

1 **Upregulated Ca²⁺ release from the endoplasmic reticulum leads to**
2 **impaired presynaptic function in Alzheimer's disease**

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7 **Abstract**

8 Neurotransmitter release from presynaptic terminals is primarily regulated by rapid Ca^{2+} influx
9 through membrane-resident voltage-gated Ca^{2+} channels (VGCCs). Also, accumulating
10 evidence indicates that the endoplasmic reticulum (ER) is extensively present in axonal
11 terminals of neurons and plays a modulatory role in synaptic transmission by regulating Ca^{2+}
12 levels. Alzheimer's disease (AD) is marked by enhanced Ca^{2+} release from the ER and
13 downregulation of Ca^{2+} buffering proteins. However, the precise consequence of impaired Ca^{2+}
14 signalling within the vicinity of VGCCs (active zone (AZ)) on exocytosis is poorly understood.
15 Here, we perform in-silico experiments of intracellular Ca^{2+} signalling and exocytosis in a
16 detailed biophysical model of hippocampal synapses to investigate the effect of aberrant Ca^{2+}
17 signalling on neurotransmitter release in AD. Our model predicts that enhanced Ca^{2+} release
18 from the ER increases the probability of neurotransmitter release in AD. Moreover, over very
19 short timescales (30-60 msec), the model exhibits activity-dependent and enhanced short-term
20 plasticity in AD, indicating neuronal hyperactivity—a hallmark of the disease. Similar to
21 previous observations in AD animal models, our model reveals that during prolonged
22 stimulation (~450 msec), pathological Ca^{2+} signalling increases depression and
23 desynchronization with stimulus, causing affected synapses to operate unreliably. Overall, our
24 work provides direct evidence in support of a crucial role played by altered Ca^{2+} homeostasis
25 mediated by intracellular stores in AD.

26

27 **Introduction**

28 Alzheimer's disease (AD) is the most common and burdensome of the late-onset degenerative
29 dementias: the world Alzheimer report estimated a global prevalence of over 50 million
30 worldwide, a number expected to triple by 2050 [85, 86]. AD manifests as progressive memory
31 impairment initially and faster rate of cognitive decline and neurodegeneration in later stages.
32 Despite the convoluted etiology of AD, experimental and theoretical investigation suggests
33 that synapses are the primary targets in the early stage of the disease [87, 88]. Histologically,
34 the AD brain is marked by extracellular deposition of senile beta-amyloid (A β) plaques—the
35 result of abnormalities in the genes encoding amyloid precursor protein (APP) or
36 intramembrane protease presenilin 1 and 2 (PS1, PS2). These are accompanied by intracellular
37 accumulation of neurofibrillary tangles (NFTs)—composed of hyperphosphorylated tau
38 proteins (pTau)—that litter the cerebral and hippocampal cortices [89—93]. Although the
39 exact mechanism is still being debated, numerous experimental studies implicate elevated
40 intracellular Ca²⁺ levels as one of the main mechanisms underlying A β toxicity [94, 95]. These
41 studies show that the AD brain is surfeit with dysregulation of Ca²⁺ signalling pathways [94—
42 97], motivating researchers to propose the Ca²⁺ hypothesis of AD and aging [126]. Indeed, it
43 has been shown that both intra- and extracellular A β oligomers and familial AD (FAD)-causing
44 mutations in presenilin cause enhanced Ca²⁺ release from the ER through inositol (1, 4, 5)-
45 triphosphate (IP₃) receptors (IP₃Rs) and/or ryanodine receptors (RyRs) [16, 17, 94—100,
46 127—129]. This upregulated Ca²⁺ release can contribute to aberrant plasticity and functional
47 disruption of neuronal networks [44, 95].

48
49 Intracellular Ca²⁺ is an important second messenger for regulating a multitude of neuronal
50 functions, including neurotransmitter release. Synaptic function at nerve terminals is tightly
51 coupled to intracellular Ca²⁺ concentration ([Ca²⁺]), as Ca²⁺ primarily regulates the biological
52 machinery responsible for exocytosis and short-term plasticity [28, 29]. The precise temporal
53 control of synaptic transmission by Ca²⁺ is achieved via local signal transduction mechanisms
54 that aim to regulate Ca²⁺ excitability at the axonal bouton. Voltage-gated Ca²⁺ channels
55 (VGCCs) are the primary mediators of the transduction of depolarization-induced Ca²⁺
56 transients into neurotransmitter release. Furthermore, Ca²⁺ influx through VGCCs leads to
57 physiological events that alter plasma membrane functions underpinning synaptic plasticity,
58 protein expression, spine maintenance, and regulation of excitability in excitatory synapses
59 [45, 46]. Likewise, investigations of the Ca²⁺-dependence of vesicular release have highlighted

60 the role of intracellular stores in Ca^{2+} handling and spontaneous exocytosis [21, 47]. Thus, the
61 close association between these Ca^{2+} pathways, their effect on numerous neuronal processes,
62 and their high sensitivity to pathological perturbations makes it especially valuable to elucidate
63 the exact nature of the coupling.

64

65 Extensive evidence supports the presence of the ER in the nerve terminal of CA3 pyramidal
66 neurons [21, 47, 44, 101—103]. In neurons, activation of Ca^{2+} -sensitive channels like IP_3Rs
67 and RyRs triggers the release of Ca^{2+} from the ER. Opening of IP_3Rs primarily depends on
68 Ca^{2+} and IP_3 . To achieve this, glutamate released into the synaptic cleft elicits the production
69 of IP_3 by the activation of membrane-bound mGluRs. RyRs activation, on the other hand, is
70 largely controlled by cytosolic $[\text{Ca}^{2+}]$. This specialized cascade underscores the importance of
71 IP_3Rs and RyRs in the regulation of the Ca^{2+} induced Ca^{2+} release (CICR) mechanism of the
72 ER. Previous works have shown that CICR is necessary for ER stores to adequately influence
73 spontaneous vesicle release and homosynaptic plasticity [21, 104]. Indeed, *in vitro* studies
74 confirm that properly sensitized CICR is necessary for normal synaptic function, whereas
75 aberrant CICR underlies presynaptic impairment associated with AD [19, 20, 80, 82]. Despite
76 this evidence, the precise role of ER Ca^{2+} handling in action potential (AP)-evoked presynaptic
77 Ca^{2+} dynamics and its downstream effect on presynaptic neuronal processes remain unclear
78 [19—21, 82].

79

80 Information encoding at the CA3 to CA1 synapses in the hippocampus, which is crucial for
81 learning and memory storage, relies on the spatiotemporal organization of Ca^{2+} events leading
82 up to synaptic transmission [108]. AP arrival at the nerve terminal activates VGCCs, leading
83 to high-amplitude, short-lived Ca^{2+} influx events into the AZ. Coupled with this specialized
84 pathway, Ca^{2+} sensors initiate a heterogeneous fusion of neurotransmitter vesicles with the
85 plasma membrane that often culminates in either fast synchronous or slow asynchronous
86 release. Neuronal communication primarily relies on the synchronous mode of exocytosis,
87 which is regulated by synaptotagmin-1 (*Syt1*) sensors with low Ca^{2+} affinity and rapid kinetics
88 that are critical for the exquisite temporal precision of vesicle fusion that characterizes synaptic
89 transmission at most CA3-CA1 terminals [37, 62, 105]. Such a high degree of synchrony is in
90 part achieved by the steep dose dependence of evoked release on the short-lived Ca^{2+} transients
91 constrained to micro- or nanodomains within the vicinity of VGCCs [28, 106]. A global
92 buildup of $[\text{Ca}^{2+}]$, on the other hand, accelerates the recruitment of release-ready vesicles,
93 controlling the degree of synaptic plasticity [130]. Thus, changes in Ca^{2+} signals at the local or

94 global scale are expected to disrupt synaptic transmission and plasticity. Consistent with this
95 assertion, experimental manipulations that perturb evoked Ca^{2+} influx alter the contribution of
96 the synchronous mode of release to overall exocytosis and compromise synaptic plasticity [38,
97 39, 107]. These findings highlight the need for a thorough investigation of the potential link
98 between impaired synaptic function and disrupted Ca^{2+} homeostasis in AD.

