wave discharges (GSWDs) in both *tottering (tg)* and inbred C3H/HeOuJ mouse lines, **with spike and wave events terminating at the onset of light delivery** (Figure 3G–I). The efficacy of on-demand cerebellar modulation in attenuating seizure events in two very different forms of epilepsy (temporal lobe versus thalamocortical absence epilepsy), with different underlying neural circuitry, suggests that the cerebellum may be a broadly applicable candidate for therapeutic intervention in epilepsy. This may make the cerebellum an especially attractive candidate in cases where the seizure focus is unknown, progressing, manifold, or otherwise inaccessible.

While this study did not look at optogenetic inhibition of nuclear neurons, pharmacological inhibition of nuclear neurons via application of the $GABA_A$-agonist muscimol was examined [66]. Consistent with the idea discussed above that excitation of nuclear neurons is required for seizure reduction, pharmacological inhibition consistently increased, rather than decreased, the frequency of GSWDs. The pharmacological approach lacked the temporal precision, as well as the cell-type specificity, that an on-demand optogenetic approach can provide, and therefore is more difficult to confidently interpret. However, pharmacological excitation (/disinhibition), via application of the $GABA_A$-antagonist gabazine, *was* able to significantly decrease GSWD occurrence (but, interestingly, had no effect on duration, in contrast to optogenetic excitation). It will be informing to see, in future studies, what the impact is of on-demand inhibition of (different populations of neurons in) the cerebellar nuclei on GSWDs.

6 Mechanisms of cerebellar inhibition of seizures

A major outstanding question is the mechanism(s) by which cerebellar modulation is able to attenuate seizures. One hypothesis regarding the mechanisms behind electrical stimulation of the cerebellum for epilepsy is that Purkinje cell activation serves to reduce excitatory output from the cerebellar nuclei to the thalamus and thereby reduce cortical excitability [124]. However, this hypothesis is in conflict with the observations described above that 1) pharmacological inhibition of deep cerebellar nuclei increases the frequency of GSWDs [66, 125], 2) pharmacological excitation of deep cerebellar nuclei decreases the frequency of GSWDs [66], 3) optogenetic excitation of deep cerebellar nuclei inhibits GSWDs [66], 4) optogenetic inhibition of deep cerebellar nuclei has no apparent effect on hippocampal seizures [126], while 5) optogenetic excitation of deep cerebellar nuclei inhibits hippocampal seizures [126]. Therefore, it appears that the reverse of the hypothesized mechanism is actually at play: effective cerebellar stimulation for inhibition of seizures may require *increased* output from excitatory projections for the deep cerebellar nuclei. Beyond that, little is currently known.

How would increased output from cerebellar nuclei neurons inhibit seizures? Neurons in the deep cerebellar nuclei project to numerous downstream structures (Figure 4) including various thalamic nuclei, the superior colliculus (which is of particular interest given its potential role as a regulator of ictal activity [9]), the pontine and medullary reticular formation, the locus coeruleus, and the amygdala [127–129]. This broad connectivity makes disentangling potential pathways influencing seizures difficult.

In the case of absence epilepsy, given the thalamic role in absence seizures [130, 131], a potential straight-forward explanation is the direct connection from the deep cerebellar nuclei to thalamic nuclei [132]. Altering excitatory input to the thalamus could, for example, shift thalamic neurons from phasic to tonic firing [133]. In the case of hippocampal seizures, however, things become more complicated.

While early research, using techniques such as examination of degenerating fibers [129] or time delays in responses recorded from the hippocampus after electrical stimulation in the cerebellum [75, 82], suggested there may be a direct connection from the cerebellum to the hippocampus, more recent studies have failed to find evidence for a direct, **monosynaptic**, connection [134–136]. Once a multi-synaptic pathway is considered, there are a great many potential routes for cerebellar modulation to influence hippocampal networks, including via the locus coeruleus, the septum, and potentially the thalamus [136–139].

A lack of a direct, mono-synaptic, connection does not imply that the cerebellum cannot have a strong impact on hippocampal networks. Indeed, a recent paper optogenetically manipulating the cerebellum in healthy animals found both increased bold signal in the hippocampus and altered neuronal firing in the hippocampus with multiunit recordings [140]. Suggesting a functional significance of these (indirect) connections, chronic cerebellar deficits can impact spatial encoding in the hippocampus [141, 142]. Similarly, cerebellar cortical activity has been shown to be synchronized with hippocampal oscillations during certain conditions [136, 143, 144]. While there are many scenarios that could produce coherent oscillations in these brain regions (including both the hippocampus and the cerebellum getting a common source of input), it minimally suggests that the two structures may be collaborating under certain conditions [136]. More generally, there has also been a great deal of accumulating evidence suggesting a role for the cerebellum in more cognitive functions, including hippocampal-dependent processes [145, 146]. Determining which, of the many possible pathways, underlie the functional connection between the cerebellum and the hippocampus in healthy animals, and the ability for cerebellar modulation to inhibit temporal lobe seizures, will require significant additional efforts. Notably, different pathways may underlie the seizure suppressive effects of cerebellar modulation and the functional connectivity that appears to be relevant to spatial navigation.

