

Synaptic Ultrastructural Alterations in Human Focal Cortical Dysplasia: Insights from Volume EM

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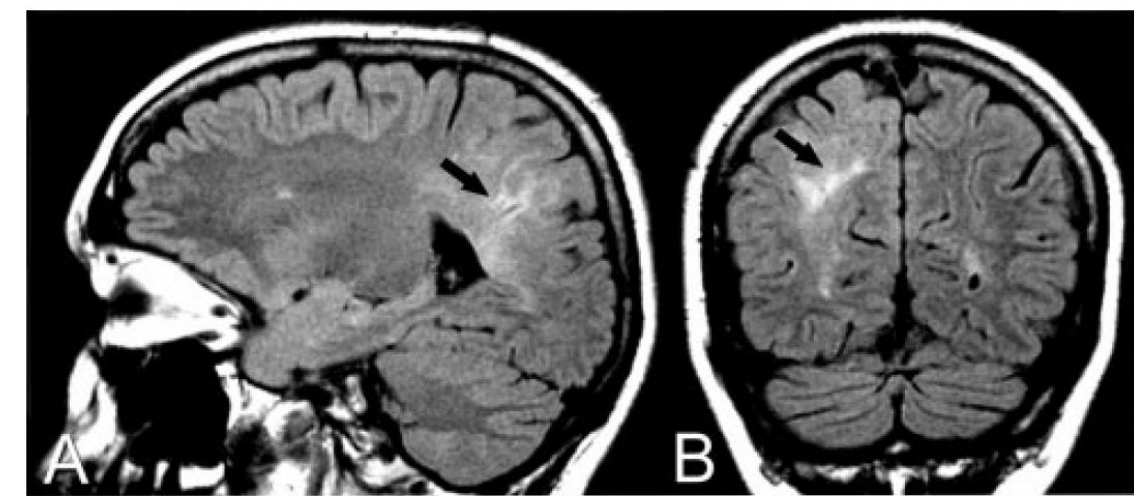
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Abstract

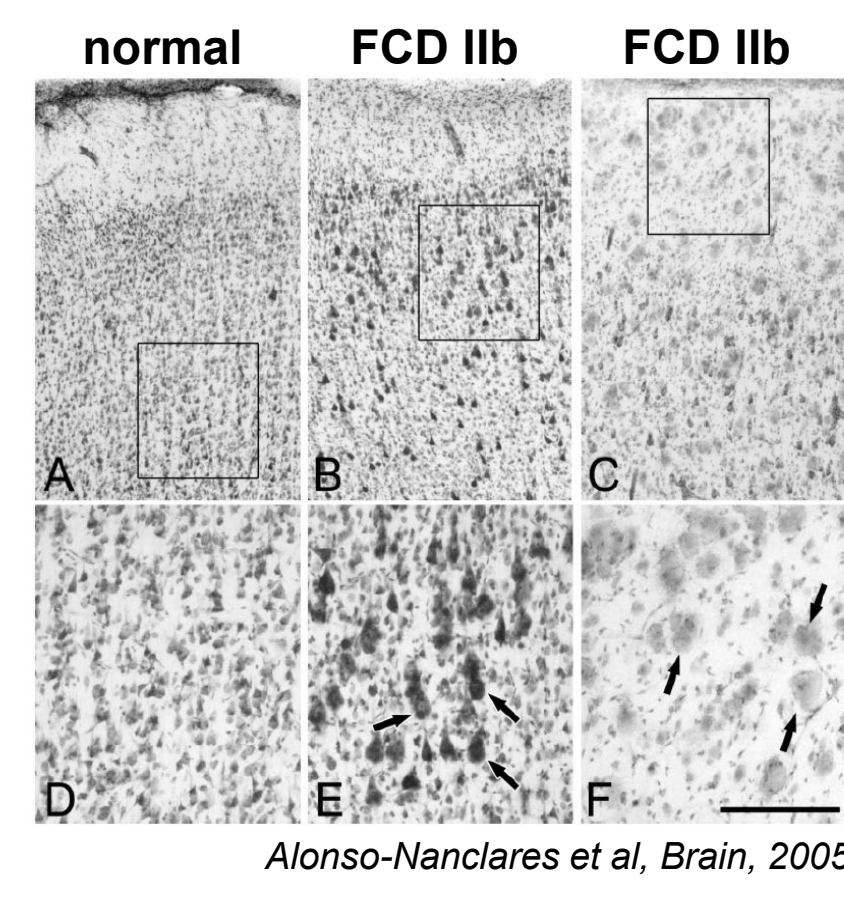
Focal cortical dysplasia (FCD) is a developmental disorder of the cerebral cortex and a leading cause of drug-resistant epilepsy in children and young adults. A disrupted excitation-inhibition (E-I) balance is a hallmark of neuronal hyperexcitability in FCD, yet the underlying synaptic ultrastructural alterations remain poorly understood. Using volume electron microscopy, we performed a detailed morphological assessment of synaptic density, size, and organelle distribution within synapses in the temporal cortical layer III of an FCD patient. Our quantitation revealed a reduced density of inhibitory (symmetric) synapses on pyramidal neuron cell bodies. Notably, the dysplastic region displayed a lower density of excitatory (asymmetric) synapses but contained extra-large excitatory synapses, which contained an increased number of synaptic vesicles. Additionally, inhibitory synapses were located further away from the nearest excitatory synapses along distal dendrites, possibly weakening the effectiveness of shunting inhibition in the dysplastic area. There was also a decrease in presynaptic boutons housing mitochondria and in postsynaptic protrusions containing a spine apparatus, pointing to potential deficits in intracellular calcium handling and synaptic plasticity in the epileptogenic area. Moreover, maladaptive myelination was a prominent feature in the dysplastic region. These findings collectively indicate that synaptic architectural modifications may contribute to the neuronal hyperexcitability associated with epilepsy in FCD.