99

100 In this study, we incorporate findings from extensive experimental and computational studies
101 to develop a detailed biophysical model of Ca^{2+} -driven exocytosis at the CA3 presynaptic
102 terminal. The model accounts for the observed Ca^{2+} and IP_3 signalling pathways necessary for
103 intracellular Ca^{2+} regulation and integrates the elaborate kinetics of neurotransmitter release—
104 vesicle docking, mobilization, priming, and fusion—aided by distinct Ca^{2+} sensors. We
105 reproduced crucial statistics of both Ca^{2+} and release events reported at small excitatory
106 synapses, such as transient timescale, amplitude, and decay time. By developing a
107 mathematical framework for coupling the Ca^{2+} domains surrounding the ER and AZ, we study
108 how AD-associated pathological Ca^{2+} release from the ER disrupts presynaptic
109 neurotransmitter release rates and consequently alter synaptic plasticity and facilitation at
110 affected synapses. Overall, our work provides novel insights on the pathologic role of aberrant
111 neuronal Ca^{2+} handling on glutamate release and the downstream effects on synaptic
112 dysfunction and cognitive decline observed in AD.

113

114 **Results**

115 *The gain-of-function enhancement of IP_3R gating in AD*

116 The exaggerated Ca^{2+} release observed in familial AD (FAD)-affected neurons is ascribed
117 mainly to the gain-of-function enhancement of IP_3Rs in the affected cells due to FAD-causing
118 mutations in presenilin [16, 17, 58, 124, 128]. Indeed, it has been shown that cell models
119 expressing PS mutations exhibit a several-fold increase in the open probability (P_o) of IP_3Rs
120 [17, 58]. Specifically, the P_o of IP_3R in cortical neurons from 3xTg-AD mice carrying PS
121 mutations was enhanced by 700% relative to control mice with wildtype (WT) PS (0.43 ± 0.05
122 in AD versus 0.06 ± 0.01 in WT mice) at a cytosolic $[\text{Ca}^{2+}]$ ($[\text{Ca}^{2+}]_c$) of $1 \mu\text{M}$ and IP_3
123 concentration ($[\text{IP}_3]$) of $10 \mu\text{M}$ [58]. Given that all models for IP_3R in WT or AD-affected cells
124 are based on non-neuronal cells, we use the above findings to build a new model for the gating

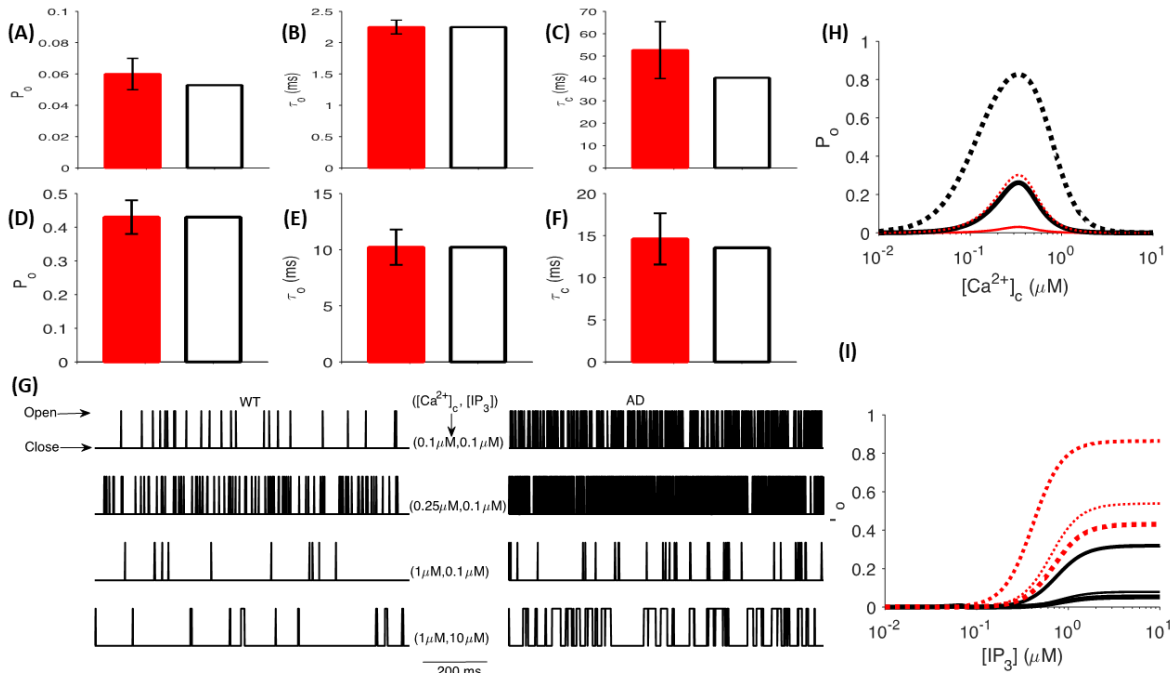
125 kinetics of IP₃Rs in neurons from WT and 3xTg-AD mice (see details in *Methods* section).
126 Parameters yielding the best fit to experimental observations are listed in *Table 6*.

127
128 Our model mimics the gating of IP₃R in neurons from WT and 3xTg-AD mice (*Fig 1*), closely
129 reproducing the observed values of the P_o (*Fig 1A, D*), mean open time (τ_o) (*Fig 1B, E*), and
130 mean close time (τ_c) (*Fig 1C, F*) reported in [128]. The significantly higher P_o of the channel
131 in AD-affected neurons is reflected in the time-traces from the model, showing that the channel
132 spends significantly more time in the open state in the diseased state (*Fig 1G*). To determine
133 how the observations about different resting $[Ca^{2+}]_c$ in AD-affected cells change the behaviour
134 of IP₃Rs, we plot the P_o of the channel as a function of $[Ca^{2+}]_c$ and $[IP_3]$ (*Fig. 1H, I*). Previous
135 studies of 3xTg and APP_{sw} AD mice models reported resting $[Ca^{2+}]_c$ of 247 ± 10.1 nM and
136 225.2 ± 11.7 nM respectively, whereas $[Ca^{2+}]_c$ of 110.8 ± 1.5 nM was recorded in WT mice [15].
137 In particular, cortical neurites of plaque bearing mice express a 6-fold increase in resting $[Ca^{2+}]_c$
138 relative to non-transgenic mice [55]. Here, our model exhibits a 4.42-fold increase in P_o of
139 IP₃Rs in WT neurons as we increase $[Ca^{2+}]_c$ from 110 nM to 250 nM (0.005626 vs 0.02484) at
140 0.3 μ M $[IP_3]$. At $[IP_3] = 0.3$ μ M and $[Ca^{2+}]_c = 250$ nM, P_o of the channel in AD-affected neurons
141 reaches 0.2565—a 10.32-fold increase relative to WT neurons (*Fig 1H, I*). Thus, an IP₃R in the
142 AD-affected neurons will exhibit an almost 45-fold increase in P_o compared to control neurons
143 with the same amount of IP₃, leading to a significantly higher Ca^{2+} release from the ER.

