protein makes heterochromatic H2A more likely to be phosphorylated by the same level of BUB1 proteins in the vicinity of *M. spretus* centromeres (Figure1). This H2A-phosphorylation results in increased Shugoshin and thereby MCAK recruitment, leading to drive by the *M. spretus* centromeres [6].

The findings of Akera and colleagues [6] recast centromere drive in molecular terms. First, they demonstrate that the asymmetry of microtubulue destabilizers is the key to centromere drive. Microtubulue-destabilizing proteins like MCAK play essential roles in the fidelity of chromosome segregation by facilitating the correction of incorrect MT attachments to centromeres. It appears that selfish genetic elements have usurped this act of quality control to manifest their selfishness. Second, the study demonstrates that centromeres in different *Mus* species rely on different mechanisms to achieve drive, potentially explaining the pervasive signatures of positive selection and gene turnover in kinetochore and condensin proteins in animal species [9, 10]. Even more opportunities to subvert meiosis likely exist based on other findings [11]. Finally, these studies highlight the unexpected role of time needed for the detachment–reattachment mechanism of centromere-drive. In *Mus spretus*, a more rapid Anaphase I in meiosis leaves little time for selfish centromeres to flip to the egg side. However, artificially delaying anaphase enables centromere drive to take place. Thus, selective pressures to block centromere drive may have fundamentally shaped many aspects of the cell division apparatus and its regulation in animals.

REFERENCES

1. Henikoff, S., Ahmad, K., and Malik, H.S. (2001). The centromere paradox: stable inheritance with rapidly evolving DNA. Science *293*, 1098–1102.
2. Iwata-Otsubo, A., Dawicki-McKenna, J.M., Akera, T., Falk, S.J., Chmatal, L., Yang, K., Sullivan, B.A., Schultz, R.M., Lampson, M.A., and Black, B.E. (2017). Expanded Satellite Repeats Amplify a Discrete CENP-A Nucleosome Assembly Site on Chromosomes that Drive in Female Meiosis. Curr. Biol. *27*, 2365–2373.e2368.
3. Chmatal, L., Gabriel, S.I., Mitsainas, G.P., Martinez-Vargas, J., Ventura, J., Searle, J.B., Schultz, R.M., and Lampson, M.A. (2014). Centromere strength provides the cell biological basis for meiotic drive and karyotype evolution in mice. Curr. Biol. *24*, 2295–2300.
4. Akera, T., Chmatal, L., Trimm, E., Yang, K., Aonbangkhen, C., Chenoweth, D.M., Janke, C., Schultz, R.M., and Lampson, M.A. (2017). Spindle asymmetry drives non-Mendelian chromosome segregation. Science *358*, 668–672.
5. Chmatal, L., Yang, K., Schultz, R.M., and Lampson, M.A. (2015). Spatial Regulation of Kinetochore Microtubule Attachments by Destabilization at Spindle Poles in Meiosis I. Curr. Biol. *25*, 1835–1841.
6. Akera, T., Trimm, E., and Lampson, M.A. (2019). Molecular Strategies of Meiotic Cheating by Selfish Centromeres. Cell *178*, 1132–1144.e1110.
7. Kawashima, S.A., Yamagishi, Y., Honda, T., Ishiguro, K., and Watanabe, Y. (2010). Phosphorylation of H2A by Bub1 prevents chromosomal instability through localizing shugoshin. Science *327*, 172–177.
8. Tanno, Y., Kitajima, T.S., Honda, T., Ando, Y., Ishiguro, K., and Watanabe, Y. (2010). Phosphorylation of mammalian Sgo2 by Aurora B recruits PP2A and MCAK to centromeres. Genes Dev. *24*, 2169–2179.
9. King, T.D., Leonard, C.J., Cooper, J.C., Nguyen, S., Joyce, E.F., and Phadnis, N. (2019). Recurrent Losses and Rapid Evolution of the Condensin II Complex in Insects. Mol. Biol. Evol. *36*, 2195–2204.
10. Drinnenberg, I.A., Henikoff, S., and Malik, H.S. (2016). Evolutionary Turnover of Kinetochore Proteins: A Ship of Theseus? Trends Cell Biol. *26*, 498–510.
11. Wu, T., Lane, S.I.R., Morgan, S.L., and Jones, K.T. (2018). Spindle tubulin and MTOC asymmetries may explain meiotic drive in oocytes. Nat. Commun. *9*, 2952.