Introduction

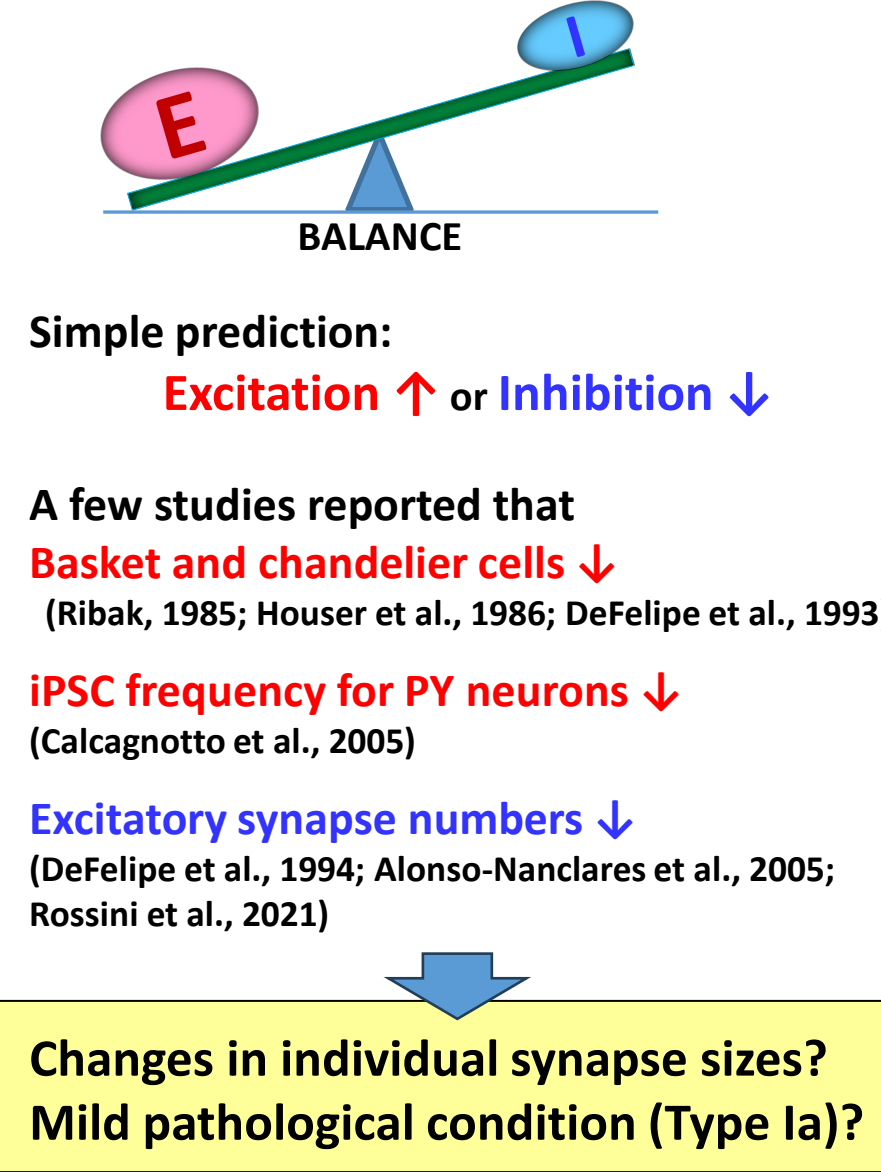
Focal Cortical Dysplasia (FCD)



- A developmental disorder of the cerebral cortex and a leading cause of drug-resistant epilepsy in children and young adults
- Treatment: anti-epileptic drugs, DBS, VNS, brain surgery

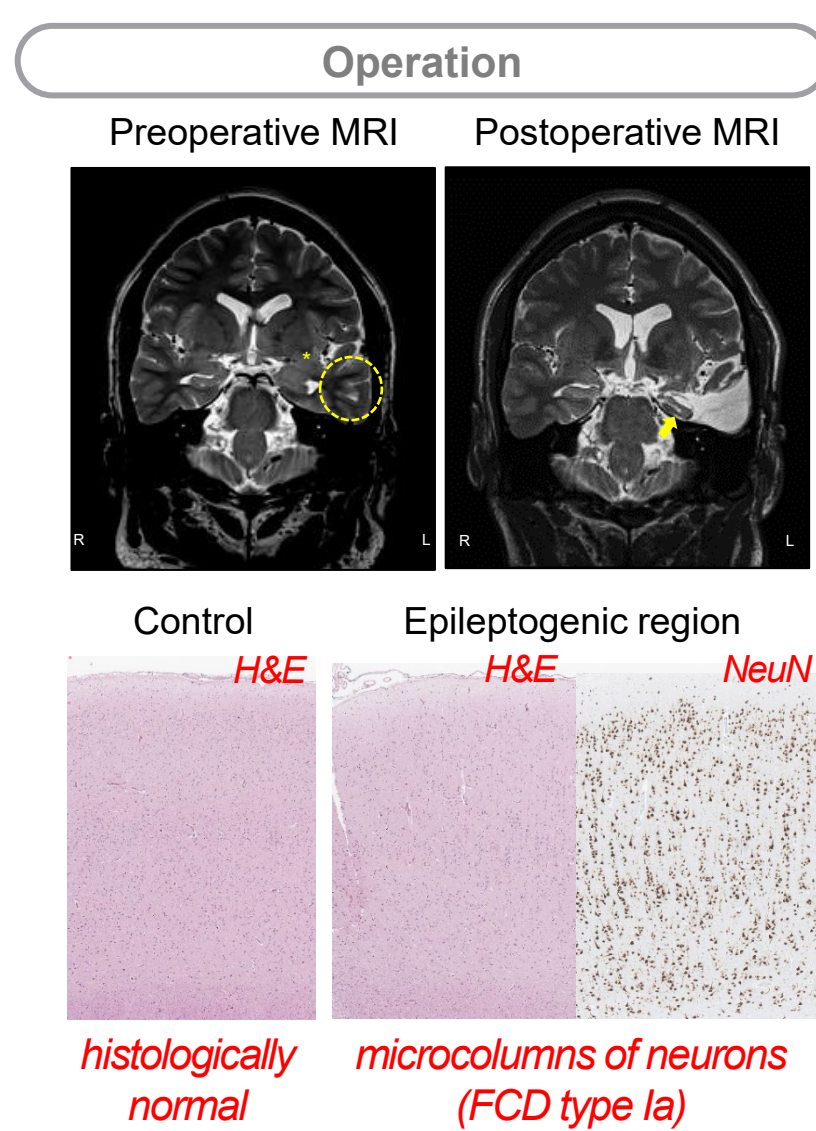


- Disrupted laminar organization
- Dysmorphic giant pyramidal neurons
- Balloon cells

