Blood vessels in the brain are organized with surprising precision, patterned in parallel with the major brain circuits tasked with sensation, memory and motion. This tight interrelationship may reflect key functional roles in neuronal normal function, disease and brain aging. I will discuss i) the molecular and cellular mechanisms in brain capillaries during astrocyte-pericyte-endothelial signal transduction that when turn awry can cause neurodegeneration; ii) the effects of Alzheimer’s-associated genes (APOE4, PICALM) on small blood vessels and blood-brain barrier (BBB) integrity; and iii) the effects of capillary micro-bleeds on motor-neuron disorder. I will discuss microstructural and connectivity changes through various diffusivity, anisotropy and fiber tracking maps derived from the diffusion weighted MR images, and how we can quantify small vessel disease and BBB breakdown in rodent models of neurological disorders and the aging human population using imaging and molecular biomarkers. Finally, I will discuss whether repairing small blood vessels can retard neuronal dysfunction and degeneration.