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EXPERIMENTAL AND HUMAN EPILEPTOGENIC CIRCUITS AS SOURCES OF COMPLEXITY AND EMERGENT PROPERTIES SUITABLE FOR NEURAL NETWORK MODELING

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Content:

RATIONALE:
The brain is a complex system, e.g. made of many parts that interfere with each other, able to produce emergent properties such as in activity-dependent plasticity. Epilepsies are neurological syndromes reaching local to widespread brain circuits. Current data support that epilepsies might be mal-adaptive emergent properties of altered brain complex systems.

METHODS:
In order to verify if the brain and epileptogenic networks are complex systems able to produce epilepsies as emergent properties we used video recordings of seizures from mesial temporal lobe epilepsy (mTLE) patients, from models such as acute and kindled audiogenic seizures, amygdala electrical kindling (ARK), Status Epilepticus (SE) and spontaneous recurrent seizures (SRS) induced by electrical/chemical manipulations of limbic areas. In patients we used video and ictal SPECT and in animals video-EEG and wavelet transform. We used also Fos, NPY and doublecortin (DCX) immuno-histochemistry, Nissl, neo-Timm and Fluorojade (FJ) histochemistry and zinc chelation in ARK. At the neural networks level we use statistical, mathematical and computational techniques.

RESULTS:
In mTLE patients we categorized ictal semiology and SPECT hemodynamics in 54 brain regions highlighted, for example, ipsilateral basal ganglia hyperperfusion linked to contralateral upper limb automatisms. In animals, acute audiogenic seizures are the signature of a brainstem-dependent complex system and limbic seizures evoked by audiogenic kindling are emergent properties of a brainstem-forebrain complex. Systemically or locally applied drugs such as pilocarpine (PILO) or electrical limbic stimulation evoke SE and SRS. At the circuit level, although SE and ARK seem extremely different, e.g. Fos expression is weaker in the ARK than in the SE model, wavelet EEG analysis did not show differences during limbic seizures of similar severity. Electrical stimulation of amygdala induces two different types of SE at behavioral and structural levels. At the cellular level, neurodegeneration and mossy fiber sprouting were detected after SE induced by PILO but not after audiogenic kindling or SE from electrical amygdala stimulation. In the latter, an interesting increase in NPY expression, an endogenous anticonvulsant, was present. BrdU+ cell proliferation appeared after audiogenic kindling and DCX+ alterations of dendritic branching after PILO-induced SE, contrasting with selective FJ+ or Nissl+ neurodegeneration after SE. Zinc chelation did not block ARK progression but decreased seizure duration. Preliminary computational analysis using ARK EEG shows that data mining is reliable for predictions based on epileptogenic signatures.

CONCLUSIONS:
Multilevel data analysis, from human to experimental models, strongly support that epilepsies are brain complex systems with mal-adaptive plasticity as emergent properties at behavioral, circuits and cellular levels. The organization of these data is fundamental to do synthesis and to further test if epilepsy-related alterations are fitting models such as small world brain networks.

FIGURES:

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