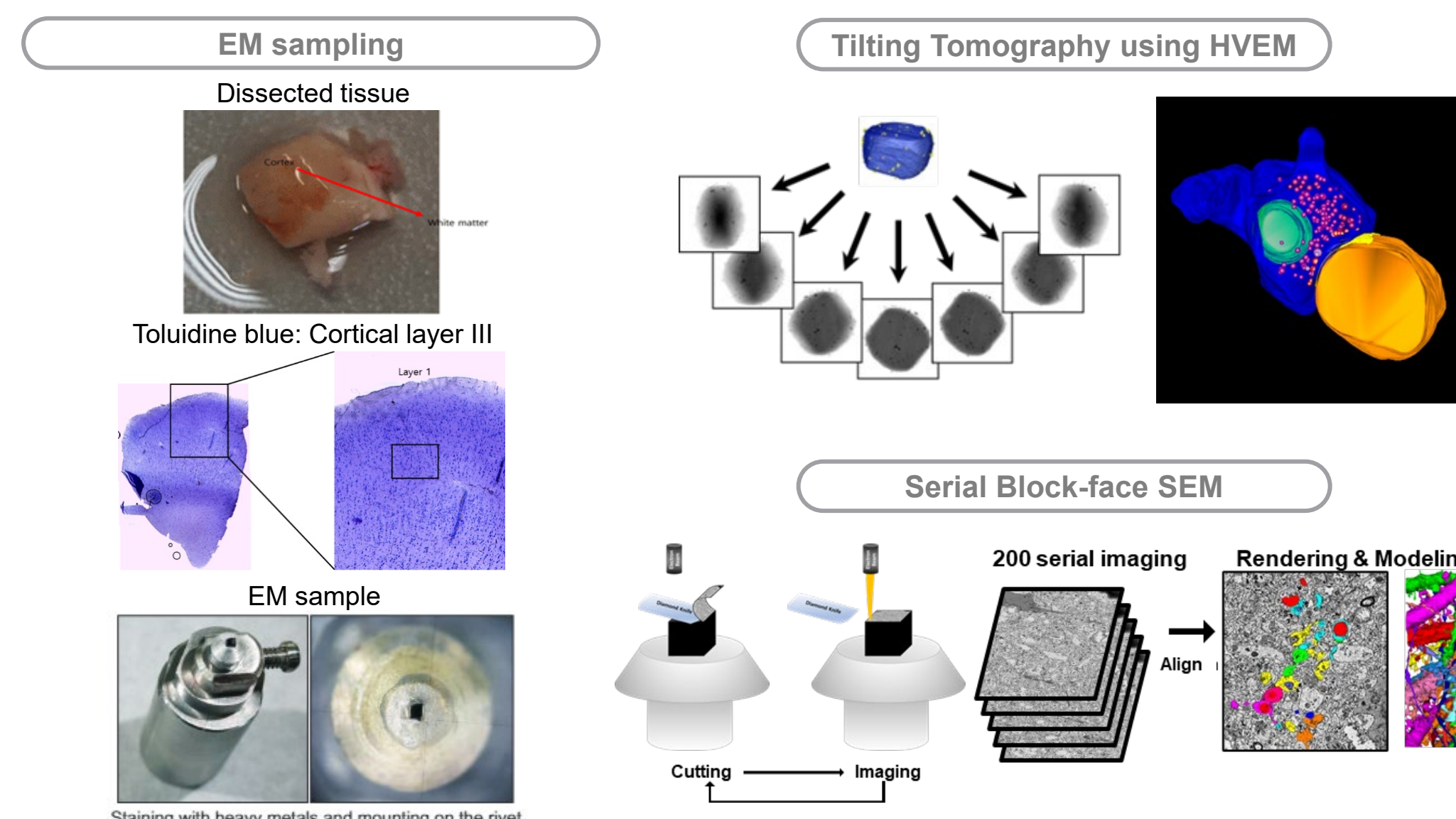


Methods

Biopsy Sample



Volume Electron Microscopy



Results

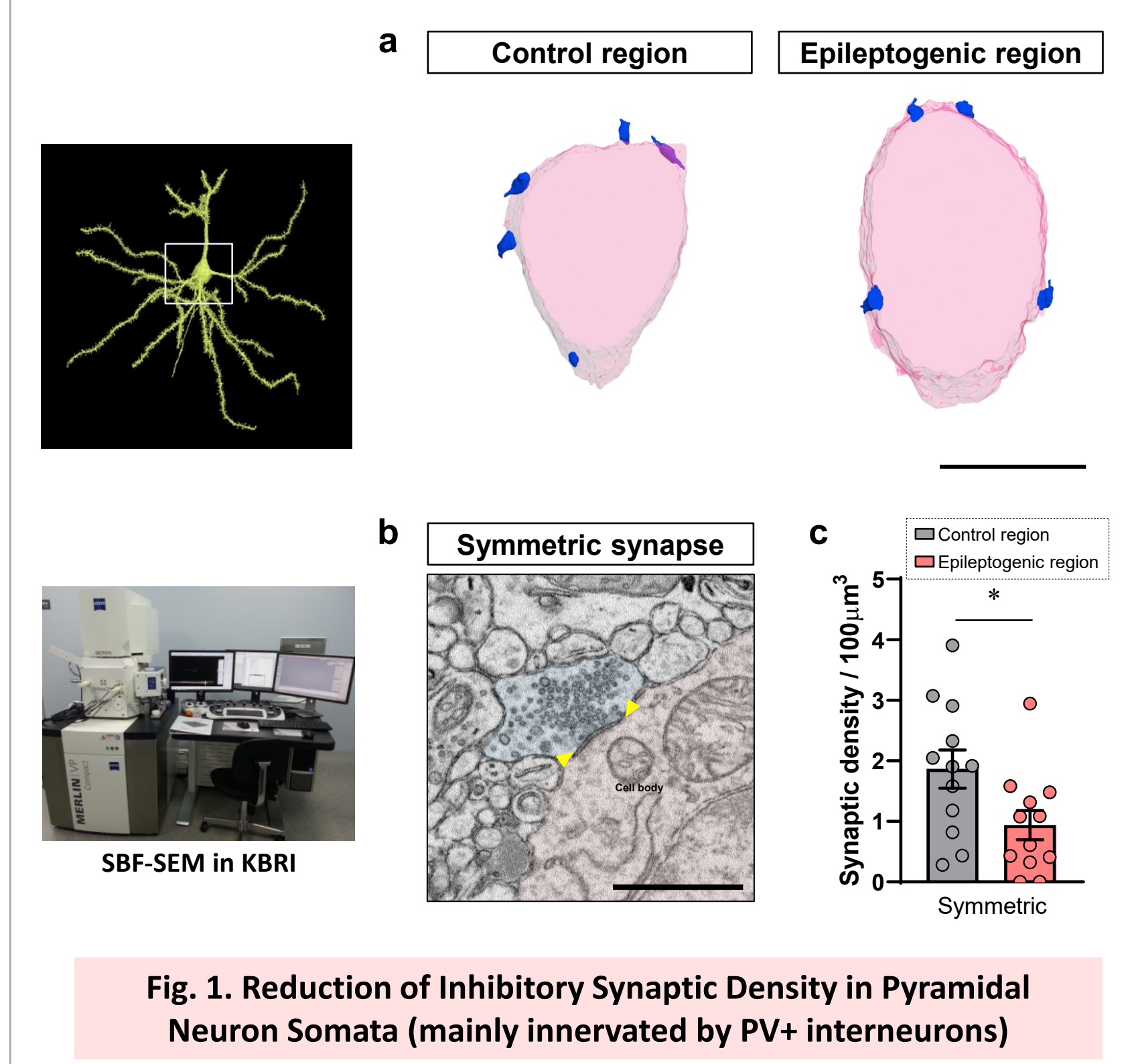


Fig. 1. Reduction of Inhibitory Synaptic Density in Pyramidal