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Structural factors leading to changes in persistent activity following focal-trauma and neurodegeneration

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Considerable research efforts have focused on the molecular mechanisms of epilepsy following trauma and neurodegeneration. In contrast to this cell-centric approach, we present a range of computational network models demonstrating that architectural factors may be critical to understanding seizure susceptibility and other changes in neural dynamics.

The models consisted of large recurrent networks of up to 10,000 spiking neurons that included both inhibitory and excitatory populations with inter-layer and columnar intra-layer connectivity. Layers were toroidal so that initial networks were homogeneous and without edges. We examined the effects of both localized and diffuse cell deletions. In the first case cells were removed at adjacent locations to emulate focal trauma. In the case of diffuse cell deletion we randomly deleted cells throughout the network. In both types of simulations, the properties of remaining cells were held constant in order to establish that changes in dynamics were indeed network-level effects and that the alterations in connectivity were the critical factor in any threshold change.

Simulations in the focal model confirmed that confined alterations in structure were sufficient to change the threshold of an entire network. We found that the lesion site acted both as an initiation point of oscillatory activity as well as a locus that increased the probability that existing waves will continue propagating. The localized deletions models thus demonstrate the possibility that structural factors may be sufficient to account for the focal activity seen in early post-traumatic epilepsy.

The diffuse cell deletions correspond to changes following cell death in aging and neurodegenerative conditions. Here we found that high levels of diffuse deletions (70–90%), representing extensive cell death, resulted in activity settling to repetitive patterns (limit-cycle oscillations). The changes in activity seen in these diffuse lesion models may thus help explain the increased incidence of epilepsy with aging. That is, such seizures may be caused by structural network changes due to age-related cell death rather than pathology in surviving cell properties.

Interestingly, the heterogeneity of connectivity that accompanied lower levels of diffuse deletions (40%) actually encouraged complex persistent activity often associated with healthy cognitive processing suggesting that heterogeneity in structure may play an important role in initiating and maintaining such activity. It is also notable that shifts in population dynamics took place independently of changes to inhibitory-excitatory balance and did not require complex connectivity assumptions (e.g., small-world networks). That is, the propensity for activity

to persist could be varied by structural changes as simple as random deletions.

The findings suggest that structural considerations may be fundamental to our understanding of trauma and age-related epileptogenesis and that we may need to look beyond intrinsic cell properties or inhibitory-excitatory balance in order to identify potential therapies.