144 ***Characterization of the glutamate release model and release event***

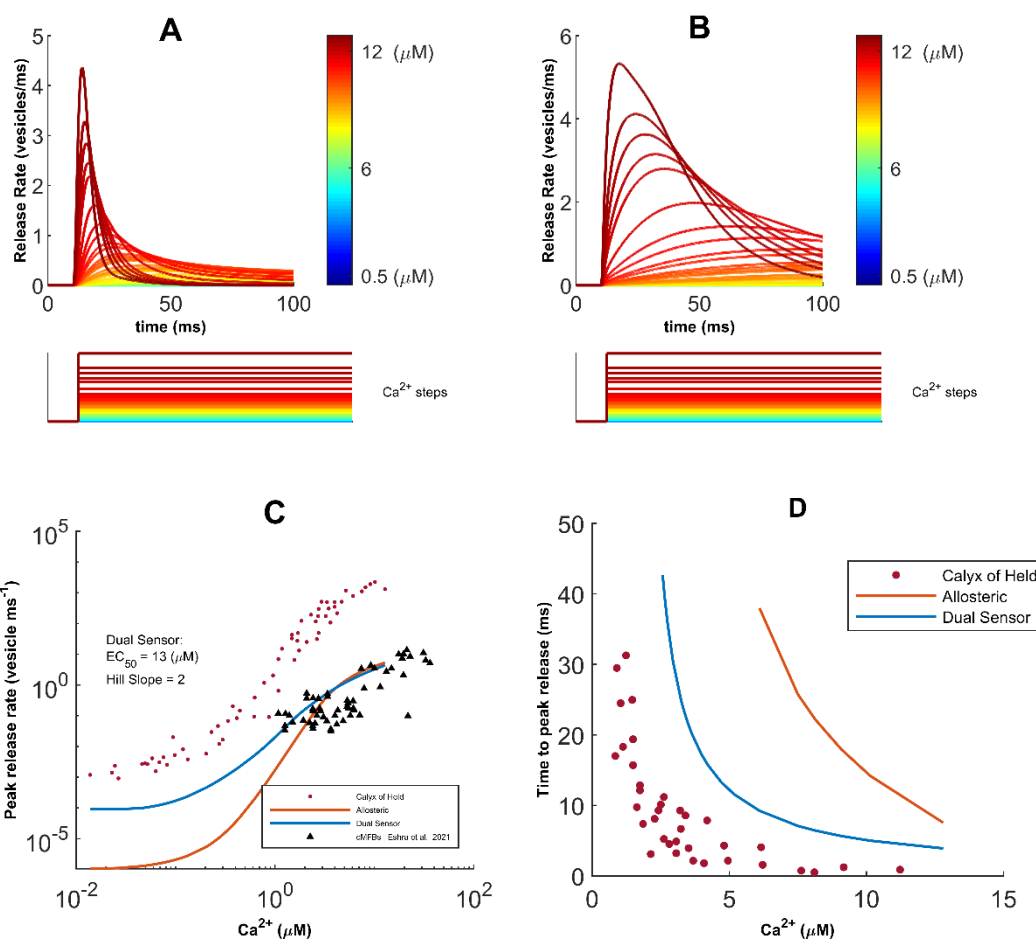
145 We next examine the relationship between total release from a single process following $[Ca^{2+}]_c$
146 clamps at different concentration steps. We observe that the release rate rapidly increases and
147 transiently decays back to basal level within tens of milliseconds—a result of the sensitivity of
148 the Ca^{2+} sensors (*Fig 2A*). For comparison, we also show the release rate given by the Allosteric
149 model at different $[Ca^{2+}]_c$ values (*Fig. 2B*). Also, we obtain results similar to quantitative
150 studies of transmission profiles in Calyx-of-Held synapse [1]. Unsurprisingly, we observed a
151 shift in the $[Ca^{2+}]_c$ dependency of the peak release rate as the response to clamped intracellular
152 Ca^{2+} levels is both lower and right-shifted relative to the experimental data for the Calyx-of-
153 Held (*Fig 2C*), whereas the time delay (time-to-peak) of peak release rate shows higher and
154 right-shifted exponential decay (*Fig 2D*). This is consistent with observations of approximately
155 hundred-fold decrease in total vesicle population in hippocampal boutons [2, 3]. In addition,
156 our model mimics the Ca^{2+} -dependent increase in peak release rate observed at high fidelity

157 synapses of cerebellar mossy fibre boutons (cMFBs), which permit direct presynaptic
 158 recordings and are reported to have high structural similarities with their hippocampal
 159 counterparts (*Fig 2C*) [131, 132]. Moreover, in agreement with previous recordings of
 160 spontaneous release events from CA3-CA1 synapses, we affirmed that the spontaneous release
 161 rate elicited by resting level $[Ca^{2+}]_c$ of 100 nM is within the reported range of 10^{-4} and 10^{-5}
 162 per ms [4, 5, 6]. The Dual-Sensor model is more in line with the findings on CA3-CA1
 163 synapses, and is used for the remaining of this paper.



164

165 **Figure 1.** Gain-of-function enhancement of IP₃R gating in AD. The P_o (A, D), τ_o (B, E), and
 166 τ_c (C, F) of IP₃R given by the model (empty bars) and observed values in primary cortical
 167 neurons from WT (A-C) and 3xTg AD mice (filled bars) (D-F) at $[Ca^{2+}]_c = 1 \mu M$ and $[IP_3] =$
 168 $10 \mu M$. (G) Sample time-traces generated by stochastically simulating a single IP₃R channel in
 169 cortical neurons from WT (left column) and AD (right column) mice at different $[Ca^{2+}]_c$ and
 170 $[IP_3]$ values shown in the figure. (H) P_o of IP₃R as a function of $[Ca^{2+}]_c$ at $[IP_3] = 0.3 \mu M$ (thin
 171 lines) and $1 \mu M$ (thick lines) in WT (solid lines) and AD-affected (dotted) neurons. (I) P_o of
 172 IP₃R as a function of $[IP_3]$ at $[Ca^{2+}]_c = 0.1, 0.25, 1 \mu M$ (the increasing value of $[Ca^{2+}]_c$ is
 173 represented by the thickness of the line) in WT (solid lines) and AD-affected (dotted) neurons.
 174 Experimental values shown for comparison in (A-F) are from [128].



175

176

177 **Figure 2.** Characterization of neurotransmission in response to $[Ca^{2+}]_c$ steps. (A) Total release
 178 events obtained from a single Dual-Sensor fusion process after clamping $[Ca^{2+}]_c$ at different
 179 values. (B) Release profile following Allosteric fusion in response to stepwise $[Ca^{2+}]_c$ clamp.
 180 (C) Regulation of the peak release rate in response to clamped $[Ca^{2+}]_c$ levels show lower and
 181 right-shifted dose-responses relative to the experimental data for the Calyx-of-Held. (D) $[Ca^{2+}]_c$
 182 dependence of time-to-peak rate indicates exponentially decreasing but longer time delay to
 183 peak release when matched with data for the Calyx-of-Held. Experimental values shown for
 184 comparison in (C, D) are from [131]

185

186 *AD-associated intracellular Ca^{2+} changes enhance neurotransmitter release*

187 Several studies have reported enhanced Ca^{2+} release from the ER in AD-affected neurons [10—
 188 14]. This enhanced Ca^{2+} release has been associated with the several fold increase in the P_O of
 189 IP_3Rs observed in multiple animal and human cell models of AD [11, 15—17, 128]. Although
 190 presynaptic plasticity and synaptic vesicle release (SVR) are tightly coupled to Ca^{2+} entry
 191 through VGCCs, several studies have established an important role for ER stores in regulating

192 presynaptic plasticity and neurotransmission [18—22]. Furthermore, strong experimental
193 evidence supports the existence of a feedback loop between the ER Ca^{2+} stores and AP
194 triggered exocytosis events [7]. Accordingly, here we explore how the observed gain-of-
195 function enhancement of IP_3Rs in AD affects neurotransmitter release. In addition to enhanced
196 Ca^{2+} release through IP_3Rs , multiple studies have implicated a significant downregulation of
197 Ca^{2+} buffering proteins in AD-affected neurons as compared to WT neurons [133—135]. We
198 incorporate the effect of observed changes in Ca^{2+} buffering proteins by considering two
199 configurations: *High Coupling (HC)* and *Normal Coupling (NC)* between the ER and AZ. The
200 *HC* configuration corresponds to the downregulation of Ca^{2+} buffering proteins (see more
201 details in *Methods* section).

202
203 In *Fig. 3A*, we show a typical release profile in response to a single AP, where a clear difference
204 between WT and AD-affected synapses can be seen. To quantify this difference, we compute
205 the release probability (Pr) by counting the number of vesicles released from the slow and fast
206 release-ready pool (RRP), divided by the number of vesicles initially in both pools. In AD-
207 affected synapse, we observe enhanced Pr over a wide range of VGCCs' expressions in dose-
208 response manner (*Fig 3B*), suggesting that the acute effects of AD-driven aberrant cytosolic
209 Ca^{2+} are not exclusive to synapses operating in the regime of sparse VGCCs. Surprisingly, we
210 observe only a marginal difference in the peak release rate between WT and AD-affected
211 synapses (*Fig 3C*). We also calculated the number of vesicles released during a single AP by
212 integrating the rate of vesicle release from the slow and fast RRP, and noticed a significant
213 increase in vesicles released in the AD-affected synapse (*Fig. 3D*). To discern the contribution
214 of enhanced Ca^{2+} release through IP_3Rs from that due to the *HC*, we simulate four scenarios:
215 (1) enhanced Ca^{2+} release through IP_3Rs but *NC* (AD-NC), (2) enhanced Ca^{2+} release through
216 IP_3Rs with *HC* (AD-HC), (3) normal Ca^{2+} release through IP_3Rs and *NC* (WT-NC), and (4)
217 normal Ca^{2+} release through IP_3Rs and *HC* (WT-HC). We notice that while *HC* causes a minor
218 increase in the release probability and vesicles released in the WT synapse, it strongly affects
219 both these features in the AD-affected synapse (*Supplementary Fig 1A, B*).