Neuron Somata (mainly innervated by PV+ interneurons)

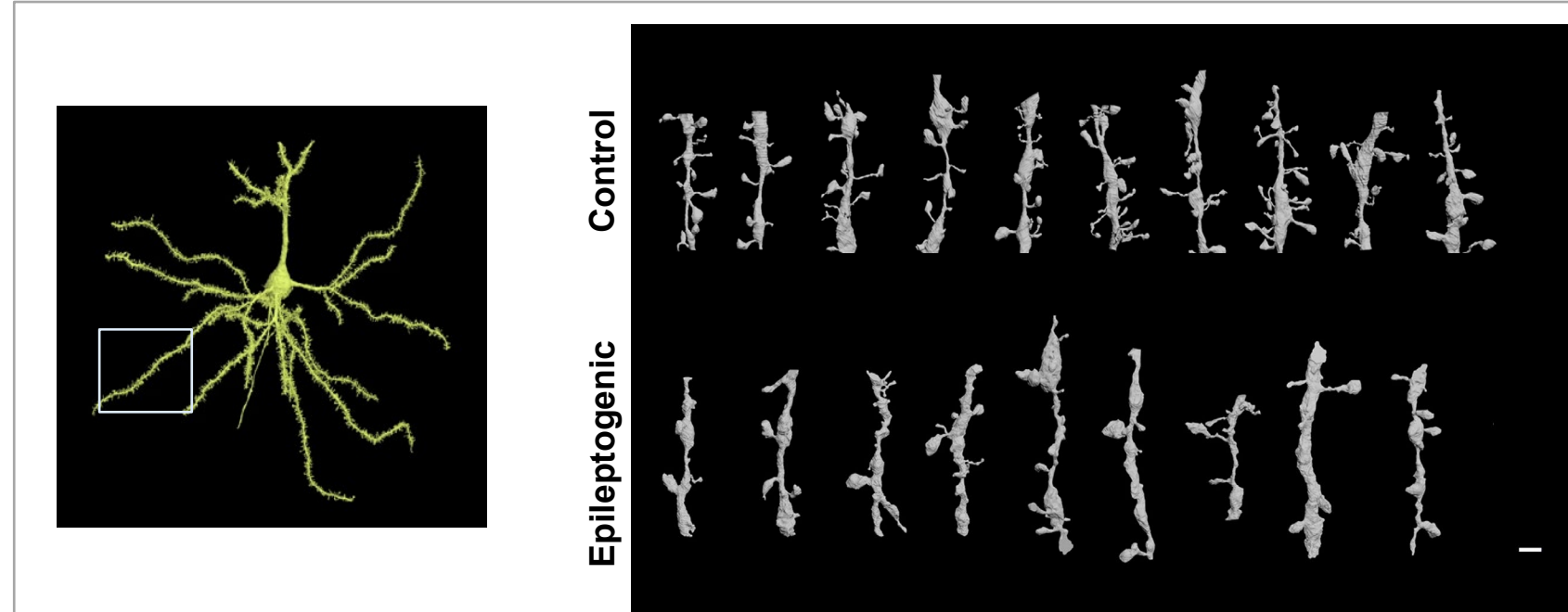


Fig. 2. Serial Block-face SEM Imaging and 3D Reconstruction of Distal Dendritic Segments with Excitatory Synapses