Epileptic Seizures: Glia–Neuron Interactions For Better or For Worse

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Investigations of the mechanisms generating epileptic seizures have primarily focused on neurons. However, more systemic research of brain circuits has highlighted an important role of non-neuronal cells such as glia in the genesis and spreading of generalized seizures in the brain.

Epilepsy is the most common serious primary neurological disorder, and is characterized by recurrent, unforeseen and sudden changes in brain activity [1]. These epileptic seizures are marked by widespread neuronal hypersynchrony, generally in the context of an impaired excitation–inhibition balance. Clinically, epileptic seizures are varied and often categorized according to their onset and spread (i.e. generalized, focal, or secondarily generalized). Understanding

of *where* and *how* this diversity emerges, and how it is linked to putative cellular mechanisms remains challenging. Yet a detailed understanding of ictogenesis (the generation of seizures) and subsequent seizure spread across whole-brain networks is crucial to better apprehend and potentially treat epileptic seizures.

The complexity of brain wiring and dynamics often limits intuitive interpretation of empirical recordings of brain function. In the context of epilepsy, computational modelling of seizures has emerged as an innovative approach to link simple rules that are often inspired by physical systems, with observable brain dynamics, such as state transitions from well-balanced, resting brain activity to generalized hypersynchrony [2]. Interestingly, these models often involve non-neuronal states that contribute to the system's dynamics [3], indicating that synaptically coupled neurons might not be the only network to consider in ictogenesis. Computational models can allow inference of unobservable states of the system, but validating these *in silico* approaches in a genuine *in vivo* context is still tricky. Small animal models, in which brain activity can be recorded at high temporal and spatial scales and in a cell type-specific fashion are therefore of prime interest in this quest. Amidst a flurry of papers using calcium imaging to record acute seizures in zebrafish [4–6], Diaz-Vertugo *et al.* tackled this issue to study the interactive role of glial cells and neurons in the state transition toward generalized seizures in the zebrafish brain [7].

After confirming that *in vivo* calcium imaging of the larval zebrafish brain can accurately recapitulate electroencephalographic recordings, the authors elegantly utilize the model organism to follow the activity of both neurons and glial cells, respectively. This allows recording of both cell types following exposure to the proconvulsant GABA-antagonist pentylenetetrazol (PTZ). Surprisingly, they showed strong, widespread activation of a network of glia *prior* to generalization of neuronal activity, the latter being characteristic of the generalized epileptic seizures. The patterns of glial activation observed were widespread through distant regions of the brain, consistent with a highly interconnected glial network. Whereas glial activation during the pre-ictal stage seems to reduce synchronous neuronal activity, a collapse of the glia-mediated homeostatic regulation may precipitate a generalized release of glutamate in the extracellular space. This consequently triggers synchronized neuronal activity, which finally pushes the whole system into the generalized seizure state (e.g. ictal state) according to the authors (Figure 1).