220
221 To gain deeper insight into the observed changes in the Pr, we examine the dependence of the
222 release rise time (*Time to peak release rate*) on Pr (Pr is increased by increasing the number of
223 VGCCs as in *Fig 3A*) and observed no significant differences between AD-affected and WT
224 synapses (*Fig 3E*). Interestingly, the decay time (*Time to basal release rate*) exhibits a biphasic
225 dependence on Pr with a longer decay time in AD-affected synapse. Strikingly, the decay time

226 as well as the concomitant AD-associated enhancement is attenuated in synapses with both
227 high and low Pr , and peaks at Pr corresponding to physiologically reasonable VGCCs
228 expression for small hippocampal synapses [35], indicating that such small hippocampal
229 synapses are more sensitive to alternations due to AD-associated Ca^{2+} disruptions (*Fig 3F*).
230 Like the release probability as a function of time and vesicles released during a single AP, HC
231 has a stronger effect on the release rise time mainly due to the changes in Ca^{2+} in AZ in the
232 AD-affected synapse (*Supplementary Fig 1C, D*).

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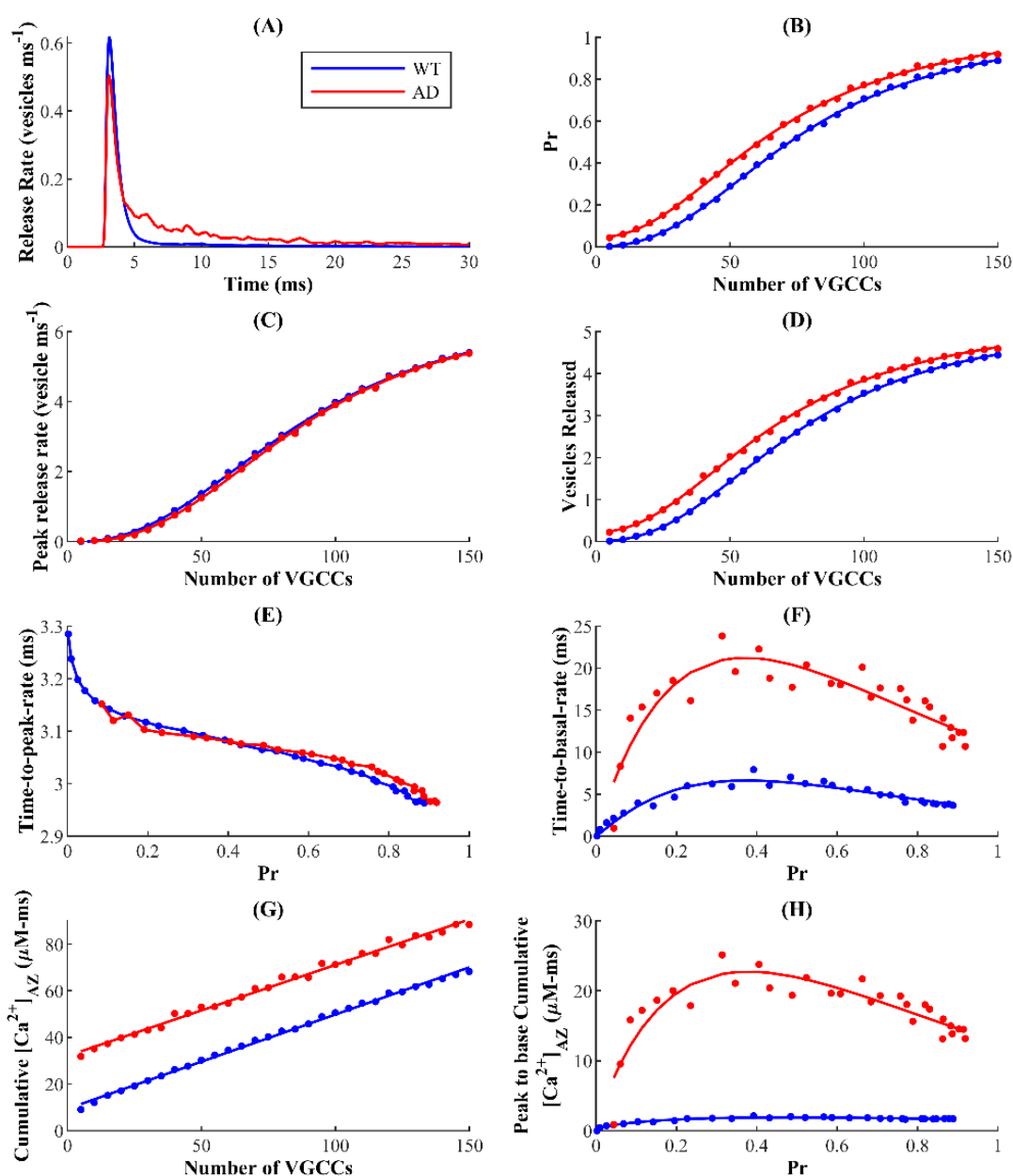
234 To assess the direct correspondence between the changes in different aspects of SVR and
235 enhanced Ca^{2+} release, we examine the cumulative Ca^{2+} at AZ. The elevated Ca^{2+} release from
236 the ER maintains larger cumulative Ca^{2+} (area under the Ca^{2+} transient) at AZ in the AD-
237 affected synapse consistently across a wide range of VGCCs expression, in agreement with
238 several studies showing that ER Ca^{2+} channels can sculpt the spatiotemporal dynamics of
239 exocytosis and consequently neuronal function (*Fig 3G*) [8, 9]. However, this continuous
240 enhancement as a function of VGCCs expression is not consistent with the biphasic behaviour
241 of the time to basal rate as a function of Pr . Next, we examined the residual Ca^{2+} in the AZ,
242 obtained as the cumulative Ca^{2+} that persists during decay phase of the Ca^{2+} transient. Our
243 results show that larger residual Ca^{2+} in AD-affected synapses also exhibits a biphasic
244 behaviour as a function of Pr similar to the time to basal neurotransmitter release rate. Again,
245 this enhancement was non-uniform, suggesting that small hippocampal synapses with
246 intermediate Pr values are highly sensitive to pathological alterations (*Fig 3H*). Taken together,
247 our data reveal that ER-driven Ca^{2+} disruption plays a critical role in shaping the observed
248 response profile, with the acute effects induced by such disruptions more severely expressed
249 in small hippocampal synapses. Our results also show that these effects are more sensitive to
250 the coupling between the Ca^{2+} domains in the vicinity of VGCCs and ER in AD-affected
251 synapses (*Supplementary Fig 1C, D*), consistent with reports on the involvement of ER Ca^{2+}
252 in the regulation of presynaptic resting $[Ca^{2+}]_c$ and neurotransmission [7—9]. Furthermore, the
253 sensitivity to the coupling between the Ca^{2+} domains is exacerbated for synapses with
254 intermediate Pr values (*Supplementary Fig 1C, D*).

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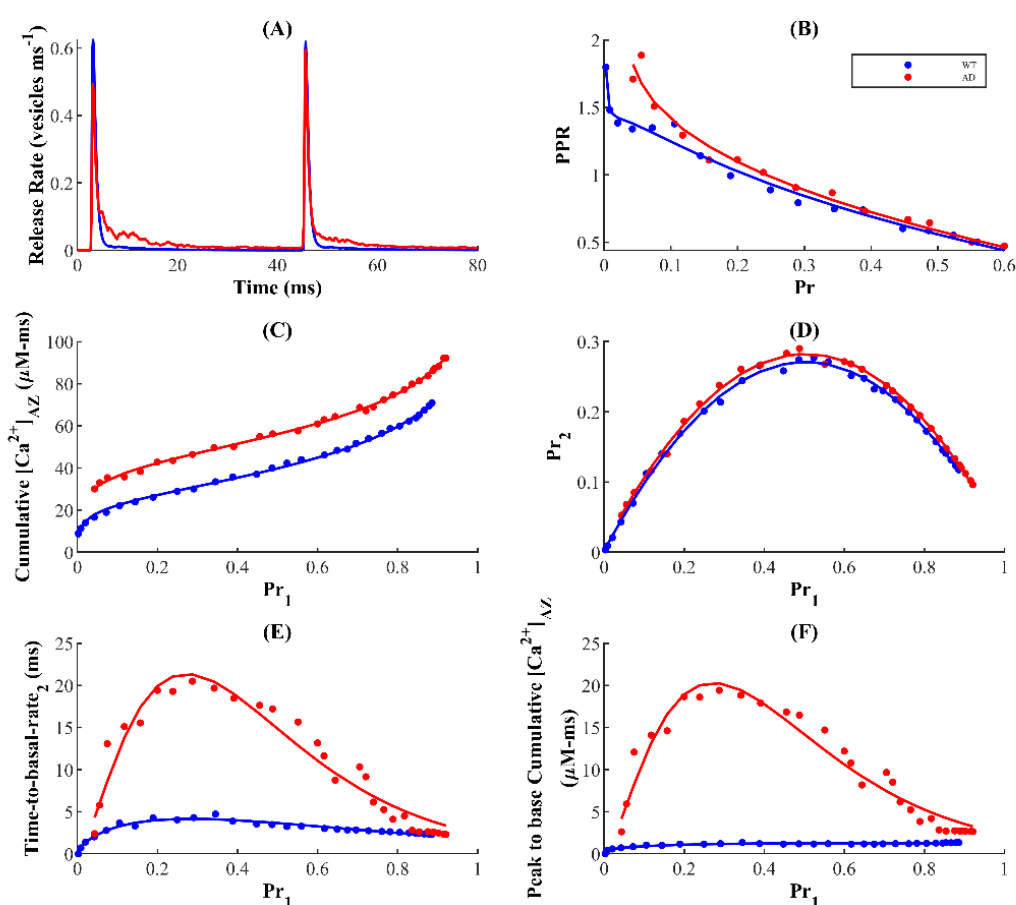
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260 **Figure 3.** ER-driven upregulation of cytosolic Ca^{2+} leads to enhanced synaptic vesicle release
 261 in AD. (A) Neurotransmitter release rate in response to a single AP in WT and AD-affected
 262 synapse. Change in the Pr of a single synaptic vesicle (B), peak release rate (C), and the average
 263 number of vesicles released (D) as functions of the number of VGCCs. (E) Time delay of peak
 264 release rate and (F) decay time to basal release rate as functions of Pr. (G) Change in $[Ca^{2+}]_{AZ}$
 265 with number of VGCCs. (H) Cumulative Ca^{2+} from peak to basal level as a function of Pr.