An additional possibility is that seizure disruption is due to a more global brain state change, rather than a specific effect on the thalamus or hippocampus. The cerebellum projects to numerous areas associated with the control of brain states, and for example, has been implicated in regulation of sleep-wake cycles [147, 148]. Brain states, including sleep-wake cycles, are known to impact seizure susceptibility for a range of seizures types [149–153]. In the context of seizure disruption, a sufficient change in brain state could be theoretically

achieved in a variety of manners. Seizure suppression, even if ultimately associated with a fairly global brain state change, could result from activation of a specific cerebellar output pathway (e.g., the reticular formation). In this scenario, stimulating that pathway selectively could replicate the benefits seen with cerebellar modulation. Alternatively, there may be a requirement for simultaneous modification of multiple downstream targets through divergent output pathways of the cerebellum, such that no single output pathway is able to replicate the seizure inhibition benefits seen with direct cerebellar modulation. This question (single cerebellar output pathway versus requirement for simultaneous modulation of multiple pathways) is addressable with currently available techniques, and is an important question to examine. If the cerebellum is impacting seizures through a specific target structure, that structure may in turn be a potential therapeutic target.

Finally, it is worth noting that excitatory projections from the cerebellar nuclei are not the only way for the cerebellum to influence downstream structures. There are also inhibitory projection neurons from the cerebellar nuclei [154], including, but not limited to, a population of glycinergic neurons in the fastigial nucleus which project ipsilaterally to vestibular and reticular neurons [155]. Additionally, while Purkinje cells classically project to neurons in the deep cerebellar (and vestibular) nuclei, they also can have direct projections to other regions (bypassing the cerebellar nuclei) including the locus coeruleus [138] and medial parabrachial nucleus [156], although much less is known about these connections. Similarly, although somewhat controversial, a population of neurons in the cerebellar granule cell layer or white matter, which appear to have projections out of the cerebellar cortex, has been noted in several species [157–161]. The projection target of these cells is essentially unknown, and provide another potential route of influence. However, findings that selective optogenetic activation of glutamatergic nuclear neurons was able to inhibit seizures (Figure 3, Table 3[126]) suggests that the bulk of seizure inhibition may be mediated by excitatory projections from the cerebellar nuclei.

6 Translational strategies

While optogenetics represents a powerful tool to selectively manipulate neuronal populations, it is still far from being successfully implemented in human epilepsy patients [115, 162]. It may, however, be possible to use the insights gleaned from on-demand optogenetic work in animal models to improve electrical stimulation efforts targeting the cerebellum. For example, in the case of cerebellar cortical stimulation, if electrical stimulation can be tuned such that it results in inhibition of Purkinje cells and thereby activation of downstream nuclear neurons, it would perhaps be more consistently effective in attenuating seizures. Additional benefits, including surgical benefits, may be achieved by directly targeting the nuclei [163, 164]. Determining the specific parameters to allow robust inhibition of seizures with electrical stimulation, unfortunately, will not be trivial. However, there are strong potential benefits, and, as mentioned above, tools available to allow a strategic and fairly comprehensive search of the parameter space. For example, Bayesian parameter optimization may be one powerful approach to tackle the dauntingly large number of combinations of potential stimulation parameters [113]. Given that optogenetic work provides strong evidence that cerebellar modulation *can* produce robust seizure inhibition,

the challenge becomes determining how to achieve similar results with methods more readily clinically available.

7 Conclusions

While the cerebellum is an area of the brain not traditionally associated with epilepsy, ample evidence suggests that it can play an important role in seizure networks. This includes changes in cerebellar activity during seizures and cerebellar abnormalities associated with epilepsy. Early stimulation efforts targeting the cerebellum for seizure control, while initially promising, produced mixed results, and the cerebellum has not been substantially revisited as a potential therapeutic target for epilepsy until recently. The use of more targeted approaches such as closed-loop optogenetics appear to have greatly increased the efficacy of cerebellar modulation in attenuating seizures. These results renew excitement in the cerebellum's potential as a possible target for therapeutic intervention. The precise mechanisms by which cerebellar modulation attenuates seizures have yet to be fully elucidated, and future efforts will need to determine if electrical stimulation parameters can be optimized to provide consistent, robust, inhibition of seizures.

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Abbreviations

GSWDs	Generalized spike and wave discharges
SUDEP	sudden unexplained death in epilepsy
GFP	Green fluorescent protein

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Highlights

- Cerebellar alterations are often observed with epilepsy, including structural changes and modulation of cerebellar activity during seizures.
- The cerebellum itself has been identified as a seizure focus in a number of case reports.
- The cerebellum was a target of early interest for therapeutic stimulation to disrupt seizures, but animal and human studies using electrical stimulation produced mixed effects.
- Recent work utilizing more targeted, closed-loop interventions reveal that the cerebellum can powerfully inhibit seizures in multiple models of epilepsy.

Box 1.