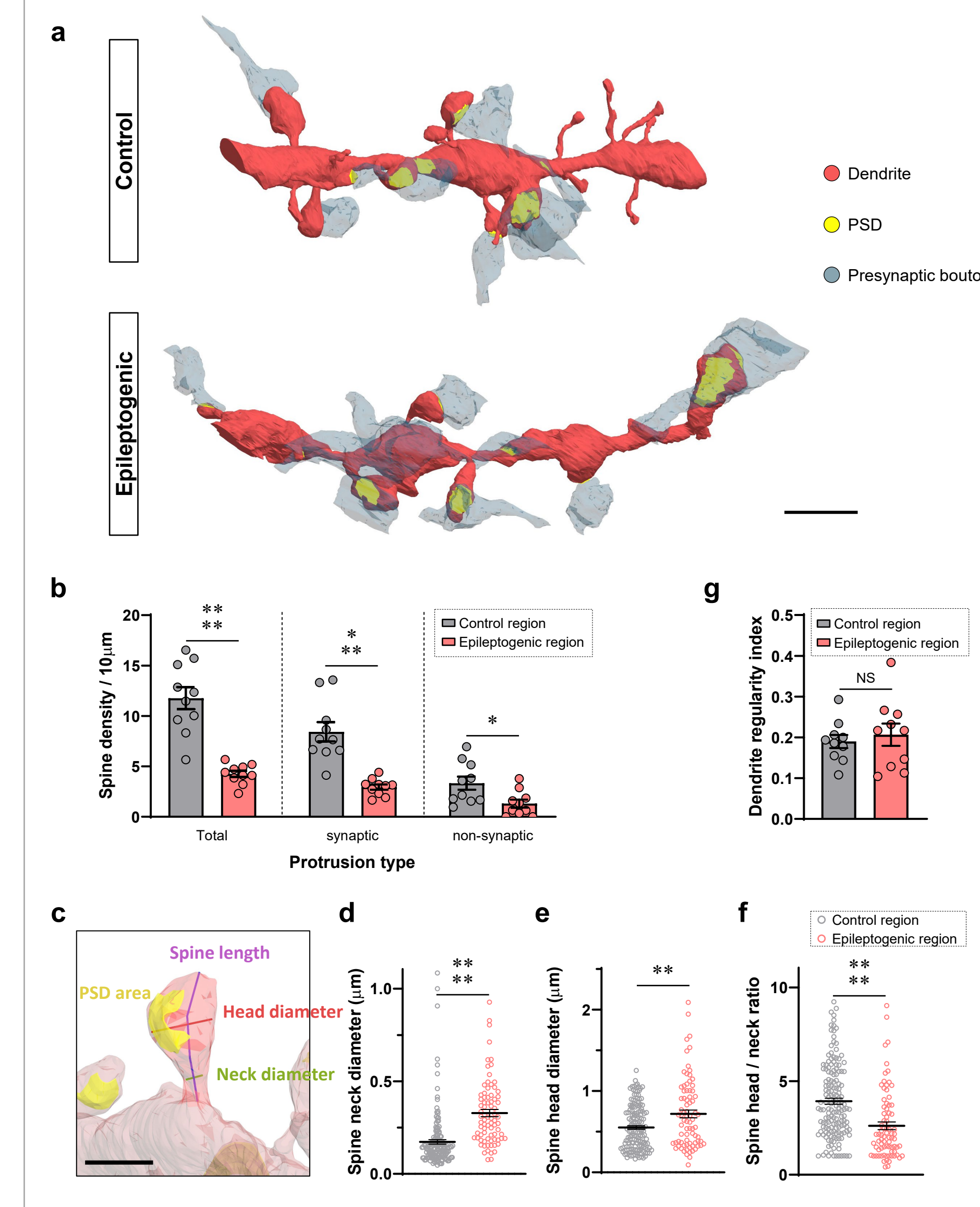


Fig. 3. Reduced spine density and abnormal spine enlargement in the epileptic cortex

