

Supplementary Figures

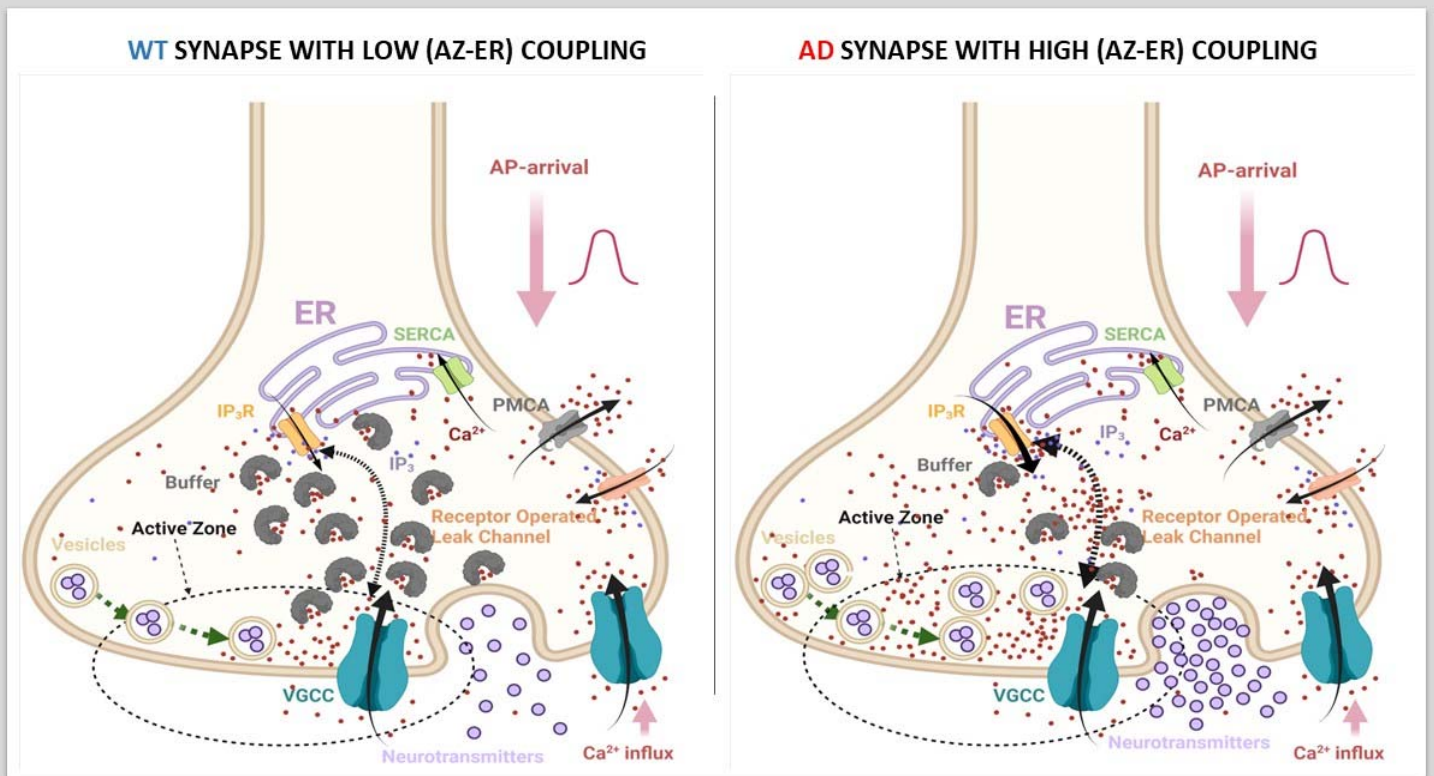


Figure S1. Ca^{2+} homeostasis and neurotransmission scheme in FAD and WT synapses. WT synapse (Left) with low ER-AZ coupling (thin dashed arrows). high buffering (grey half annuli), moderate AZ Ca^{2+} concentration, neurotransmission, and IP₃R activity (thin arrows), and FAD synapse (Right) with high 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.