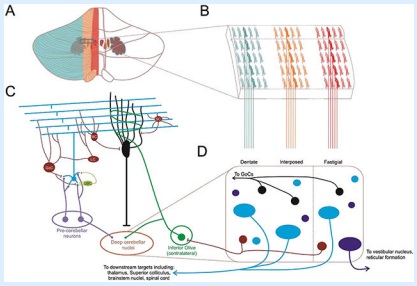
Overview of cerebellar circuitry

The cerebellum contains roughly 80% of the neurons in the central nervous system [165]. Classically considered a motor control structure, the cerebellum is essential for the production of smooth continuous movements [166] as well as the processing and correction of motor errors [167], but accumulating evidence suggests it also plays a role in higher order functions and cognitive processes [145, 146]. Located inferior to the occipital cortex and dorsal to the pons and medulla, the cerebellum integrates inputs in the cerebellar cortex (illustrated in panel A, modified from [166]), which generally exhibits a high degree of homogeneity in terms of cytoarchitecture [168], and sends outputs to downstream structures in the deep cerebellar nuclei (though Purkinje cells have been noted to project to other areas including the locus coeruleus [138, 156]). Note that integration also likely occurs in the nuclei, which receive collateral input from fibers projecting to the cerebellar cortex. The cerebellum (both the cerebellar cortex and the cerebellar nuclei) receives inputs via mossy fibers originating from a large number of sites including the spinal cord, brainstem nuclei, and cerebral cortex (including motor and sensory areas) via the pontine nuclei and reticular formation (light purple in panel C) [109, 127, 169]. These ascending mossy fibers synapse onto cerebellar granule cells (blue in panel C). Granule cells provide the first of two major excitatory synaptic inputs onto Purkinje cells (black in panel C). Axons from granule cells ascend into the molecular layer of the cerebellar cortex, where they then bifurcate and form parallel fibers. The parallel fibers then pass orthogonally through the expansive but almost two dimensional dendritic trees of Purkinje cells, which are oriented sagittally along the cerebellar cortex ([109, 169], illustrated in panel B). Purkinje cells also receive powerful synaptic inputs from climbing fibers originating in the contralateral inferior olive (green in panel C) [170]. There are several types of inhibitory interneurons within the cerebellar cortex (red in panel C). For example, Golgi cells receive excitatory inputs from parallel fibers and inhibit granule cells. Two other populations, Basket and stellate cells, provide inhibitory input to Purkinje cells. Other populations of both inhibitory and excitatory interneurons exist in the cerebellar cortex including lugaro cells and unipolar brush cells, respectively ([159] Panel C). Either directly or indirectly, these neurons shape the high frequency (50 to 150 spikes/s) simple spike output of Purkinje cells. Importantly, Purkinje cells sustain a high (~60Hz) baseline firing rate due to intrinsic channel conductances [171].

Purkinje cells project to and inhibit the deep cerebellar nuclei, which exhibit a far more heterogeneous cytoarchitecture and contain both local and projection excitatory and inhibitory neurons, many of which have yet to be fully characterized (illustrated in panel D). All four of the deep cerebellar nuclei: fastigial, globose and emboliform (often referred to together as the interposed nucleus), and dentate contain glutamatergic projection neurons (blue in panel D) which send excitatory output to numerous downstream structures including descending motor tracts, the cerebral cortex via the thalamus, the superior colliculus, and brainstem nuclei such as those of the reticular formation. The fastigial nucleus also contains a unique population of large, glycinergic projection neurons (purple in the panel D), which project to and inhibit ipsilateral

brainstem and vestibular nuclei [155]. The deep cerebellar nuclei also contain a population of GABAergic projection neurons (red in panel D), which send inhibitory input to the inferior olive, creating a closed loop along with climbing fiber input from the inferior olive to cerebellar cortex [172–174]. GABA/Glycine co-releasing nucleocortical neurons (black) provide an inhibitory feedback loop back to the cerebellar cortex [175]. There is also a population of glutamatergic neurons that project to the cerebellar cortex via mossy fibers [176]. Finally, two populations of local interneurons have been identified: GABA/glycinergic inhibitory and small glutamatergic interneurons [154].

Functionally, the cerebellum exhibits a longitudinal organization, in which Purkinje cells integrate specific afferent inputs and project to a specific deep cerebellar nucleus (fastigial, interposed, or dentate) depending on where the Purkinje cells are positioned on the medial-lateral plane (panels A-B). Purkinje cells in and near the midline (vermis) project to and inhibit the fastigial deep cerebellar nucleus (outlined in red in the figure) as well as the vestibular nucleus; Purkinje cells in the cerebellar hemispheres predominantly project to the dentate nucleus (outlined in blue), and Purkinje cells in the intermediate regions between the vermis and lateral hemispheres predominantly project to the interposed nuclei (outlined in yellow) [109]. Classically, the midline cerebellum is considered to be part of the functional region known as the vestibulocerebellum, essential for maintenance of balance and equilibrium and coordinating eye movements [166]. Emerging evidence indicates a role for the vermis beyond these functions, however, and the midline cerebellum has also been associated with limbic structures [177]. The intermediate zones, along with portions of the midline are considered part of the spinocerebellum, contributing to fine control of limb movements [166]. The lateral cerebellar hemispheres are enlarged in humans and nonhuman primates and are considered part of the cerebrocerebellum due to the large number of feedback loops formed by inputs from cortex via pontine nuclei and outputs via the thalamus [166]. However, the full spectrum of downstream structures targeted by deep cerebellar nuclear outputs have not been characterized, and there is a large amount of evidence suggesting the cerebellum and its different subregions are highly engaged in processes beyond those outlined here.