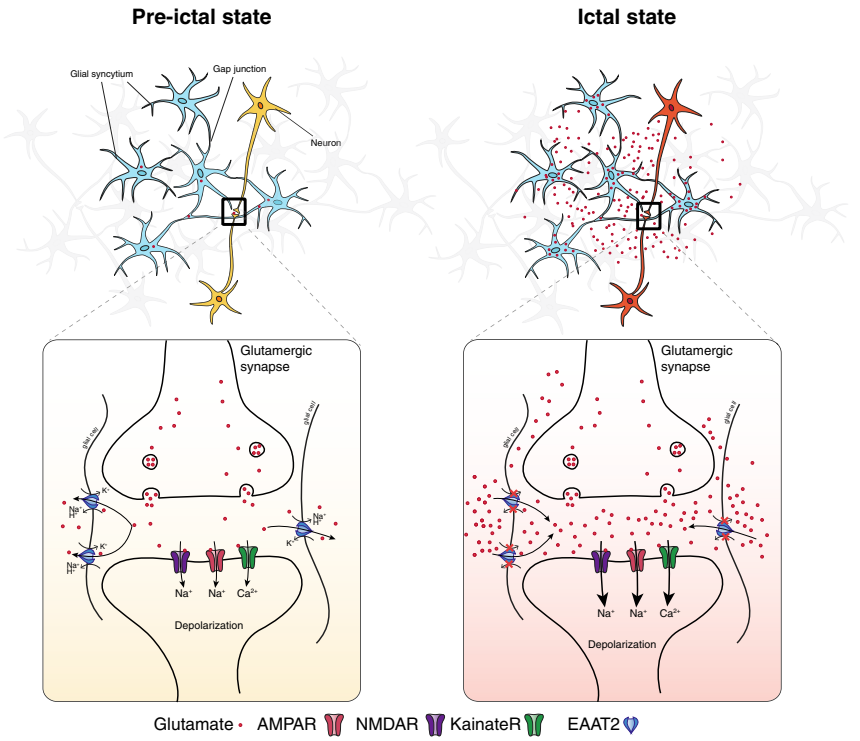

Figure 1. Schematic view of the model supported by Diaz Verdugo *et al.* describing the role of glia in the switch from pre-ictal to ictal states.
During the pre-ictal state (during which neuronal hypersynchrony is not yet generalized) astroglia dampen local excess of excitatory signaling by sequestering glutamate at the synapse through active pumping from EAAT transporters. Glutamate is stored throughout the highly connected glial syncytium over large distances. At one point, the buffering function of glia collapses leading to a broad release of glutamate throughout brain circuits ultimately initiating generalized neuronal hyperexcitation (ictal state). One possible mechanism causing the sudden collapse of glial buffering could be through the fatigue of the EAAT transporters, possibly caused by an imbalance in several ion gradients (Na^+, K^+, H^+) that are crucial for their activity.

Although the role of glia in the central nervous system has been primarily associated with physical support, it is now well established that they are master regulators of many cellular processes. These roles include metabolic support for neurons, neuro-protection, myelin wrapping, as well as supporting neurotransmission. The latter has mainly been studied at the level of the tripartite synapse where astroglia (the brain's most abundant glial cells) are often seen enveloping the synaptic cleft between pre- and postsynaptic neurons. One main function of astroglia at the synapse is to remove neurotransmitters from the cleft in between synaptic events, in order to preserve the integrity of the synaptic transmission and to prevent leakage in between them [8–10].

In the last year, zebrafish have been central to providing direct empirical evidence for a broader role of glial cells in the computation and dynamics of brain circuits. Recent work in zebrafish helped unravel a role of radial astrocytes in the integration of an adaptive behavioral response [11]. Specifically, the authors showed that radial glia are an essential computational element in a brain circuit governing adaptive behaviors (e.g. swimming inhibition after multiple failed attempts). Integrating noradrenergic

inputs, and accumulating Ca^{2+} over successive failed swimming attempts, radial glia finally relay this cumulative evidence signal to GABAergic neurons that ultimately inhibit the swimming response. This evidence positions radial glia as a main computational component of sensory-motor brain circuits. In other words, it shows that the glial network can mediate input–output transformation through an integrative process within neural networks.

Moreover, although the investigations of seizure mechanisms were originally mainly neurocentric (since neuronal firing is one main hallmark of seizures), several studies emerged in the last 15 years proposing a previously unexpected role of glia (mainly astroglia) in the genesis and maintenance of ictal discharges [12]. In particular, Tian *et al.* reported that local release of glutamate from nearby astrocytes in a calcium-dependent fashion could trigger local neuronal depolarization [13]. Consistently, experiments using an *ex vivo* model of focal seizures (rat cortex slices exposed to NMDA) showed a correlation of Ca^{2+} increase in astroglia and nearby neuronal hypersynchrony [14]. More recently, investigations in fly unraveled an involvement of glia in extracellular K^+ buffering that can modulate neuronal excitability. However, no particular Ca^{2+} activity in astrocytes was observed during inter-ictal discharges [15].