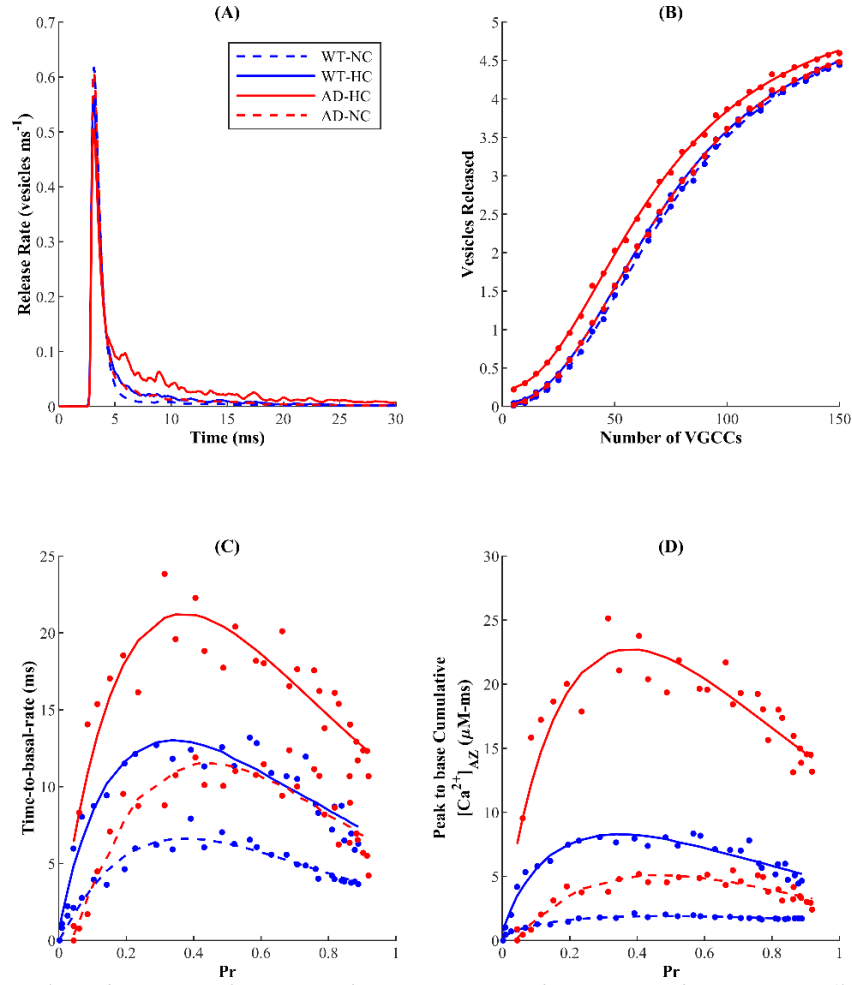


Figure S2. *Coupling between the microdomains around IP_3Rs and VGCCs influences Ca^{2+} in the AZ and neurotransmission profiles in FAD and WT synapses.* Transmitter release rates within 30 ms of stimulus (A) and total vesicles released (B) for different coupling configurations. Decay time of peak release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