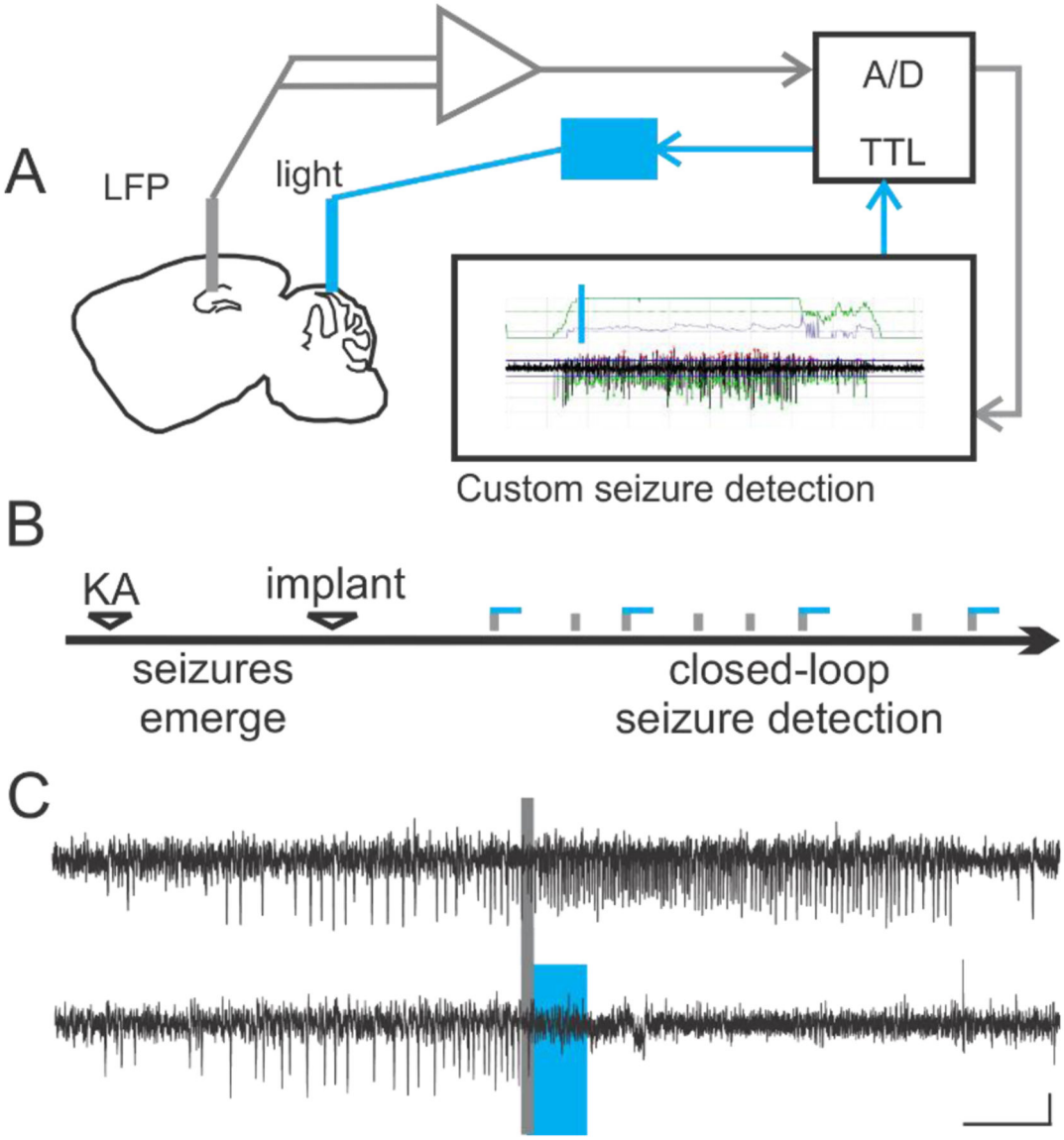


Figure 1. Closed-loop optogenetic interventions align intervention to the time of seizures.

A) Schematic of an example on-demand optogenetic intervention strategy. Chronic hippocampal LFP recordings (near the presumed seizure focus) are digitized and fed into seizure detection software, allowing on-line detection through user-specified criteria, such as ictal spike frequency. Seizure detection in turn automatically triggers light delivery, for example to the cerebellum, for optogenetic interventions. **B)** On-demand optogenetic intervention can be implemented during the chronic phase of epilepsy in the intrahippocampal kainate model, such that spontaneous seizures which occur weeks after the initial insult are detected (gray vertical bars in the schematic denote detected seizures) and trigger light delivery. Blue horizontal lines in the schematic indicate light delivery. Note that only approximately half of detected events are followed by blue lines: detected events not receiving light intervention can serve as no-light internal controls. **C)** Example electrographic seizure events in the intrahippocampal kainate mouse model of temporal lobe

epilepsy which were detected on-line (denoted by gray bar) and were either randomly selected to not receive light (top trace) or receive 3 seconds of pulsed light delivery to the cerebellar cortex (bottom trace, light delivery denoted by blue box). Scale bar: 5s, 0.05mV. Panels B-C reproduced from [50].