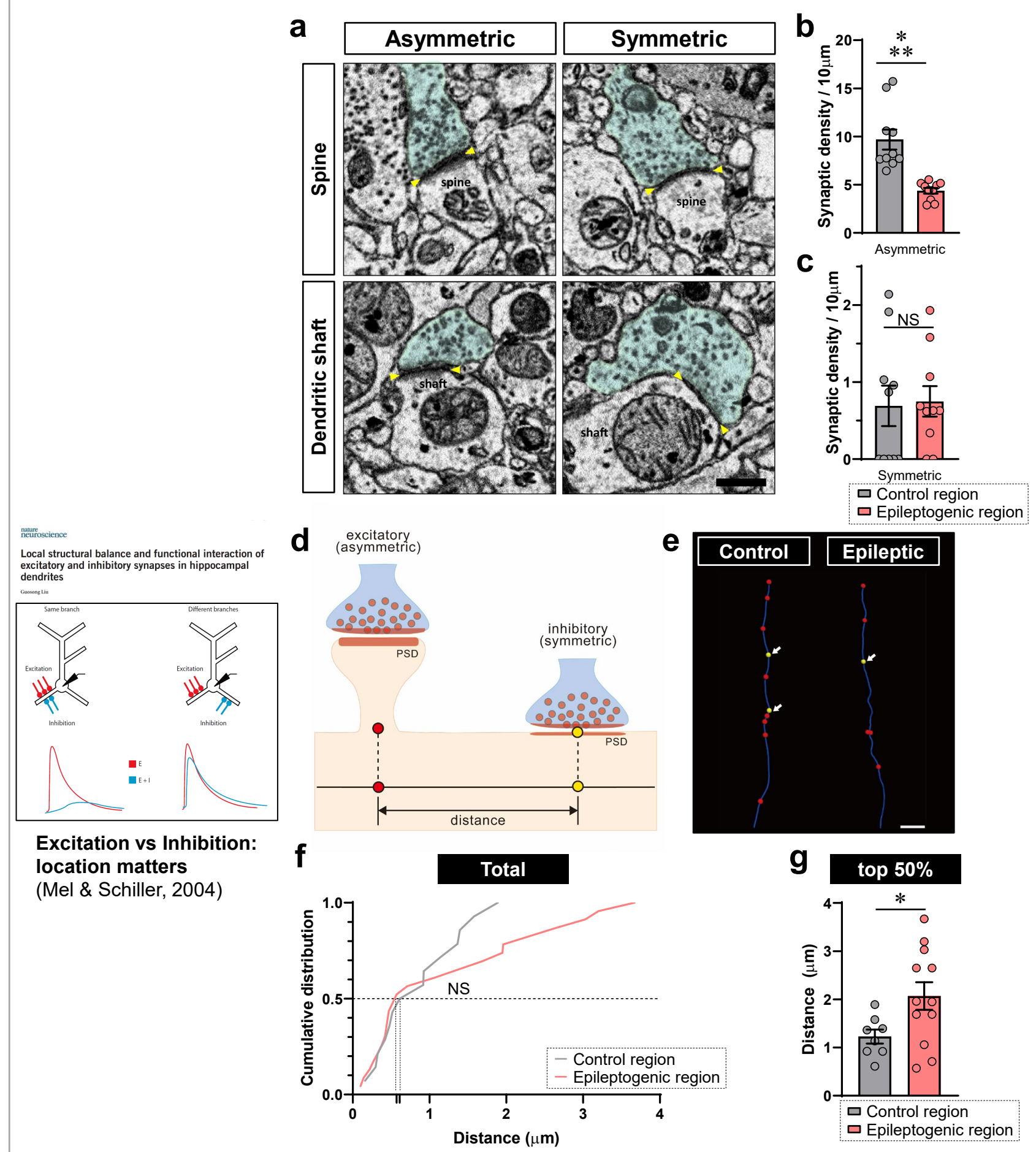


Fig. 5. Spatial distribution of excitatory and inhibitory synapses along distal dendrites

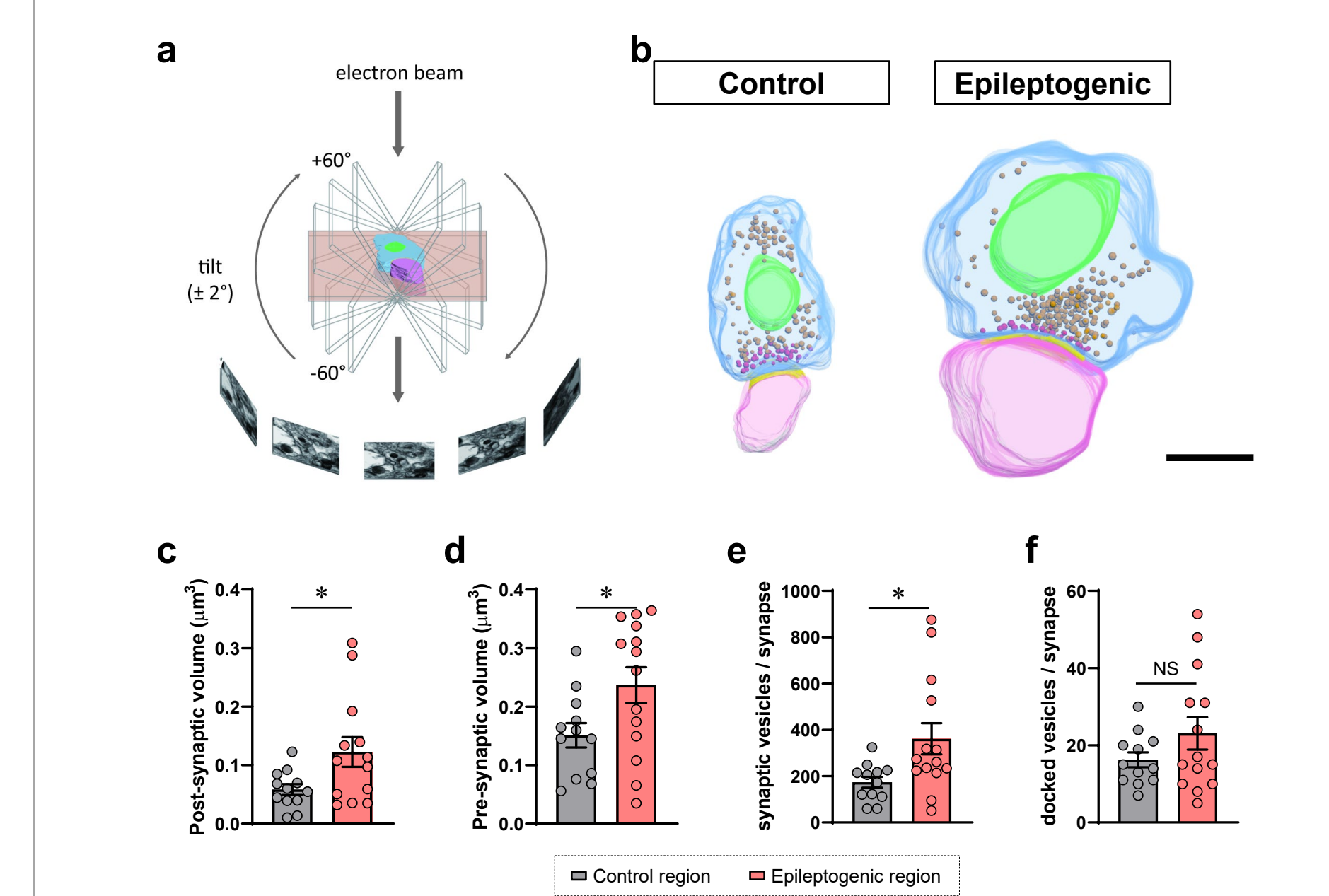


Fig. 6. Enlarged excitatory synapses with increased vesicles in the epileptogenic area