266

267 **Very short-term plasticity is enhanced in the AD-affected synapse**

268 Next, we investigate how the enhanced Ca^{2+} release from the ER affects very short-term
 269 presynaptic plasticity (STP). STP is assessed by determining the paired-pulse ratio (PPR): a
 270 classical measure of presynaptic modulation in response to paired stimuli separated by very
 271 short time interval [23]. After stimulating the nerve terminal with two pulses separated by a 40
 272 ms interval (*Fig 4A*), we define PPR as the ratio of the Pr following the second pulse (Pr_2) to
 273 that of the first pulse (Pr_1) averaged over several trials. Therefore, the response to the second
 274 stimulus can either be enhanced with $Pr_2/Pr_1 > 1$ (short-term facilitation (STF)) or depressed
 275 with $Pr_2/Pr_1 < 1$ (short-term depression (STD)).



276
 277 **Figure 4.** AD-associated Ca^{2+} upregulation enhances STF. (A) Release profile following
 278 paired-pulse stimulation protocol. (B) PPR is inversely related to intrinsic Pr (obtained after
 279 first pulse), and is higher in the AD-affected synapse. (C) Similar to the first pulse (Figure 3G),
 280 cumulative $[\text{Ca}^{2+}]_{\text{AZ}}$ after the second pulse increases with the Pr and is higher in AD-affected
 281 synapse. (D) Pr in response to the second pulse (Pr_2) as a function of Pr following the first

282 pulse (Pr_1). Higher values indicate that the synapse responds more strongly to the subsequent
283 stimulus in a paired-pulse protocol. (E) Decay time of release rate after second pulse also
284 exhibits a biphasic behaviour. (F) Cumulative $[Ca^{2+}]_{AZ}$ following the second pulse reflects the
285 biphasic behaviour observed in time delay of peak-to-basal release rate in panel E.

286
287 On average, both WT and AD-affected synapses exhibited an inverse relationship between Pr_1
288 and the PPR, consistent with previous findings in phasic synapses such as small glutamatergic
289 synapses in the hippocampus (*Fig 4B*) [9, 24, 25, 30]. This negative correlation, thought to be
290 a universal feature of these synapses, is assumed to be caused by the spike-driven depletion of
291 vesicles in the RRP after the first pulse which is unlikely to be recovered by Ca^{2+} -driven
292 facilitation upon the next stimulation. Therefore, whether a synapse exhibits STF or STD is
293 largely dependent on the recent activation history, which implies that synapses with large
294 number of VGCCs and consequently very high intrinsic release probabilities tend to depress
295 their response more severely to a second pulse, allowing them to operate at low PPR [9, 23—
296 26, 29, 30].

297
298 While additional mechanisms may contribute to STD, the depletion model of depression in
299 phasic synapses suggests that at rest, the priming sites containing the RRP of vesicles is mostly
300 occupied and reflects the inability of residual Ca^{2+} —left over from the previous stimulation—
301 and the incoming flux to potentiate release during the second stimulation [27, 28]. In agreement
302 with these findings, our model establishes the dynamic equilibrium between the RRP (primed
303 pool) and the unprimed pool by ensuring a relatively faster priming rate. As a result, we find
304 here that most synapses operating in the intermediate-release-probability regime, characteristic
305 of hippocampal excitatory synapses, display low STD with $PPR < 1$ in both WT and disease
306 states (*Fig 4B*). Strikingly, AD-affected synapse displays enhanced presynaptic strength
307 relative to WT synapse, in contrast to the notion that the activity-dependent tunability of PPR
308 ensures that periods of elevated activity results in subsequently depressed response. A simple
309 explanation for this is that in the AD-affected synapse, the elevated residual Ca^{2+} in the nerve
310 terminal after the conditioning stimulus is longer-lasting and facilitates additional release upon
311 subsequent stimulation (*Fig 4A*). To test the veracity of this claim, we examined whether the
312 $[Ca^{2+}]_{AZ}$ remains elevated following the second pulse. Consequently, we find that the AD-
313 associated enhancement of residual $[Ca^{2+}]_{AZ}$ is sustained after the second stimulation and
314 increases with Pr_1 (*Fig 4C*). These results suggest that on short timescales, the reduced

315 depression observed in AD synapses is orchestrated by Ca^{2+} released from internal stores and
316 induces a history-dependent enhancement of STP with respect to the WT synapse.

317

318 Although our results suggest that higher-probability synapses always express greater
319 depression, it is still unclear whether probability of transmission of consecutive spikes
320 monotonically relates to intrinsic release probability, and what role the ER plays in sculpting
321 the concomitant profile. For this purpose, we examine the Pr_2 as a function of Pr_1 (*Fig 4D*),
322 which reflects the conditional probability that a successful release event on the first pulse is
323 followed by another successful release on the second pulse. Our data reveal that the success of
324 a transmission event in response to the second stimulus depends on that for the first stimulus
325 in a bell-shaped manner, indicating that the probability of vesicle release upon consecutive
326 spikes is attenuated at both low and high probability synapses. This implies that synapses with
327 intermediate synaptic transmission failures display higher success of transmission of
328 consecutive spikes, in agreement with the idea that the stochasticity/unreliability of
329 transmission probability can enhance the efficacy of information transmission across the
330 synapse [31—33]. Unsurprisingly, the AD-affected synapse facilitates transmission in
331 response to the second stimulus more strongly compared to the WT synapse. This suggests that
332 diseased synapses retain longer history of Ca^{2+} events, which consequently contributes to
333 hyperactivation of release at short time scales. To verify this claim, we examined whether the
334 biphasic response of the decay time and cumulative $[\text{Ca}^{2+}]_{\text{AZ}}$ due to the first stimulus is
335 sustained after the second stimulus. Indeed, we observe that both decay time and cumulative
336 $[\text{Ca}^{2+}]_{\text{AZ}}$ retain their bell-shaped dependence on Pr_1 (*Fig 4E & 4F*). Importantly, the AD-
337 affected synapse exhibits markedly enhanced response to the second stimulus following the
338 elevated residual $[\text{Ca}^{2+}]_{\text{AZ}}$ due to the first pulse, in agreement with the notion that AD-affected
339 synapses can result in enhanced excitation of neuronal processes. These findings are consistent
340 with previous work showing that, particularly in the early stages of AD, over-excitation
341 dominates neuronal circuits with soluble $\text{A}\beta$ oligomers and contribute to cognitive dysfunction
342 and impairments [34—36]. In summary, AD-associated enhanced Ca^{2+} release from
343 intracellular stores leads to a history-dependent enhanced STP and hyperactivation of neuronal
344 processes at short time scales with respect to WT synapses. We also notice that the higher
345 coupling strength between the AZ and microdomain of IP_3Rs cluster exacerbate the enhanced
346 PPR but has a marginal effect on the bell-shaped behaviour of Pr_2 as a function of Pr_1 in AD-
347 affected synapses (*Supplementary Fig 2*).