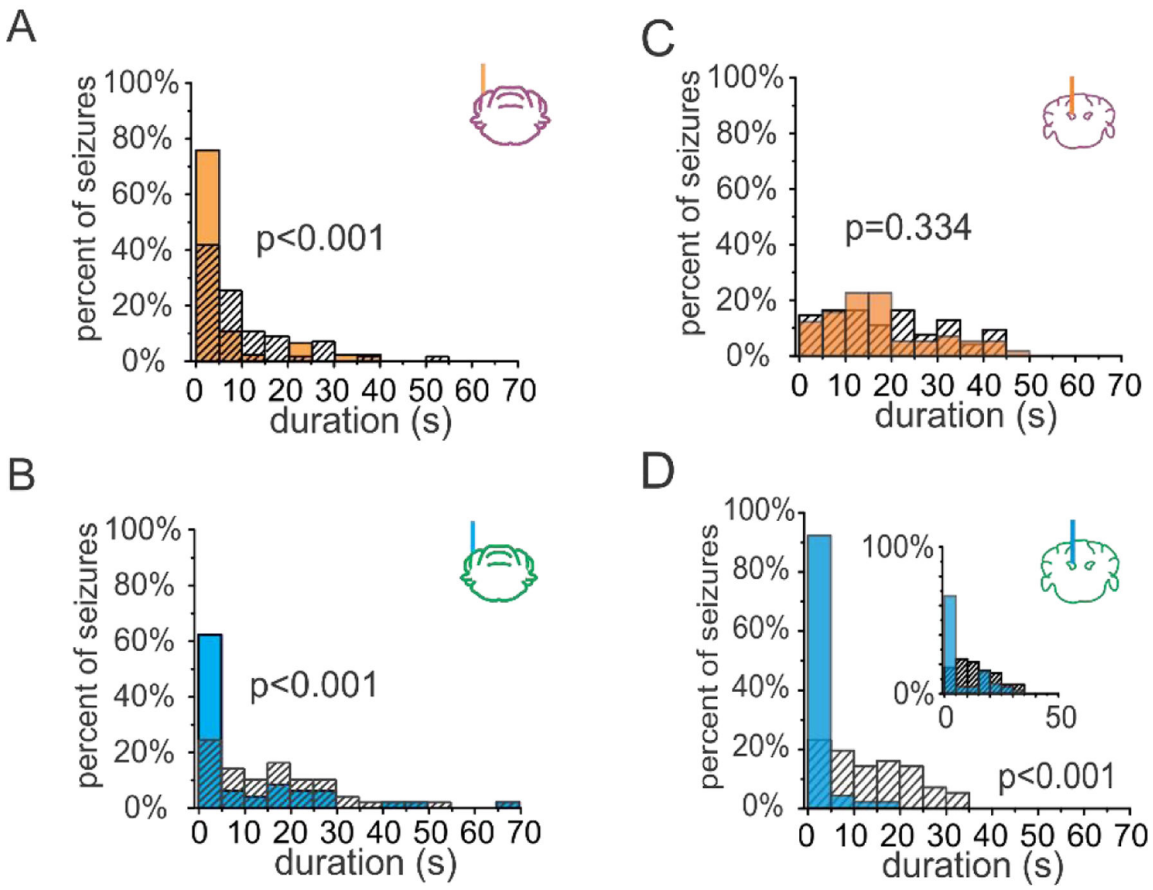


Figure 2. Excitation or inhibition of the cerebellar cortex can attenuate hippocampal seizures, while excitation of the deep cerebellar nuclei is required for successful seizure intervention.

A-B) Example post-detection seizure durations for animals receiving three seconds of pulsed on-demand optogenetic intervention targeting the cerebellar cortex. Both on-demand inhibition (orange bars in A) and excitation (blue bars in B) of the cerebellar cortex robustly attenuate hippocampal seizures. Hashed bars: no light internal controls. **C-D)** Direction of modulation matters when instead targeting the cerebellar nuclei. **C)** Post-detection seizure durations for an example animal illustrating that on-demand inhibition of the fastigial nucleus fails to attenuate hippocampal seizures. **D)** Conversely, on-demand excitation of the fastigial nucleus robustly attenuates seizures. Even a single 50 msec pulse of blue light delivered to the fastigial nucleus is sufficient to reduce hippocampal seizure duration (inset, $p < 0.01$). P values from two sample Kolmogorov-Smirnov tests. Panels A-B reproduced and modified with permission from [50], panels C-D reproduced and modified with permission from [126]tr).

