EBioMedicine 7 (2016) 19–20

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Early Life Seizures and Learning Impairment: Neither the Time nor the Place

Steven N. Roper

Department of Neurological Surgery, University of Florida, 1149 South Newell Drive, Gainesville, FL 32611, USA

ARTICLE INFO

Available online 4 May 2016

Children who experience early life seizures, prolonged febrile convulsions being the most common scenario, often have demonstrable problems with learning and memory later in life (Martinos et al., 2012). Although some of the children may go on to have epilepsy (recurrent unprovoked seizures) later in life, the problem with memory does not seem to be dependent on these subsequent seizures. What happens during this relatively brief storm of electrical activity in the brains of children that can have such a lasting effect on cognition? That is the basic question that the current paper by Barry et al. (2016) attempts to address. They have focused not on the initial insult but on the complex neuronal processes that control learning and memory months after the seizure event.

In the model used, immature (P10) rats were exposed to a period of elevated temperature for about half an hour. This produces a period of febrile status epilepticus (FSE) that is similar in many respects to the seizures that children can experience — albeit at the severe end of the spectrum. The rats do not show evidence of neuronal death or brain structure abnormalities (Dube et al., 2004). However, the neurons of the hippocampal region definitely show abnormalities in terms of excitability (Chen et al., 2001), but how this translates into chronic cognitive changes is still unclear. Some of the rats go on to develop epilepsy; however, as animal models of epilepsy go, the subsequent seizures are relatively rare. So, the late changes in learning in memory that are seen in this model are not likely due to actual loss of any neurons or due to the effect of late seizures; they are the chronic residue of the initial FSE episode.

In the present study, two months after the FSE event, treated rats can be divided into those that can learn a complex avoidance task and those that can't. The task involves navigating around a rotating disc in which one sector, which remains constant with respect to the larger environment (i.e., the room), is associated with an electric shock. This is a test of learning and memory that is highly dependent on the hippocampus and the action of hippocampal place cells — the ingenious cells that fire preferentially when an animal occupies only certain areas in its environment (O'Keefe and Dostrovsky, 1977). Control animals easily learned to avoid this sector over the course of (less than) fifteen trials whereas the treated rats fall into one of two groups: learners (FSE-L) and non-learners (FSE-NL). One of the interesting secondary findings of the current study is that, although the FSE-L rats learn to avoid the "hot" sector, their strategies for exploration and avoidance are different than the controls.

Three months after the FSE episode, the animals' hippocampal activity was recorded. The animals were allowed to forage for randomly dropped pellets and then exposed to the avoidance test again. Predictably, the non-learners did poorly in the avoidance task. At the cellular level, the non-learners did possess place cells in both CA1 and CA3; however, the CA1 place cells did not have any preference for firing in relation to the hippocampal theta rhythm. This is very important since this relationship is known to be critical for an animal to assess and remember where it is as it maps out its environment (Buzsaki, 2002). CA1 place cells in Controls and FSE-L rats did show a theta phase preference that shifted to align more closely with CA3 place cells when the rats went from the foraging task to the avoidance task (i.e., remembering the prior experience from a month ago). CA1 place cells in the FSE-NL rats continued to show no theta preference during the avoidance task, just as in the foraging task. So the question remains: Are these rats stupid or just lost? As I have occasionally been reminded on summer driving vacations by close family members, the distinction can, at times, be a subtle one. To follow the analogy, I think "lost" is more appropriate for the non-learners. Obviously, since they never learned the avoidance task, they couldn't be expected to remember it a month later. The CA1 data seem to support this. Although the place cells exist, something critical is missing in their ability to interact with the local network in the form of the hippocampal theta rhythm. In addition, the authors show problems in the way that CA1 and CA3 interact in the non-learners. So while the rats aren't wandering aimlessly — since they find and eat the pellets that are presented during the foraging task — they don't seem to be making sense of their spatial environment in the same way that the controls and FSE-L rats do.

Barry and colleagues have successfully used sophisticated and demanding in vivo recording techniques to correlate behavior and brain function at the mesoscale level. This is but one example of the power of those techniques that attempt the difficult task of bridging the behavior of single cells with large ensembles of neurons regionally and across

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2016.03.039.

http://dx.doi.org/10.1016/j.ebiom.2016.05.001

the brain with a goal of better understanding behavior and cognition under normal and pathological conditions (Voytek and Knight, 2015). It is likely too early to make any direct comparisons between the non-learner rats and children with learning problems after early life seizures. But the uncoupling of CA1 place cell firing and the hippocampal theta rhythm provides a compelling confirmation that early life seizures have a lasting deleterious effect on hippocampal function. Like any good study, it raises more questions than it answers. But the authors have provided a number of tantalizing findings both in the FSE learners and FSE non-learners that will serve as a foundation for future studies that may ultimately inform diagnosis or treatment of patients who develop or are at risk of developing cognitive dysfunctions stemming from early life FSE.

Conflicts of Interest

The author declares no conflict of interest.

References

Barry, J.M., Sakkaki, S., Barriere, S.J., Patterson, K.P., Lenck-Santini, P.P., Scott, R.C., Baram, T.Z., Holmes, G.L., 2016. Temporal coordination of hippocampal neurons reflects cognitive outcome post-febrile status epilepticus. EBioMedicine 7, 175–190.
Buzsaki, G., 2002. Theta oscillations in the hippocampus. Neuron 33, 325–340.
Chen, K., Aradi, I., Thon, N., Eghbal-ahmadi, M., Baram, T.Z., Soltesz, I., 2001. Persistently modified h-channels after complex febrile seizures convert the seizure-induced enhancement of inhibition to hyperexcitability. Nat. Med. 7, 331–337.
Dube, C., Yu, H., Nalcioglu, O., Baram, T.Z., 2004. Serial MRI after experimental febrile seizures: altered T2 signal without neuronal death. Ann. Neurol. 56, 709–714.
Martinos, M.M., Yoong, M., Patil, S., Chin, R.F., Neville, B.G., Scott, R.C., de Haan, M., 2012. Recognition memory is impaired in children after prolonged febrile seizures. Brain 135, 3153–3164.
O'Keefe, J., Dostrovsky, J., 1977. The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res. 34, 171–175.
Voytek, B., Knight, R.T., 2015. Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. Biol. Psychiatry 77, 1089–1097.