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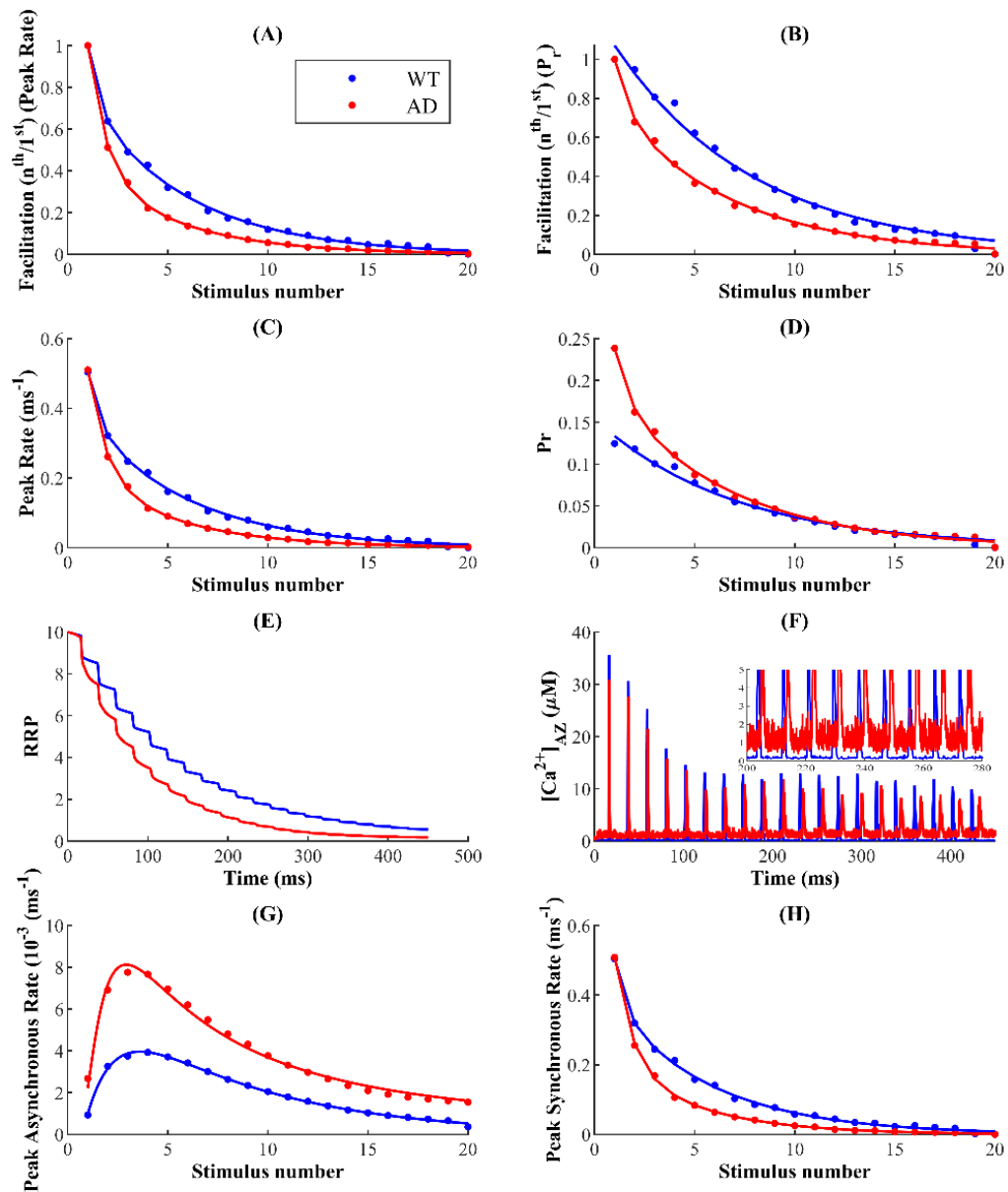
349 ***AD-associated Ca^{2+} rises differentially regulate synchronous and asynchronous release***
350 ***during repetitive stimulation***

351 Next, we investigate the effect of upregulate cytosolic Ca^{2+} on synaptic response following
352 trains of stimuli. As in the previous section, we stimulate the synapse with a train of 20 APs
353 delivered at 20 Hz and defined facilitation as the ratio of response following the n^{th} stimulus
354 (R_n) to that of the first (R_1) averaged over several trials. Therefore, synaptic response to
355 successive stimuli in the pulse train can either be depressed, with $R_n/R_1 < 1$, or facilitated, with
356 $R_n/R_1 > 1$. In both WT and AD-affected synapses, repetitive activation leads to depression of
357 both peak release rate (*Fig 5a*) and Pr (*Fig 5b*) that increase with subsequent stimuli. Here, the
358 AD-affected synapse exhibits lower peak release rate (*Fig. 5C*) and baseline Pr (*Fig. 5D*)
359 leading to lower facilitation that persists throughout activation. The depression due to higher-
360 frequency longer (~450 msec) stimulus train observed in the AD-affected synapse results from
361 rapid depletion of the vesicles in the RRP relative to the WT synapse (*Fig 5E*).

362
363 Although evoked peak release rate and Pr exhibit similar decay as functions of pulse number,
364 AD-associated Ca^{2+} disruptions differentially affect these two properties. While the peak
365 release rate in case of the WT synapse remains mostly higher than that of the AD-affected
366 synapse, the Pr in case of AD-affected synapse is consistently higher following successive
367 stimuli (*Fig 5C & 5D*). These results indicate that during ongoing activity, ER-mediated Ca^{2+}
368 disruptions drives a competition between the primary modes of exocytosis; short-lived
369 synchronous release that dominates evoked release during low-frequency stimulation, and
370 slower asynchronous release which persists for several milliseconds and builds up during
371 higher-frequency stimuli trains [1, 37]. Consistent with previous reports, we observe that
372 during the pulse-train depression, synchronous release progressively declines, whereas
373 asynchronous release peaks and subsequently decays with stimulus number (*Fig 5G & 5H*).
374 These results also show that while both forms of release compete for the same pool of releasable
375 vesicles, residual Ca^{2+} , which builds up during repetitive stimulation may allow asynchronous
376 release access to a larger subset of the RRP initially [38, 39, 40]. Our findings here indicate
377 that impairments such as AD pathology, which trigger elevated levels of residual intracellular
378 [Ca^{2+}] (*Fig 5F*), significantly enhance asynchronous release during first few pulses (*Fig 5G*).
379 For both WT and AD-affected synapses, the decrease in asynchronous release after the peak is
380 dictated by competition with synchronous release for the same vesicle resources, which are
381 rapidly depleted with subsequent stimuli (*Fig 5G & 5H*) [39, 41]. Interestingly, the greater

382 degree of depression in the AD-affected synapse is positively correlated with profound increase
383 and decrease in the rates of asynchronous and synchronous release respectively. Together, our
384 data suggest that during the stimulus train, AD pathology elicits significantly more
385 asynchronous release at the expense of synchronous release, consistent with the notion that
386 elevated residual Ca^{2+} underlies asynchronous release. Since the majority of evoked exocytosis
387 occurs synchronously with AP-triggered Ca^{2+} influx, the enhanced switch from synchronous
388 to asynchronous release in the AD-affected synapse reflects the increased depression of
389 synaptic transmission with repetitive stimulation. As clear from *Supplementary Fig 3*, the
390 higher coupling between the microdomain around IP_3Rs cluster and AZ exacerbate the synaptic
391 depression in AD-affected synapses more than WT synapses.

392



393

394 **Figure 5.** *The AD-affected synapse exhibit stronger depression in response to 20 pulse*
 395 *stimulus-train delivered at 20 Hz. Facilitation obtained from peak rate (A) and Pr (B) shows*
 396 *that AD pathology induces more severe depression relative to control conditions. Peak release*
 397 *rate (C) and Pr (D) following each AP in the train. (E) Pulse train depression is primarily*
 398 *governed by RRP depletion, which is more severe in synapses with AD pathology. (F)*
 399 *[Ca²⁺]_{AZ} (top) and zoom-in (inset) showing the differences in basal [Ca²⁺]_{AZ} levels. (G)*
 400 *Asynchronous release peaks and subsequently decays following depletion of RRP. (H) Peak*
 401 *synchronous release mimics the response seen in the overall release.*

402

403 ***Synchrony of release events is reduced in the AD-affected synapses***

404 Motivated by substantial evidence supporting reduced temporal coordination of neural activity
405 in AD-affected networks, we next examine the degree of synchronization between stimulus
406 and response in WT and AD-affected synapses during repetitive stimulation [118—120]. Given
407 the loose temporal coordination of neuronal response during asynchronous release, the
408 observed shift from synchronous to asynchronous release during stimulation in AD should
409 reduce the synchrony between the pulse and response [39]. To test this hypothesis, we measure
410 the event synchrony between each spike in the pulse train and corresponding release using a
411 modified Pinsky-Rinzel algorithm (see Methods for details) [121, 123]. In extreme cases, pulse
412 and release event times can either be perfectly aligned with synchrony value of 1, reflecting
413 pristine temporal stimulus-response coordination, or desynchronized where synchrony value
414 of 0 reflects temporally uncorrelated activity and stimulus patterns.