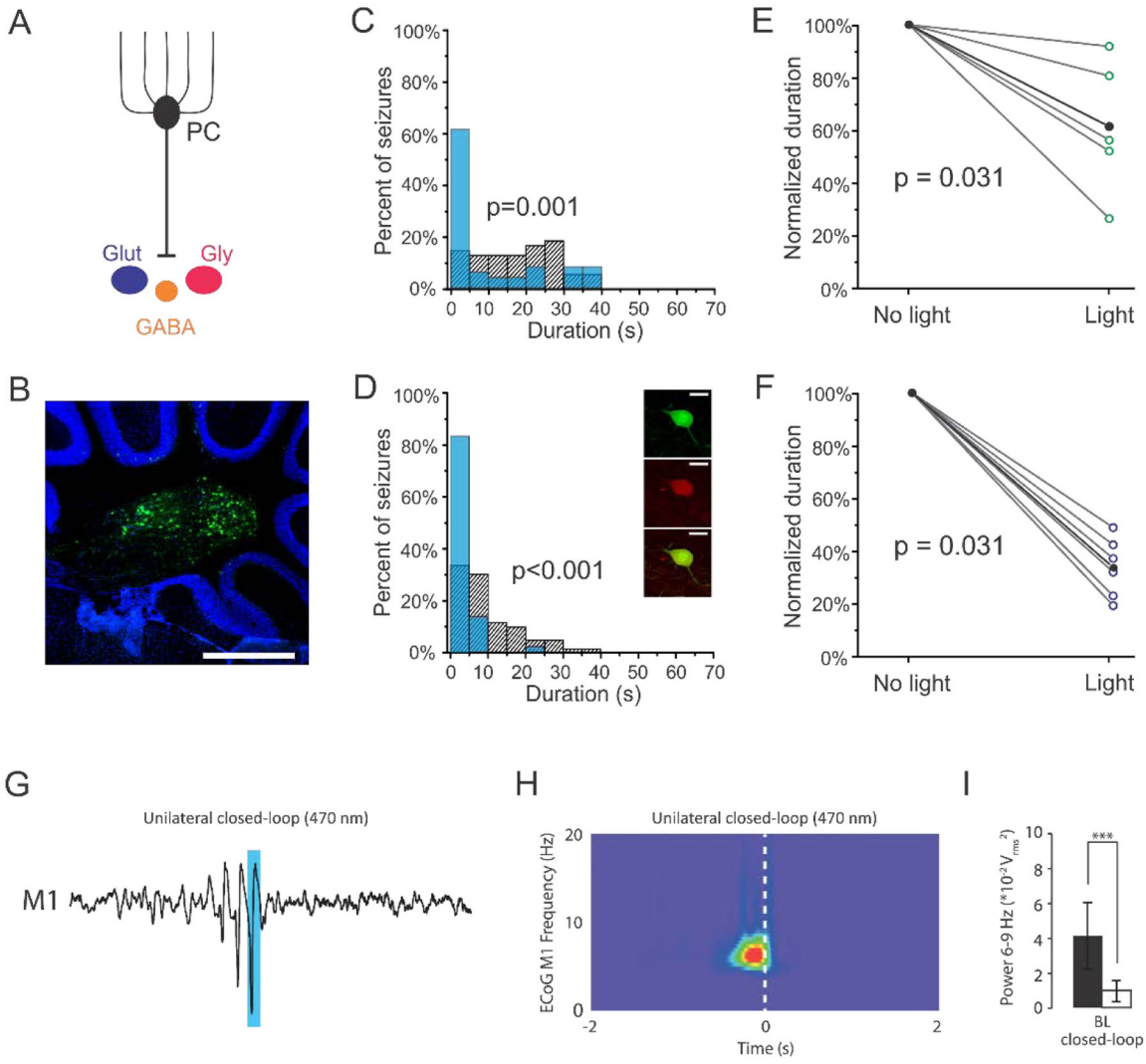


Figure 3. Viral targeting of nuclear neurons in mouse models of temporal lobe and absence epilepsy

A) Viral approaches allowed for broadly targeting nuclear neurons or selective targeting of glutamatergic nuclear neurons (dark blue). **B)** GFP expression in nuclear neurons following injection of cre-dependent virus in a VGluT2-cre mouse. Scale bar: 500μm. **C)** Post-detection seizure durations for an example animal, illustrating that light delivery significantly reduces seizure duration when virally targeting the fastigial nucleus broadly (in this example, a 44% reduction, p = 0.001, two sample Kolmogorov-Smirnov test). Blue bars: events receiving light intervention; hashed bars: no-light internal controls. **D)** Seizure inhibition is also achieved by selectively targeting glutamatergic nuclear neurons (in this example, an 81% reduction, p < 0.001, two sample Kolmogorov-Smirnov test). Inset: Immunocytochemistry confirmed selective expression in glutamatergic neurons following injection of cre-dependent virus in VGluT2-cre animals (Top- green: GFP, middle- red: VGluT2 immunohistochemistry, Bottom- overlay. Scale bar: 70μm.) **E-F)** Selective targeting of glutamatergic neurons in the fastigial nucleus (F) produces significantly greater seizure attenuation than targeting fastigial neurons more broadly (E; broad targeting versus selective

targeting: p = 0.026, Mann-Whitney). Each open circle represents one animal; black data points represent mean. **G) Closed-loop optogenetic excitation of the deep cerebellar nuclei (targeting all nuclear neurons broadly using a viral approach) attenuates generalized spike and wave discharges in primary motor cortex in the C3H/HeOuJ mouse model. Blue bar indicates timing of light delivery. H) Wavelet spectrogram of the electrocorticograph during closed-loop stimulation, showing cessation of the GSWD event was time-locked to the onset (dashed bar) of intervention. I) Closed-loop intervention significantly reduces motor cortex band power associated with the GSWDs (p < 0.05, repeated measures ANCOVA). Panels A-F r**eproduced with modification and permission from [126]. **Panels G-I reproduced with permission from** [66].