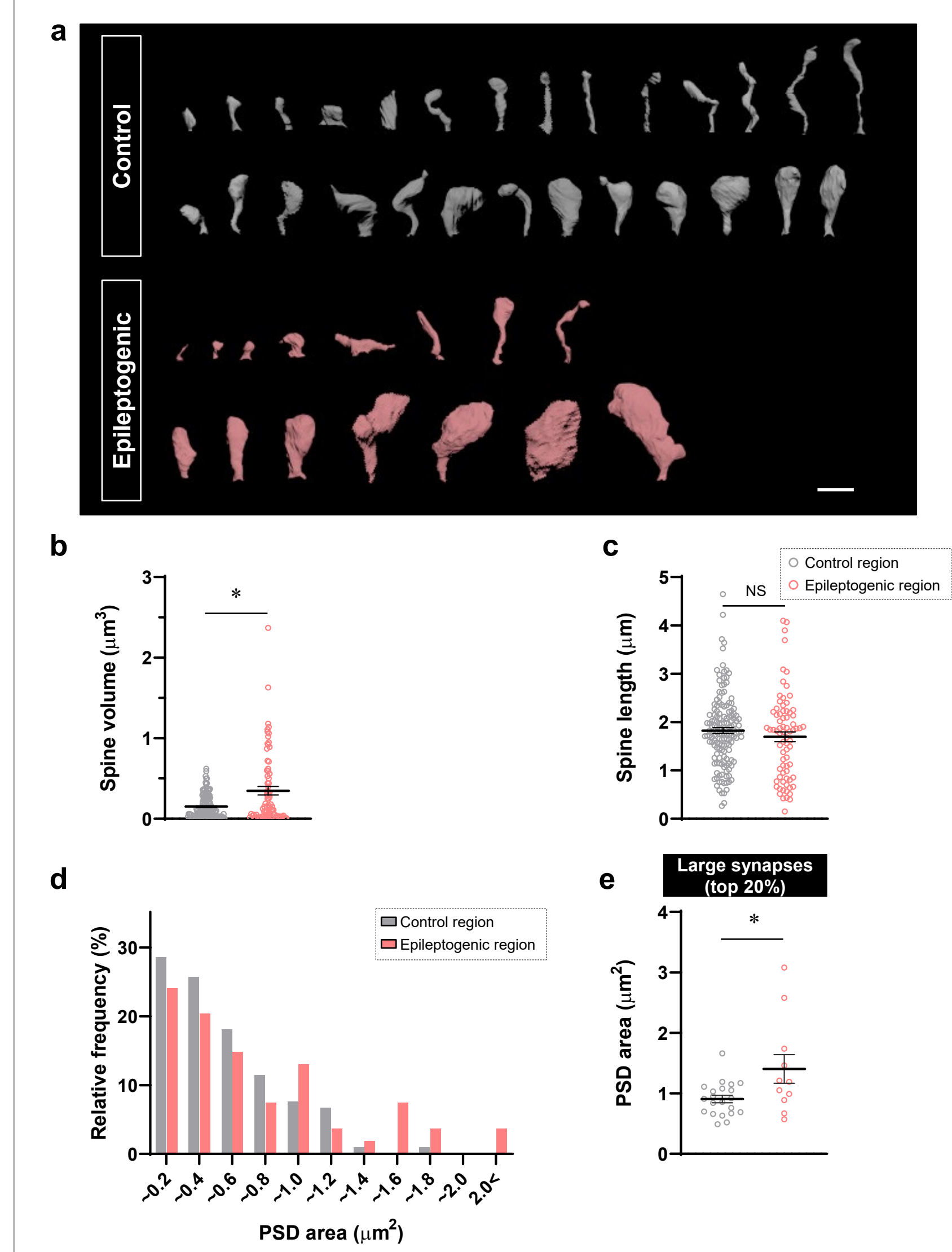
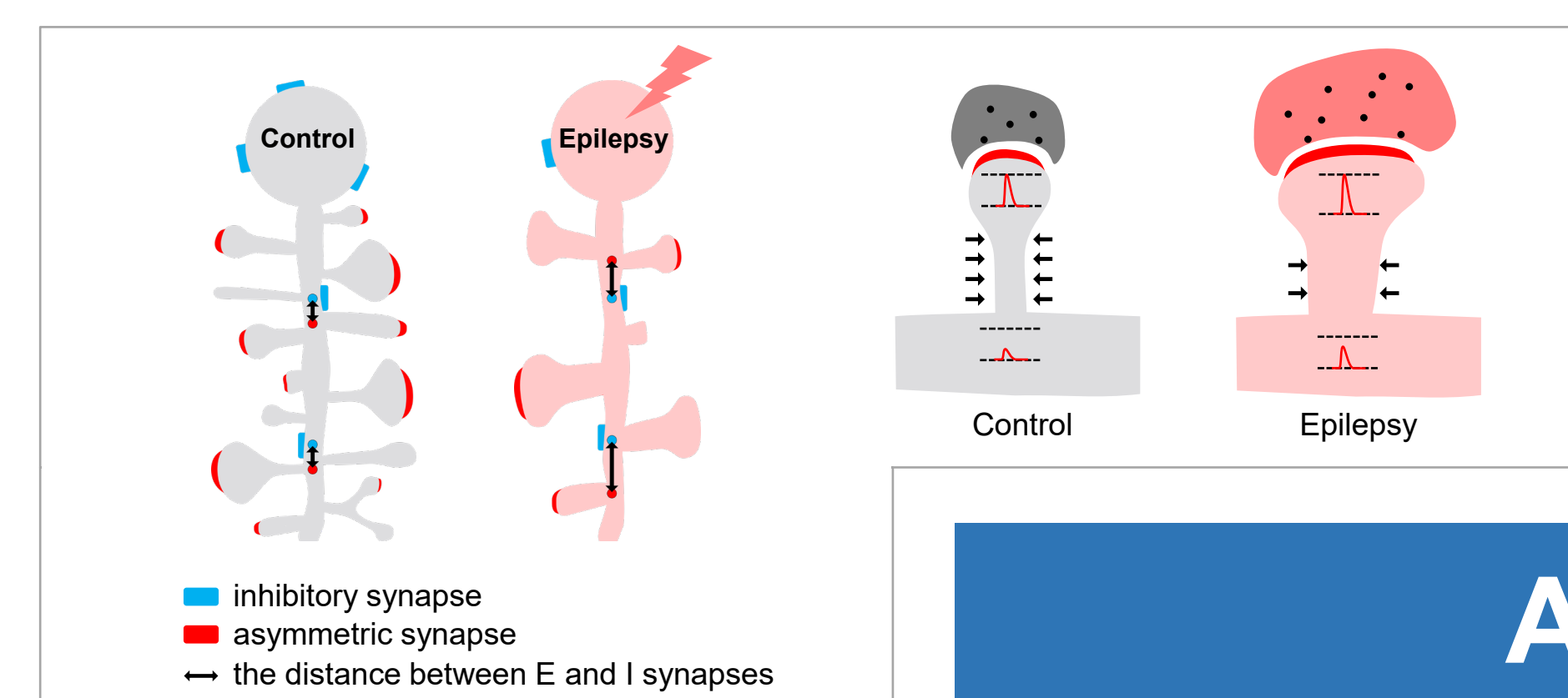