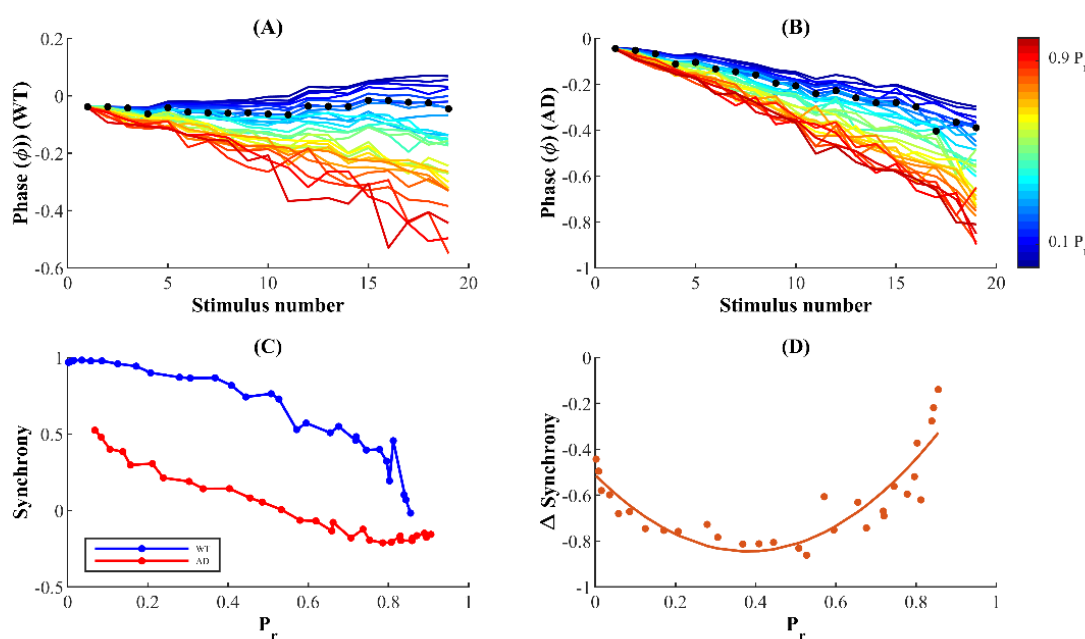
415

416 The phase of individual release events in response a stimulus train reveals that synapses with
417 AD pathology exhibit significant decrease in coherence of stimulus and release events, an
418 observation that is seen consistently across a wide range of the Pr values (*Fig 6a & b*). In-silico
419 studies of the effect of presynaptic Ca²⁺ stores on exocytosis at the CA3 terminal suggest that
420 the ER allows highly stochastic hippocampal synapses with low intrinsic release probability to
421 operate with increased reliability [9]. Unsurprisingly, in both the diseased and WT cases,
422 synapses with low Pr exhibit relatively higher phase coherence that persists upon subsequent
423 stimulation (*Fig 6a & b*). Thus, our findings here suggest that the alternative strategy to achieve
424 robust firing rates—employed by synapses with high intrinsic Pr that deplete the RRP
425 quickly—may render the synapses unreliable during repetitive stimulation.

426

427 Furthermore, a quantitative comparison of the synchrony measure reveals that AD-affected
428 synapses with altered intracellular Ca²⁺ signalling exhibit significantly reduced temporal
429 coordination of activity as compared to WT synapses. This suggests that in addition to other
430 impairments discussed above, unreliability in the temporal coordination of neuronal activity is
431 also a key hallmark of AD-affected synaptic terminals (*Fig 6c*). This conclusion is consistent
432 with *in vivo* recordings from neocortical pyramidal neurons where amyloid- β plaques in APP-
433 Sw (Tg2576 transgenic mice model of AD) increased jitter in evoked AP, consequently
434 reducing synaptic integration and information transfer [122]. Although our data so far indicate

435 that synapses with higher P_r express reduced synchronization in both WT and AD conditions,
436 the relative sensitivity of synapses with low, intermediate, and high P_r to pathological
437 alternations is yet to be explored. Thus, we next examine the relative change in synchrony from
438 WT to AD condition across a wide range of P_r values (*Fig 6d*). Our results show that there is
439 an inverted bell-shaped relationship between relative synchrony and intrinsic P_r , suggesting
440 that the physiological (intermediate) P_r which allows small hippocampal synapses to operate
441 with reliable firing rates also renders them more sensitive to pathological alterations. Taken
442 together, these data suggest that the pathophysiological manifestations of impaired intracellular
443 Ca^{2+} handling include suboptimal neuronal synchronization, reducing the fidelity of
444 information integration and transmission. In addition, the results confirm that hippocampal
445 synapses with intermediate P_r values exhibit a more severe impairment of their otherwise finely
446 tuned temporal rate codes when subject to AD-related alterations in Ca^{2+} signalling.



447

448 **Figure 6.** *AD-related Ca^{2+} disruptions impair spike-SVR synchrony.* The phase of individual
449 release events with respect to AP in WT (A) and AD-affected (B) synapses over a wide range
450 of P_r values. Black dots indicate the event phases corresponding to 35 VGCCs with initial P_r
451 during pulse train (P_{r1}) equal to 0.14. (c) Synchrony of release event in response to the
452 preceding pulse in WT and AD-affected synapses. (d) The magnitude of relative synchrony
453 change from WT to AD conditions as a function of initial release probability during prolonged
454 stimulation.

455

456

457 **Discussion**

458 Despite extensive experimental studies reporting the ubiquitous presence of ER in both axonal
459 and dendritic compartments of neurons, little is known about its role in modifying major
460 components of synaptic transmission during AD related pathologies [42–44]. In this study, we
461 fill this gap by building a detailed biophysical model that accurately captures the
462 compartmentalized signalling of Ca^{2+} at axonal terminals. In particular, our model incorporates
463 ER-driven and AP-triggered presynaptic Ca^{2+} signalling as well as the resulting release
464 mechanism in WT and AD-affected synapses. This is especially motivated by reports of distinct
465 regulatory mechanisms for intracellular Ca^{2+} , which primarily includes a cluster of ligand-
466 gated IP_3R Ca^{2+} channels situated on the ER as well as voltage activated Ca^{2+} channels
467 constrained to the AZ, that result in tight microdomain signalling [6, 66–69]. In hippocampal
468 synapses, the formation of evoked transient Ca^{2+} microdomains in the AZ is predominantly
469 mediated by the rapid kinetics of P/Q-type VGCCs which open with minimal delay upon the
470 arrival of AP, while subcellular domains in the vicinity of the ER occurs via the stochastic
471 gating of IP_3Rs that require IP_3 and Ca^{2+} binding. In order to make meaningful quantitative
472 predictions, we proceeded by developing a model that accurately captures the characteristic
473 IP_3R 's gating in WT and AD-affected neurons [16, 17, 128]. We next, incorporated a
474 comprehensive description of presynaptic processes including evoked Ca^{2+} influx through
475 VGCCs; Ca^{2+} release and uptake by the ER; and synchronous, asynchronous, and spontaneous
476 modes of synaptic transmission. Inspired by several lines of evidence elucidating the existence
477 of a bidirectional interaction of intracellular Ca^{2+} channels and presynaptic VGCCs mediated
478 by stromal interaction molecules (STIM-1) and Orai channels, we have implemented a bi-
479 directional coupling between the ER and AZ in our model that uncovers a unique biphasic
480 dependence of decay times of release and Ca^{2+} on the baseline probability [7, 73]. Our model
481 incorporates these critical components of presynaptic signalling and especially reproduced the
482 observed spatiotemporal characteristics of intracellular Ca^{2+} —rise times, decay times, and
483 amplitudes of corresponding events—and accounts for the stochasticity of presynaptic Ca^{2+}
484 dynamics driven by stochastic channel openings [6, 16, 70, 71]. Release rate, facilitation and
485 depression varies dramatically among phasic and tonic synapses—phasic synapses are
486 dominated by depression, whereas tonic synapses can facilitate tremendously by vesicle
487 recruitment [27, 28]. Constrained by kinetics data of vesicular release observed in other phasic

488 cell types, our model closely reproduces essential determinants of neurotransmitter release,
489 which consequently promoted close estimation of PPR and facilitation requirements necessary
490 to maintain normal plasma membrane function [23, 24, 28]. Following these independent
491 validations, it is reasonable to assume that the biophysical model and protocols developed in
492 this work are physiologically realistic representation of neuronal processes in control and
493 disease cases.