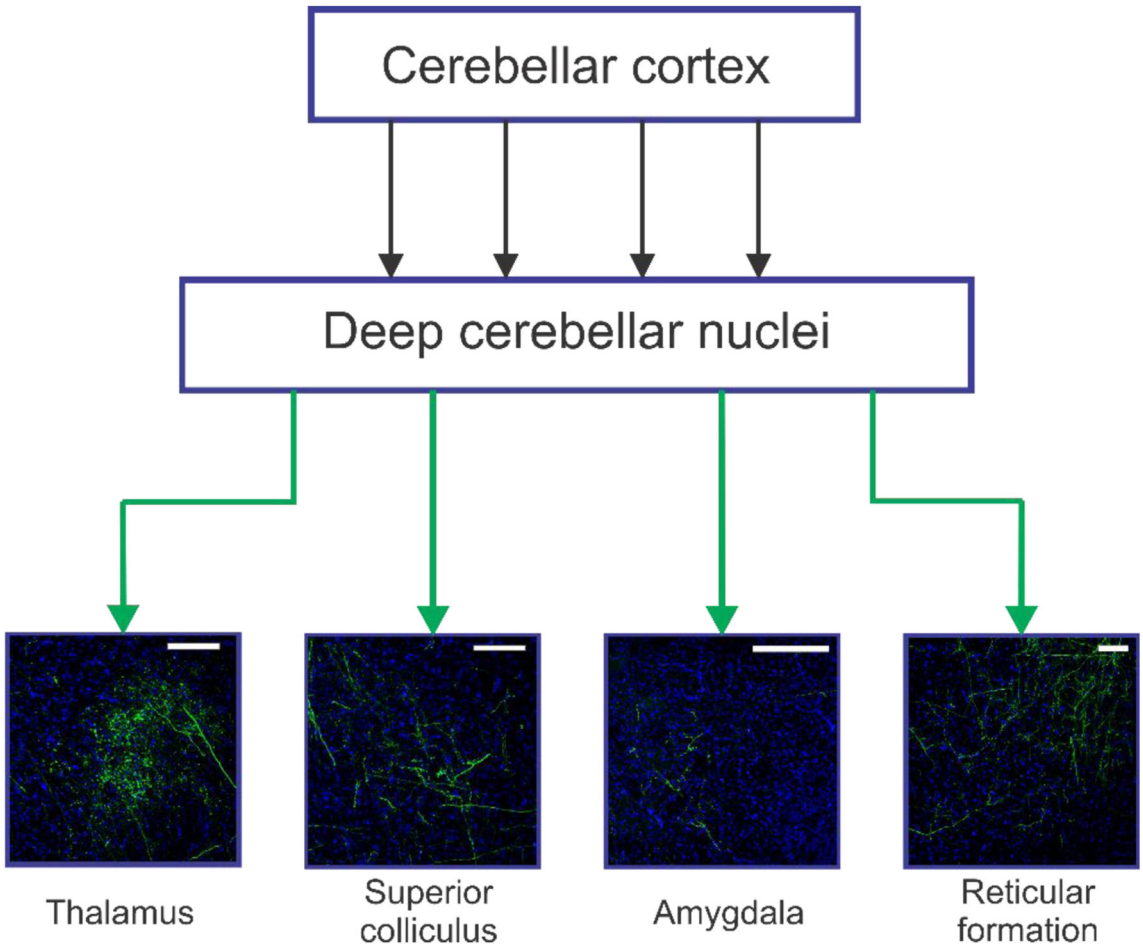


Figure 4. A few cerebellar output channels of potential relevance to seizure networks. The deep cerebellar nuclei contain numerous downstream projections to both ascending and descending structures, including but not limited to the thalamus, superior colliculus, amygdala, and reticular formation. The projections from deep cerebellar nuclei to these areas are visualized here from mice injected with viruses inducing GFP expression in nuclear neurons similar to the studies outlined in Figure

3. Scale bars: 100μm (Thalamus, Superior colliculus), 200μm (Amygdala, Reticular formation)

Table 1:

Summary of cerebellar stimulation studies in animal models of epilepsy. Abbreviations: pw = pulse width.

Study	Target	Number of patients	Stimulation protocols	Outcome
Bidzinski et. al, 1982	Hemispheres	14	1–7V; 10Hz; 1msec pw; 30min-1hr duration	5 patients seizure free, 6 patients with reduced seizures, 2 patients with slight improvement, 1 patient with no change
Chkhenkeli et. al, 2004	Dentate nucleus	54	6–8mA; 50–100Hz; 2msec pw; 10sec epochs	>50% reduction in seizures
Cooper et. al, 1973	Cerebellar cortex	32	1msec pw; other parameters not reported	Over half of patients had >50% reduction in seizure frequency
Davis et. al, 1983	Midline cerebellar cortex	32	10–180Hz; other parameters not reported	19 patients seizure free, 8 patients with reduced seizures, 4 patients with no change, 1 patient with increased seizures
Davis et. al, 1992	Midline cerebellar cortex	30	1–1.4mA; 150Hz; 0.5msec pw	>50% patients seizure free
Gilman et. al, 1977	Anterior lobe, hemispheres	6	10Hz; 1msec pw	5 patients with reduced seizures
Klun et, al, 1987	Hemispheres	6	5–50Hz; 0.6msec pw	3 patients seizure free, 3 patients with reduced seizures
Levy et. al, 1979	Not given	6	3–10V; 10Hz	3 patients with reduced seizures, 2 patients with no change, 1 patient with increased seizures
Sramka et. al, 1976	Dentate nucleus	4	10V; 10 or 100Hz; 1msec pw; 3 min duration	Temporary improvement
Van Buren et. al, 1978	Cerebellar cortex	5	Range	No change
Velasco et. al, 2005	Midline cerebellar cortex	5	3.8mA; 10Hz; 0.45msec pw	41% mean decrease in seizure frequency
Wright et. al, 1984	Cerebellar cortex	12	7mA; 10Hz	No change

References [70, 75–79, 81–95]

Table 2:

Summary of human cerebellar stimulation studies for the treatment of epilepsy.

