The cerebellum on the epilepsy frontline

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Keywords (2 to 6): temporal lobe epilepsy, Hippocampus, fastigial nucleus, optogenetics, seizure suppression

In a recent study, Streng and colleagues revealed that targeted activation of a specific fastigial output of the cerebellum can powerfully inhibit hippocampal seizures in mice. This study provides insights into how the cerebellum impacts hippocampal activity and opens the way to possible applications for treating temporal lobe epilepsy.

Epilepsy, one of the most common neurological diseases, is characterized by recurrent unprovoked seizures. Current treatments are based either on anti-epileptic drugs or neurosurgical resection of the epileptic focus. Unfortunately, not all epileptic foci are operable, and in some patients, the drug option has limited efficacy or is associated with problematic side effect. Thus, approximately 30–40% of epileptic patients end up with uncontrolled seizures. These patients are therefore strong candidates for alternative potential treatment approaches, such as neurostimulation [1].

Temporal lobe epilepsy is the most common form of epilepsy in adults. The discovery that the cerebellum is able to shape hippocampal activity in mice [2] opened the way to the idea that the cerebellum can influence hippocampal activity and that cerebellar neurostimulation may carry a therapeutic potential for temporal lobe seizures [3]. Subsequent studies confirmed that the cerebellum can modulate the activity of hippocampal neurons [4] and recently raised the idea that the cerebellum may act as a coordinator of cerebral communication [5].

The converging lines of evidence that the cerebellum interacts closely with the hippocampus has led to the question of how precisely the cerebellum is able to influence the hippocampus. Recent studies in mice have focused on the anatomical pathways between the deep cerebellar nuclei – the main outputs of the cerebellum – and the hippocampus, revealing the absence of monosynaptic connection [6]. Besides, following the injection of a retrograde transsynaptic virus in the hippocampus, the strong labeling observed at the center of the dentate nuclei on the one hand and the caudal portion of the fastigial nuclei on the other hand, points toward the existence of several specific modes of communication between the cerebellum and the hippocampus.

In addition to the hippocampus, the thalamus, which receives important ascending inputs from the cerebellum, is also the seat of epileptic seizures [7]. In mice, photo-activation of the

neurons in the deep cerebellar nuclei disrupts spike-and-wave discharges observed during thalamocortical absence seizures [7]. In particular, stimulation of the fastigial nuclei has shown a consistent cessation of seizures in the thalamus [9] as in the temporal lobe [8]. However, the fastigial nucleus projects to more than 60 downstream structures [10] and the need to target the entire fastigial nucleus or a specific subregion of it to stop seizures remains an unresolved issue despite its importance for translational aspects.

In a recent study, Streng et al. [8] worked on the hypothesis that the modulation of a specific cerebellar output channel may be sufficient for seizure control in the mouse hippocampus. The authors studied the anatomical and functional aspects of three fastigial output channels: to the superior colliculus (SC), the ventral medullary (MdV) reticular formation and the central lateral (CL) thalamus nucleus. Using a dual viral approach, the authors confirmed downstream projections of the rostral and caudal portions of the fastigial nucleus to the CL, the MdV, and the SC and revealed that these three fastigial targets receive projections from largely non-overlapping neuron sets. Taking advantage of the intrahippocampal kainic acid model of temporal lobe epilepsy, the authors investigated whether optogenetic modulation of specific sets of fastigial neurons is able to inhibit seizures. They studied the three aforementioned pathways as well as the ventral lateral nucleus (VL) of the thalamus, and revealed that selective excitation of the fastigial-CL output channel is sufficient to attenuate hippocampal seizures. Even if the experiment does not allow knowing which specific part of the hippocampus is affected by the stimulation, the inhibition of seizure was specific to the fastigial-CL output and not observed with the activation of the fastigial-SC or fastigial-VL pathways, neither with the fastigial-MdV pathway, confirming the selectivity of the effect (Figure 1).

These results bring important clarifications to our understanding of the influence that the cerebellum exerts on the hippocampus. Although the possibility remains that additional fastigial regions not targeted by Streng et al. may also be relevant for the control of temporal lobe seizures, this study already reveals a particular pathway of cerebellar influence on the hippocampus and rules out several others.

The study points toward the central lateral thalamus as an intermediate structure along the pathway that connects the cerebellum to the hippocampus. Whereas previous studies reported positive effects of the stimulation of the central median thalamic region for primarily generalized seizures in patients (reviewed in [7]), the specificity reported by Streng et al. [8] opens interesting perspectives for neurostimulation application in temporal lobe epilepsy. The study shows that excitation, and not inhibition, of this deep cerebellar nucleus has a reliable effect on hippocampal seizures, more reliable than the stimulation of the cerebellar cortex [7] or the hippocampus itself [3]. The fact that a targeted activation of a fastigial output channel is sufficient to control the seizures is particularly relevant information if one wants to avoid possible adverse effects in the case of therapeutic application.

Beyond the interest that these findings represent for clinical application, the work of Streng et al. also documents the strong functional specialization of the projections between the cerebellum and the forebrain. The caudal region of the fastigial nuclei targeted in their study is interestingly the one also observed by Watson et al [6] following injection of a transsynaptic retrograde virus into the hippocampal dentate gyrus. These consistent results suggest an important role for the caudal region of the fastigial nuclei in the functional links between the cerebellum and the hippocampus. It also raises questions about the existence of different

intermediate brain regions between these two structures. Is this particular part of the fastigial nucleus the starting point for a pathway (or pathways) influencing the hippocampus? Does the fastigial nucleus influence a neurotypic hippocampus and a hippocampus with seizures in the same way? Are the different hippocampal regions, i.e. the different fields of Ammon's horn or the dentate gyrus, influenced by the same cerebellar outputs? These are some of the unanswered questions that emerge from Streng et al.'s article.

In conclusion, by demonstrating that activation of a specific fastigial output channel is sufficient to stop seizures in a mouse model of temporal lobe epilepsy, the work by Streng et al. provides crucial information to envision translational applications while possibly avoiding the undesirable side effects of a broad neurostimulation. Beyond the obvious need to generate targeted stimulation, this work also provides important insights into the specificity of cerebellar-forebrain circuits. A goal for future work is to decipher how the cerebellum influences the hippocampus at a mechanistic level, in addition to mapping the full anatomical pathway(s) between these brain regions.

Acknowledgments
LRR was supported by the National Agency for Research ANR-17-CE16-0019-03 (SynPredict), ANR-18-CE16-0010-02 (RewInhib), ANR-17-CE37-0015-02 (Navi-GPS) and SATT Lutech. We thank members of the CeZaMe team for helpful comments on the manuscript.

Declaration of Interest

The author declare no competing interests in relation to this work

Figure Legend

Figure 1. Testing fastigial output channels and their modulation of hippocampal seizures. A study by Streng et al. [8] demonstrated that optogenetic excitation of fastigial neurons projecting to the central lateral nucleus (CL) of the thalamus is sufficient to attenuate hippocampal seizures. In sharp contrast, similar optogenetic excitation of fastigial neurons projecting to the ventral medullary (MdV) reticular formation, the superior colliculus (SC) or the ventral lateral (VL) nucleus of the thalamus failed to attenuate hippocampal seizures. Solid lines represent direct projection of the fastigial neurons to the noted structure. Dashed lines represent currently unidentified intermediate structures to the hippocampus. Part of the image created with Biorender.com. Abbreviation: LFP, Local Field Potential.

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