

Supplementary Figures

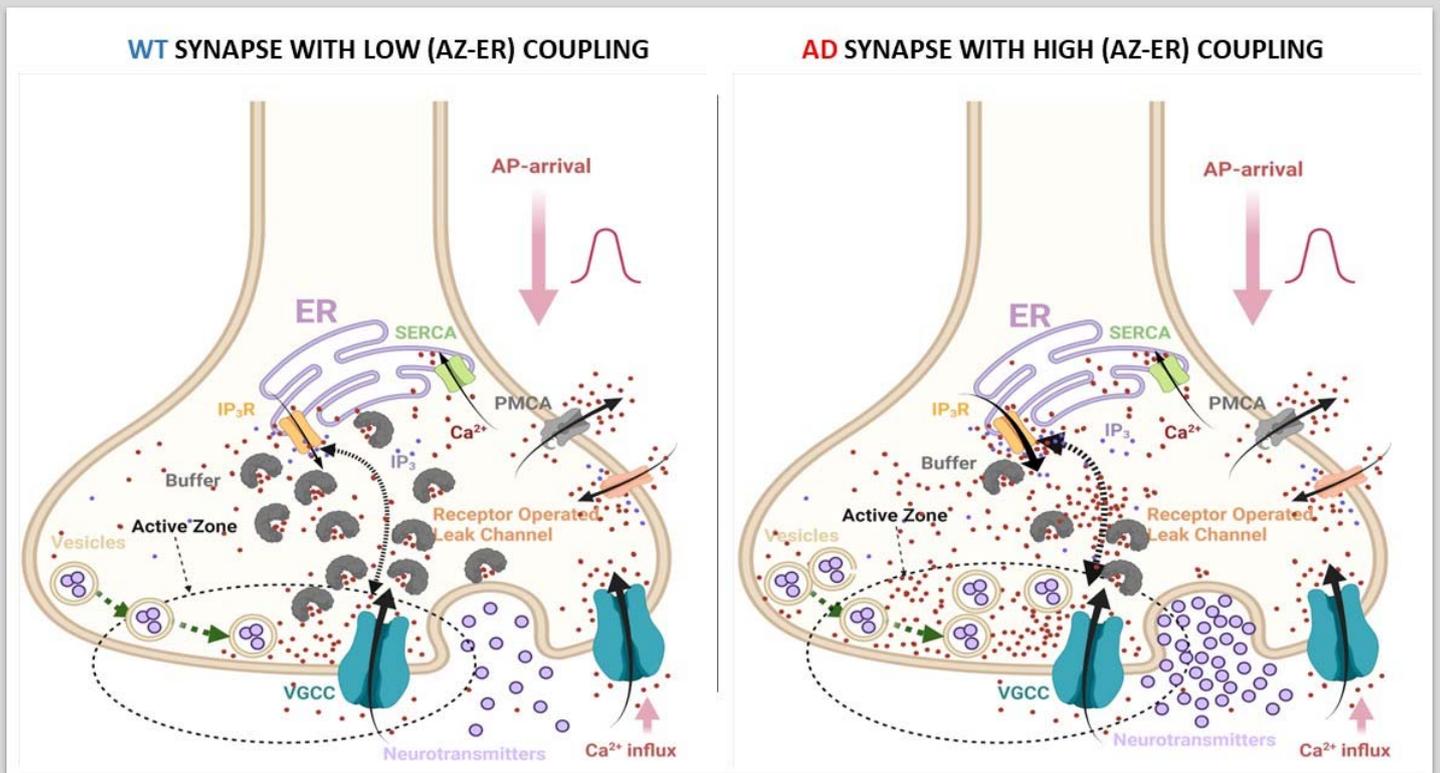


Figure S1. Ca^{2+} homeostasis and neurotransmission scheme in FAD and WT synapses. WT synapse (Left) with low ER-AZ coupling (thin dashed arrows), high buffering (grey half annuli), moderate AZ Ca^{2+} concentration, neurotransmission, and IP₃R activity (thin arrows), and FAD synapse (Right) with high ER-AZ coupling (thick dashed arrows), low buffering, elevated Ca^{2+} concentration, dysregulated and initially elevated release of neurotransmitters (purple) into the synapse, and IP₃R activity (thick arrows). Ca^{2+} is represented by small red circles and IP₃ by small blue ones.