Study	Target	Epilepsy model	Stimulation protocols	Electrode information	Animal model	Results
Babb et. al, 1974	Vermis, fastigial, dentate	Cobalt: Hippocampus	1.0mA; 45Hz; 0.6msec pw	1mm between tips	Cat	Fastigial vermal stimulation inhibited epileptic activity. Dentate could either inhibit or prolong seizures
Cooke et. al, 1955	Cerebellar cortex and nuclei	Electrical stimulation: cortex	40V; 20–300Hz; 5–10sec duration	Not stated	Cat	Stimulation could either inhibit or prolong epileptic activity
Dauth et. al, 1974	Vermis	Cholarose, electrical stimulation: cortex	3–5mA; 200Hz; 1msec pw; 0.2–10sec duration	Not stated	Cat	Inhibition of epileptic activity
Dow et. al, 1962	Lobules V-VII	Cobalt: Cortex	1–5V; 20–50 or 200–400Hz; 0.3–1 msec pw; 1–3sec duration	Not stated	Rat	Inhibition of epileptic activity
Fanardjian et. al, 1963	Not stated	Electrical stimulaiton: Hippocampus	50V; 300Hz; 0.1msec pw	Not stated	Cat	Stimulation could inhibit epileptic activity
Godlevsky et. al, 2004	Nodulus, uvula	Penicillin: Systemic	10–12Hz or 100–300Hz; 0.5msec pw or 0.25msec pw	0.12mm diameter 1.0mm between tips	Rat	Low frequency stimulation evoked seizures, higher frequency stimulation inhibited seizures
Grimm et. al. 1970	Fastigial, dentate	Cobalt: Cortex	0.6–0.9V; 250–300Hz; 1msec pw	Not stated	Monkey	Failed to inhibit epileptic activity
Hablitz, 1975	Vermis, hemispheres	Alumina-Gel: Cortex	1–10V; 5–15Hz or 100Hz; 1msec pw, 1–30sec duration	5mm diameter	Monkey	Low frequency stimulation failed to inhibit seizures, higher frequency stimulation evoked seizures
Hablitz, 1976	Vermis	Penicillin: Systemic	0.25–2.0mA; 10 or 100Hz; 1msec pw; 10 sec duration	3mm diameter	Cat	Inhibition of epileptic activity
Hemmy et. al, 1977	Hemispheres, dentate nucleus	Electrical stimulation: cortex	10mA; 4–100Hz; 1msec pw;	1mm diameter disc electrodes (cortex); bipolar electrodes (denate)	Monkey	Failed to inhibit epileptic activity
Hutton et. al, 1972	Vermis, paramedian lobules, dentate	Penicillin: Cortex	0.3–5V; 200Hz	Not stated	Cat	Inhibition of epileptic activity
Iwata et. al, 1959	Vermis	Electrical stimulation: Hippocampus	5–15V; 30–100Hz; 1msec pw; 30sec duration	Not stated	Cat	Inhibition of epileptic activity
Kreindler, 1962	Paleo and neocerebellum	Penicilin: Cortex	0.25–3mA; 2.5Hz; 1msec pw	Not stated	Cat	Stimulation could either inhibit or prolong epileptic activity
Lockard et. al, 1979	Vermis	Alumina-Gel: Cortex	2.0mA; 10Hz; 1msec pw; 10min duration	3 electrodes, 2mm apart	Monkey	Increased seizure frequency, decreased interictal bursting

Study	Target	Epilepsy model	Stimulation protocols	Electrode information	Animal model	Results
Maiti et. al, 1975	Vermis, fastigial	Electrical stimulation: Hippocampus and amygdala	5–12V; 1–10, 30–200Hz; 0.1–1msec pw; 5–15sec duration	Not stated	Monkey, Cat	Vermal stimulation inhibited epileptic activity, fastigial stimulation prolonged epileptic activity
Mutani et. al, 1969	Vermis lobules III-V	Cobalt: Amygdala and Hippocampus	6–8V; 100Hz; 0.6msec pw; 1 second duration	1–2mm between tips	Cat	Inhibition of epileptic activity
Myers et. al, 1975	Paleo and neocerebellum	Penicillin, pTZ, enflurane, cholarose	8V; 1–250Hz	2mm between tips	Cat	Failed to inhibit epileptic activity
Reimer et. al, 1967	Vermis, hemispheres	Cobalt: Cortex	1–7.5V; 4–300Hz; 0.1msec pw; 1–10sec duration	1mm between tips	Cat	Initiated or prolonged epileptic activity
Rucci et. al, 1968	Anterior lobules	Hyperbaric oxygen	4–5V; 30–300Hz; 1msec pw	Not stated	Rat	Stimulation could either inhibit or prolong epileptic activity
Snider et. al, 1974	Anterior lobules, fastigial	Electrical stimulation: Cortex and Hippocampus	0.5–3mA; 8–300Hz; 5sec duration	Not stated	Monkey	Inhibition of epileptic activity
Wada et. al, 1974	Cerebellar cortex	Electrical stimulation: amygdala		Not stated	Monkey	Failed to inhibit epileptic activity

References [96–107]

Table 3:

Summary of optogenetic interventions targeting the cerebellum in animal models of epilepsy.

Study	Target	Epilepsy model	Stimulation protocols	Opsin, targeting	Animal model	Results
Krook-Magnuson et. al, 2014	Vermis, simplex lobules IV/V	Intrahippocampal kainate (chronic phase)	7Hz, 1Hz; 3sec duration	ChR in parvalbumin expressing neurons, Purkinje cells	Mouse	Seizure inhibition with all parameters
Krook-Magnuson et. al, 2014	Vermis, simplex lobules IV/V	Intrahippocampal kainate (chronic phase)	7Hz, 1Hz; 3sec duration	HR in parvalbumin expressing neurons, Purkinje cells	Mouse	Seizure inhibition with all parameters
Streng et. al, 2019	Fastigial nucleus	Intrahippocampal kainate (chronic phase)	1Hz, 7Hz, 10Hz; 3sec duration or single 50msec pulse	HR in VGluT2-expresisng neurons	Mouse	No effect
Streng et. al, 2019	Fastigial nucleus	Intrahippocampal kainate (chronic phase)	1Hz, 7Hz, 10Hz; 3sec duration or single 50msec pulse	ChR in VGluT2-expresisng neurons	Mouse	Seizure inhibition with all parameters
Kros et. al, 2015	Medial and lateral deep cerebellar nuclei	*tottering (tg)*	Single 30–300msec pulse	ChR2 under hSyn promoter	Mouse	Seizure inhibition with all parameters
Kros et. al, 2015	Medial and lateral deep cerebellar nuclei	*C3h/HeOuJ*	Single 30–300msec pulse	ChR2 under hSyn promoter	Mouse	Seizure inhibition with all parameters

References [50, 66, 126]