Synaptic loss is the major correlate of cognitive impairment in Alzheimer’s disease (AD); however, general synaptic loss by itself cannot describe many of the cognitive alterations and the neuropathologic change observed across the many levels of dementia of the AD type. In this talk we will explore how alterations in the activity and number of counteracting excitatory and inhibitory synapses measured from autopsy specimens show differential regional alterations that relate to the clinical symptoms. We will also delve into how the physiological activity of these receptors relates to proteomic and gene expression observed across large datasets to study larger cohorts. By using the function of receptors, we validate the use of gene synaptic markers to explore discrete cognitive scores, and are in the way of finding some answers to the question of resilience in people with severe AD neuropathology, which are those individuals that remain cognitive intact despite the severe neuropathologic change, and are a clear living example of the possibility of therapeutic treatment for AD.