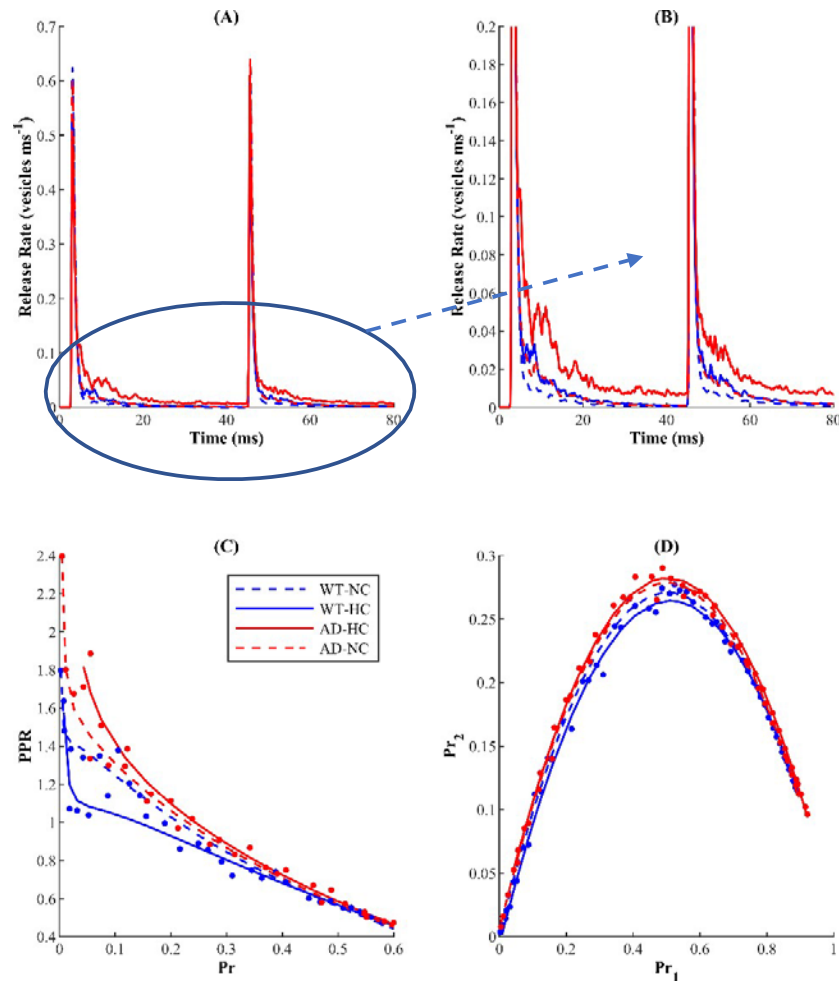


Figure S3. Stronger coupling between the microdomain of IP₃Rs cluster and AZ exacerbate the release rate and enhanced PPR in FAD-affected synapses but only marginally affect the bell-shaped behavior of Pr_2 as a function of Pr_1 . Release profile (A) (zoomed-in (B)) following paired-pulse stimulation protocol shows an increase in release rate by stronger coupling in the microdomain of IP₃Rs 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.

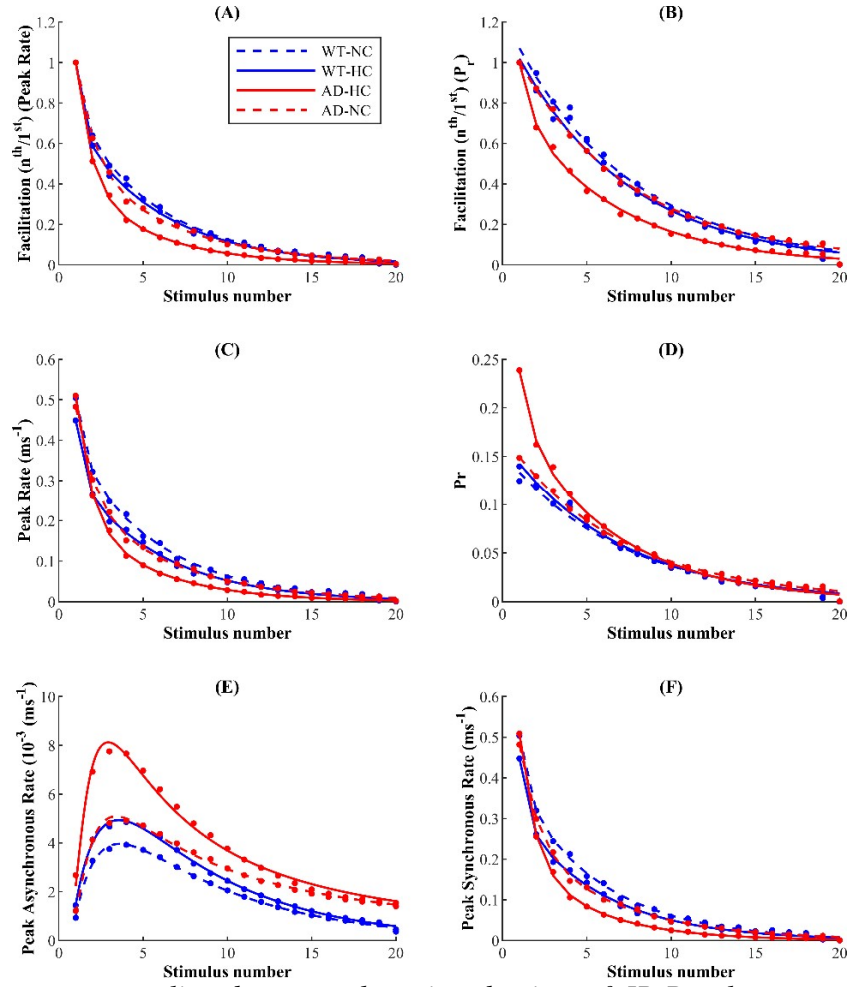


Figure S4. Stronger coupling between the microdomain of IP_3Rs cluster and AZ exacerbate the stronger depression in FAD-affected synapses. Facilitation obtained from peak rate (A) and P_r (B) shows that HC enhances the synaptic depression in FAD-affected synapses. Peak release rate (C) and P_r (D) following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