Amyotrophic lateral sclerosis (ALS) is a progressive and lethal disorder marked by the loss of motor neurons. The vast majority of individuals with ALS show mislocalization of TDP43, an essential RNA binding protein. Here, I discuss data suggesting that TDP43 pathology in ALS is mechanistically linked to neuronal hyperactivity, another conserved feature of ALS. I also discuss new results indicating that neuronal hyperactivity may broadly disrupt RNA binding protein metabolism in ALS and related neurodegenerative disorders.