In light of this novel view of glia as part of functionally integrated cellular networks, particularly in the context of seizure pathogenesis, recognizing the functional importance of glia is becoming more pressing [16–18]. The circuit-wide effects of the dense, mainly gap junction-mediated glia-to-glia connectivity forming a glial syncytium are one of the forefronts of current research. In this context, Diaz-Vertugo *et al.*'s work provides a new perspective on how the glial syncytium could affect whole-brain dynamics, using the transition into an acutely induced generalized seizure as the empirical example. There are multiple interesting features in the dynamics of glial cells and neurons and their interactions. For example, during the pre-ictal phase, glia seem to act like a homeostatic buffer by dampening localized excess neuronal excitation. Taking advantage of the zebrafish model, where whole-brain recordings can be done at single cell resolution, they showed a broad synchronous activation of the radial glia network across large distances during this pre-ictal stage. Another interesting observation is that this glial activation collapses abruptly and is associated with excess extracellular glutamate. According to the authors, this could indicate a massive and sudden release of glutamate, triggering the generalization of the seizure in the whole brain (Figure 1). The exact mechanisms underlying the sudden collapse of glial buffering function is still not clear, although it may be linked with a chronic fatigue of ion transporters at the glial membrane. In a set of experiments, the authors suggest that the high level of connectivity of the glial network is, at least in part, responsible for the generalized neuronal excitability over large distances (thus generalized seizures). According to the authors, this is one reason why the switch from the pre-ictal to ictal phase does not follow canonical functional connectivity rules but rather appears to be broad.

Altogether, the role of glia has now become irrefutable in the origin, the spreading and the sustaining of seizures. Although glial cells can be considered as helper cells at the first stages of local neuronal state imbalances, they can later act as a foe against brain activity homeostasis on a global scale. Future work will need to investigate the dynamic relationship between glia and neurons in genetic models of epilepsy in which spontaneous and/or reflex seizures are one step closer to the genuine context of epileptic seizures. In the pursuit of this aim, genetic models of epilepsy in simple model organisms that are already available (fly and fish) will be of prime interest to advance our understanding on the role of glia in epilepsy pathogenesis. Interestingly, these insights also position glial-related pathways as a new therapeutic target aiming at alleviating both the ignition and the spreading of seizures. A recent study using fruit fly identified calcineurin as a major targetable pathway that can modulate the pathogenic role of glia in ictogenesis [15]. Thus, although the development of anti-epileptic drugs in the past has mainly revolved around specific targeted pathways (e.g., carbamazepine targeting sodium channels, methsuximide targeting calcium channels, clobazepam targeting GABA activity, and perampanel targeting glutamate receptors), these data open new doors for further development of anti-seizure medications with novel mechanisms of action.

REFERENCES

1. Fisher, R.S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J.H., Elger, C.E., Engel, J., Jr., Forsgren, L., French, J.A., Glynn, M., *et al*. (2014). ILAE official report: a practical clinical definition of epilepsy. Epilepsia *55*, 475–482.

2. Lopes da Silva, F., Blanes, W., Kalitzin, S.N., Parra, J., Suffczynski, P., and Velis, D.N. (2003). Epilepsies as dynamical diseases of brain systems: basic models of the transition between normal and epileptic activity. Epilepsia *44* (*Suppl 12*), 72–83.

3. Ullah, G., and Schiff, S.J. (2010). Assimilating seizure dynamics. PLoS Comput. Biol. *6*, e1000776.

4. Turrini, L., Fornetto, C., Marchetto, G., Mullenbroich, M.C., Tiso, N., Vettori, A., Resta, F., Masi, A., Mannaioni, G., Pavone, F.S., *et al*. (2017). Optical mapping of neuronal activity during seizures in zebrafish. Sci. Rep. *7*, 3025.