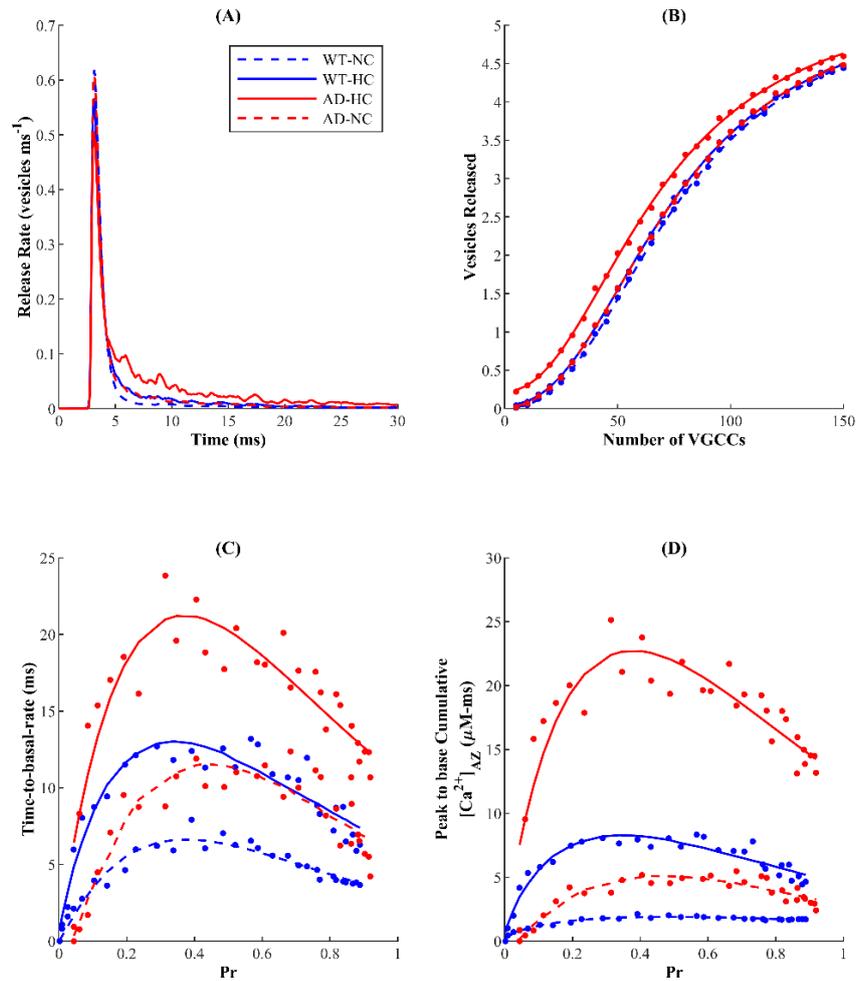


Figure S2. Coupling between the microdomains around IP_3Rs and VGCCs influences Ca^{2+} in the AZ and neurotransmission profiles in FAD and WT synapses. Transmitter release rates within 30 ms of stimulus (A) and total vesicles released (B) for different coupling configurations. Decay time of peak release rate (C) and cumulative Ca^{2+} concentration from peak to basal rate in the AZ (D) are markedly influenced by coupling.