Fig. 4. Abnormal Enlargement of Spines in the Epileptogenic Region

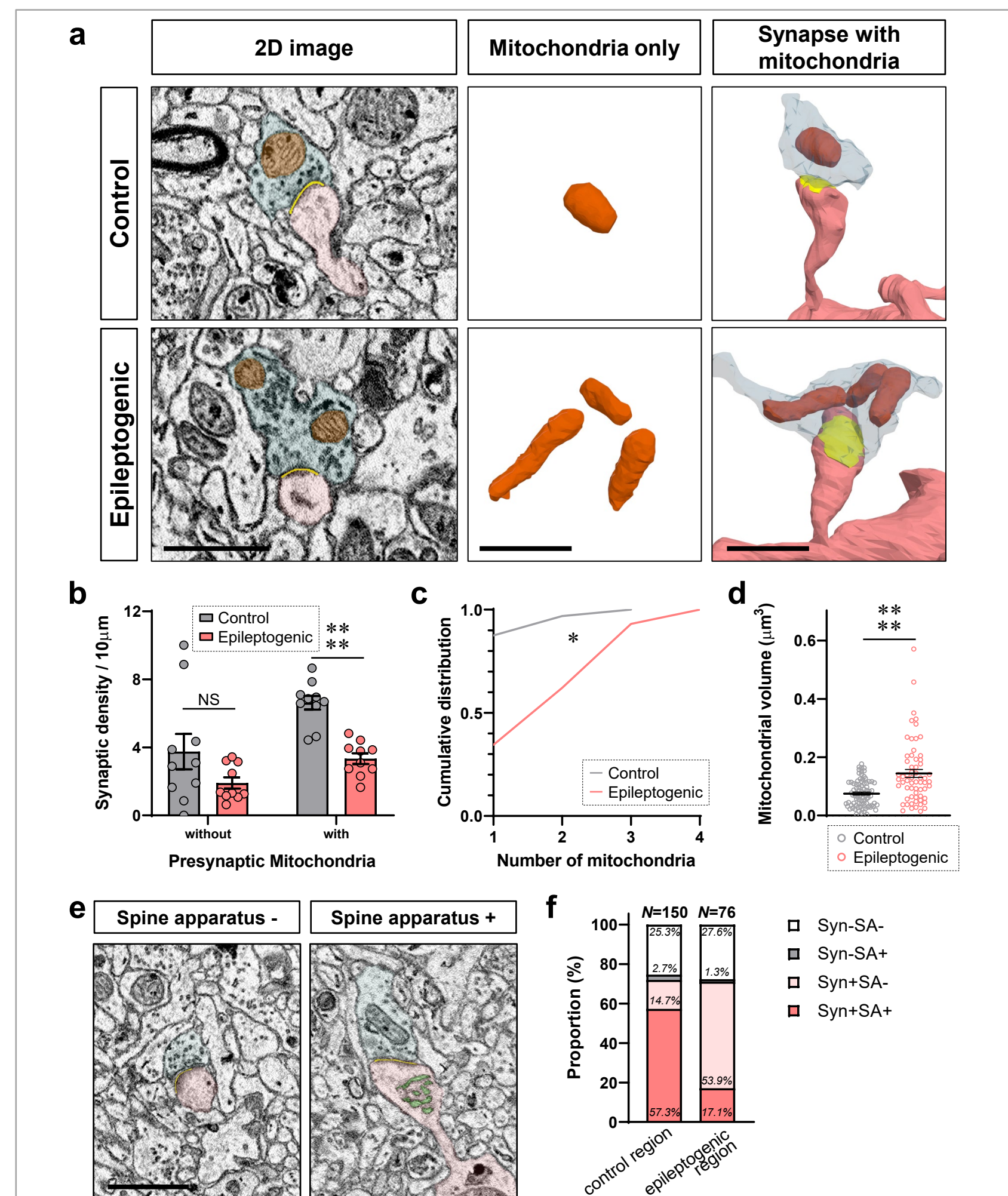


Fig. 7. Altered presynaptic mitochondria and spine apparatus in the epileptogenic cortex

Summary

- A reduced number of inhibitory synapses on pyramidal neuron somata.
 - The presence of extra-large excitatory synapses with increased presynaptic vesicles.
 - An elongated distance between inhibitory and excitatory synapses.
- These alterations may contribute to neuronal hyperexcitability in FCD.

Acknowledgements

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