5. Rosch, R.E., Hunter, P.R., Baldeweg, T., Friston, K.J., and Meyer, M.P. (2018). Calcium imaging and dynamic causal modelling reveal brain-wide changes in effective connectivity and synaptic dynamics during epileptic seizures. PLoS Comput. Biol. *14*, e1006375.

6. Liu, J., and Baraban, S.C. (2019). Network properties revealed during multi-scale calcium imaging of seizure activity in zebrafish. eNeuro. *6*, e0041–19.2019.

7. Diaz Verdugo, C., Myren-Svelstad, S., Aydin, E., Van Hoeymissen, E., Deneubourg, C., Vanderhaeghe, S., Vancraeynest, J., Pelgrims, R., Cosacak, M.I., Muto, A., *et al*. (2019). Glia-neuron interactions underlie state transitions to generalized seizures. Nat. Commun. *10*, 3830.

8. Perea, G., Navarrete, M., and Araque, A. (2009). Tripartite synapses: astrocytes process and control synaptic information. Trends Neurosci. *32*, 421–431.

9. Dallerac, G., Chever, O., and Rouach, N. (2013). How do astrocytes shape synaptic transmission? Insights from electrophysiology. Front. Cell Neurosci. *7*, 159.

10. Deemyad, T., Luthi, J., and Spruston, N. (2018). Astrocytes integrate and drive action potential firing in inhibitory subnetworks. Nat. Commun. *9*, 4336.

11. Mu, Y., Bennett, D.V., Rubinov, M., Narayan, S., Yang, C.T., Tanimoto, M., Mensh, B.D., Looger, L.L., and Ahrens, M.B. (2019). Glia accumulate evidence that actions are futile and suppress unsuccessful behavior. Cell *178*, 27–43.e19.

12. Patel, D.C., Tewari, B.P., Chaunsali, L., and Sontheimer, H. (2019). Neuron–glia interactions in the pathophysiology of epilepsy. Nat. Rev. Neurosci. *20*, 282–297.

13. Tian, G.F., Azmi, H., Takano, T., Xu, Q., Peng, W., Lin, J., Oberheim, N., Lou, N., Wang, X., Zielke, H.R., *et al*. (2005). An astrocytic basis of epilepsy. Nat. Med. *11*, 973–981.

14. Gomez-Gonzalo, M., Losi, G., Chiavegato, A., Zonta, M., Cammarota, M., Brondi, M., Vetri, F., Uva, L., Pozzan, T., de Curtis, M., *et al*. (2010). An excitatory loop with astrocytes contributes to drive neurons to seizure threshold. PLoS Biol. *8*, e1000352.

15. Weiss, S., Melom, J.E., Ormerod, K.G., Zhang, Y.V., and Littleton, J.T. (2019). Glial Ca(2+) signaling links endocytosis to K(+) buffering around neuronal somas to regulate excitability. eLife *8*, e44186.

16. Adamsky, A., Kol, A., Kreisel, T., Doron, A., Ozeri-Engelhard, N., Melcer, T., Refaeli, R., Horn, H., Regev, L., Groysman, M., *et al*. (2018). Astrocytic activation generates de novo neuronal potentiation and memory enhancement. Cell *174*, 59–71.e14.

17. Pabst, M., Braganza, O., Dannenberg, H., Hu, W., Pothmann, L., Rosen, J., Mody, I., van Loo, K., Deisseroth, K., Becker, A.J., *et al*. (2016). Astrocyte intermediaries of septal cholinergic modulation in the hippocampus. Neuron *90*, 853–865.

18. Srinivasan, R., Huang, B.S., Venugopal, S., Johnston, A.D., Chai, H., Zeng, H., Golshani, P., and Khakh, B.S. (2015). Ca(2+) signaling in astrocytes from Ip3r2(-/-) mice in brain slices and during startle responses in vivo. Nat. Neurosci. *18*, 708–717.