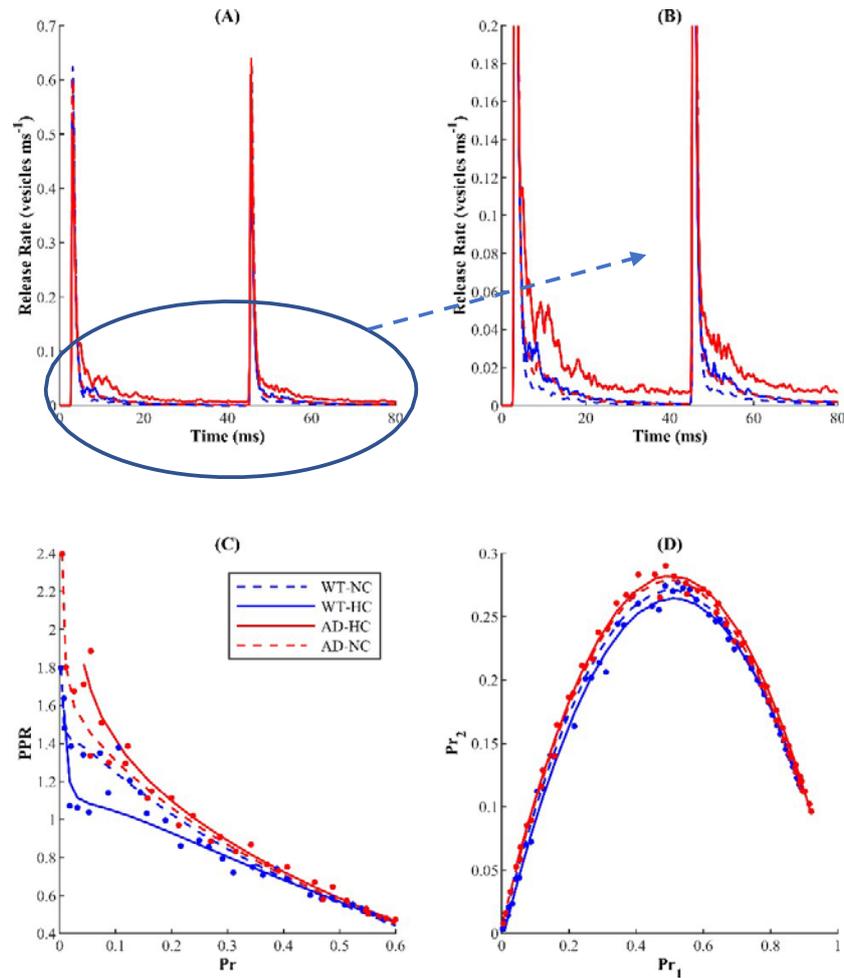


Figure S3. Stronger coupling between the microdomain of IP_3Rs cluster and AZ exacerbate the release rate and enhanced PPR in FAD-affected synapses but only marginally affect the bell-shaped behavior of Pr_2 as a function of Pr_1 . Release profile (A) (zoomed-in (B)) following paired-pulse stimulation protocol shows an increase in release rate by stronger coupling in the microdomain of IP_3Rs cluster and AZ in both WT and FAD-affected synapses. (C) The enhanced PPR in FAD-affected synapses with respect to WT synapses is exacerbated by stronger coupling. (D) Pr in response to the second pulse ($Pr_{\#}$) as a function of Pr following the first pulse (Pr_s) shows that the bell-shaped response is marginally affected by the coupling strength.

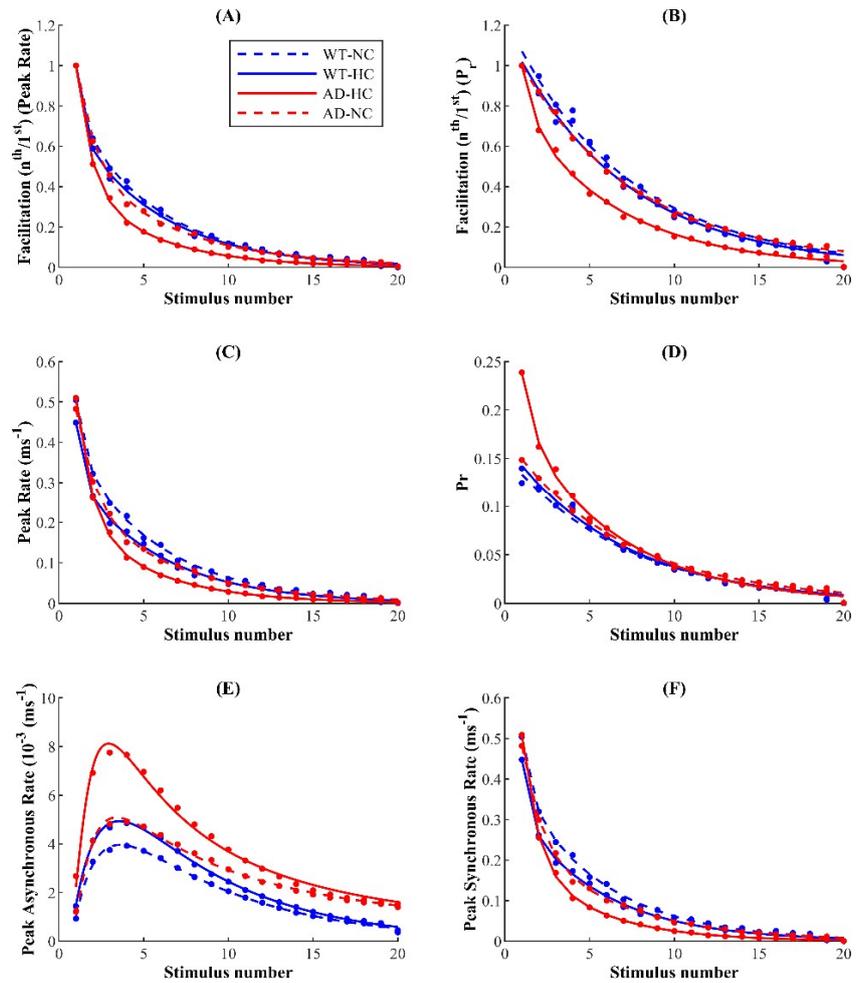


Figure S4. Stronger coupling between the microdomain of IP_3Rs cluster and AZ exacerbate the stronger depression in FAD-affected synapses. Facilitation obtained from peak rate (A) and P_r (B) shows that HC enhances the synaptic depression in FAD-affected synapses. Peak release rate (C) and P_r (D) following each AP in the train under different coupling conditions. (E) Asynchronous and (F) peak synchronous release under different coupling conditions.