494
495 Broadening of Ca^{2+} waveforms and response profiles affect the reliability of synaptic
496 information transfer at affected terminals. Our results suggest that AD-associated increase in
497 Ca^{2+} release from the ER affect nearly all aspects of SVR. Despite the high stochasticity at the
498 hippocampal CA3 terminal, the ER allows individual synapses operating in the low- and
499 intermediate-probability regime maintain relatively higher reliability of information-rate
500 coding [9]. Here, our results show that the AD-associated enhanced Ca^{2+} selectively diminishes
501 the reliability of intermediate-Pr synapses, suggesting that low- and intermediate Pr synapses
502 are more susceptible to AD-associated Ca^{2+} disruptions. Importantly, the model predicts that
503 aberrant Ca^{2+} rise in AD-affected neurons may trigger hyperactivity over very short timescales
504 (~30-60 msec) and lowers facilitation during prolonged (~450 msec) stimulation. We also
505 report enhanced excitability in pathological synapses when simulated with higher coupling,
506 which corresponds to a tighter feedback loop between the ER and AZ. Thus, our findings here
507 provide a plausible explanation for why alterations in ER Ca^{2+} handling, which result in
508 excessive efflux, induce a severe perturbation of neuronal processes that can in turn decrease
509 the reliability of information encoded in the firing rate of neurons affected by AD pathology
510 [9, 72]. Overall, our findings provide novel insights into the role of aberrant ER Ca^{2+} release
511 in altering the release profile of a synapse in AD and other neurodegenerative diseases where
512 such Ca^{2+} impairments are observed [136].

513
514 Many explorations into the Ca^{2+} -dependence of release have proposed that periodic Ca^{2+}
515 release from the ER, which occurs predominantly via the rapid gating kinetics of IP_3R , could
516 trigger a series of physiological events—such as activating Ca^{2+} -sensing G proteins—that
517 eventually manifest as changes in the global $[\text{Ca}^{2+}]$ and, in turn, influence spontaneous release:
518 a miniature form of exocytosis [21, 47]. Although IP_3Rs are differentially expressed according
519 to cell type, several studies report the functional involvement of IP_3Rs in sculpting long-term
520 potentiation (LTP) or depression (LTD) profiles in the CA1 region of the hippocampus [48,
521 50]. In particular, immunocytochemical evidence reveals the expression of IP_3Rs in presynaptic

522 terminals of the rat CA3-CA1 hippocampal synapses and elucidates their modulatory role in
523 presynaptic neurotransmitter release and synaptic plasticity [49]. Shorter opening times and
524 longer closing times are characteristic features of the gating kinetics of IP₃R_s in cortical
525 neurons and are essential for the homeostasis of local and global Ca²⁺ in the norm. Consistent
526 with these requirements, studies on AD patients have implicated exaggerated Ca²⁺ release
527 mediated by altered IP₃R activity to dysregulation of bulk Ca²⁺ which consequently triggers
528 progressive loss of synaptic function [51—54]. From our model it is clear that these intrinsic
529 biophysical properties of IP₃R make it highly effective at maintaining physiological bulk Ca²⁺
530 and *Pr*, whereas upregulated IP₃R orchestrates exaggerated Ca²⁺ from the ER and in turn
531 increases the *Pr*.

532

533 Consistent with experimental evidence, our model reproduces the well-established inverse
534 relationship between the *Pr* and PPR but suggests that the enhanced STP over rapid timescales
535 observed in AD merely indicates hyperactivity rather than increased synaptic reliability [23,
536 59]. The most crucial insight from this finding is that pathological synapses retain a longer
537 history of Ca²⁺ dynamics, which consequently causes them to exhibit enhanced excitation in a
538 paired-pulse protocol. The traditional view claiming the massive reduction in the efficacy of
539 excitatory synaptic transmission in early stages of AD has been challenged recently by several
540 studies reporting aberrant Ca²⁺ homeostasis and hyperactivity in AD-affected neuronal
541 networks [10, 36, 34]. A key finding of these studies is that hyperactivity is an early dysfunction
542 in hippocampal synapses, whereas neuronal silencing emerges during later stages of the
543 disease. Our model predicts that synaptic facilitation and depression depend on the timescale
544 and frequency of stimulation. Relatively short low-frequency stimuli cause facilitation, which
545 supports the idea that by enhancing potentiating over rapid time scales, aberrant Ca²⁺ release
546 from intracellular stores plays an important role in the history-dependent neuronal
547 hyperactivity observed during early states of AD.

548

549 Our model shows that long high-frequency pulses trigger depression in AD-affected synapses,
550 which is governed by depletion of RRP of vesicles. Experimental evidence reports three
551 distinct molecular pathways for exocytosis [37]. Indeed, synchronous, asynchronous, and
552 spontaneous modes of vesicular release, characterized by distinct release timescales, have been
553 reported in cultured hippocampal synaptic terminals [21, 38]. Synaptotagmin-1 (Syt1) and 7
554 (Syt7) are the Ca²⁺ sensors controlling the timescales of synchronous and asynchronous release
555 in CA3 pyramidal neurons respectively [37, 60]. The rapid kinetics and low Ca²⁺ affinity of

556 Syt1 satisfies the remarkable temporal precision of synchronous release, where most vesicles
557 immediately fuse with the membrane following stimulation. On the other hand, the slow
558 kinetics of Syt7 promotes progressive desynchronization of release later in the spike train [61].
559 Studies on Syt1 knockout mice reported selective abolishment of synchronous release and
560 increase in the magnitude of asynchronous release. Likewise, knockdown of Syt7 enhanced
561 synchronous release in zebrafish's neuromuscular junction, suggesting that the primary modes
562 of exocytosis draw from the same vesicle resources in the RRP, which causes their activity
563 patterns to be negatively correlated [38, 61—65]. The most critical insight of these findings is
564 that manipulations that suppress synchronous release increases the vesicle resources available
565 for asynchronous release and indirectly enhance its magnitude. In agreement with the above,
566 during ongoing activity, we observed a shift from synchronous to asynchronous exocytosis
567 leading to increased depression of synaptic transmission during AD pathology.

568

569 CA3-CA1 presynaptic terminals are equipped with a conspicuously low release probability that
570 allows them to maintain a delicate balance between facilitation and reliability, giving rise to
571 finely tuned rate codes with remarkable temporal precision. Thus, perturbations of release
572 mechanisms are expected to alter the fidelity of neural rhythms in AD. Indeed, cortical neurons
573 with A β peptide expressed reduced N-methyl D-aspartate (NMDA) receptor density, resulting
574 in rapid and persistent depression of NMDA-evoked currents [120]. Moreover, the severe
575 impairment of evoked synaptic response latency observed in Tg2576 mice overexpressing APP
576 provides direct evidence for reduced temporal coincidence of response in AD [122]. These
577 findings suggest that impaired response precision is an acute effect of perturbations due to AD
578 that leads to overt cortical deficits. In agreement with these observations, our results reveal
579 increased latency of release events in AD and uncover unique dependence of synchrony
580 change—from control to AD—on intrinsic Pr. The loss in temporal coordination of release in
581 AD is more severely expressed at a physiologically plausible Pr range for hippocampal
582 synapses, although lower-Pr synapses exhibit relatively elevated temporal precision in both
583 WT and AD-affected synapses. Thus, despite the high fidelity of hippocampal synapses, their
584 conspicuously low response success may make them more susceptible to AD pathology. We
585 hope that future experiments will uncover the molecular mechanisms underlying the
586 pathological enhancement of susceptibility in low-Pr hippocampal synapses.

587

588 We remark that while our model is developed to be consistent with most observations in the
589 hippocampal CA3-CA1 synapses, it does not incorporate the uneven distribution of P/Q-type,

590 N-type and R-type VGCCs specifically found in the AZ of central synapses [74, 75]. At
591 hippocampal glutamatergic synapses, Cav2.1—P/Q-type—channels are thought to be most
592 enriched at the presynaptic AZ and predominantly govern Ca^{2+} influx at the axon terminal [78].
593 Thus, like others, we value parsimony and use a formulation with only P/Q VGCCs [70].
594 Furthermore, results from cultured hippocampal and superior cervical ganglion neurons
595 provide evidence for direct interactions between the release machinery and VGCCs, implying
596 that channel distribution is important for accurately predicting the spatiotemporal profiles of
597 evoked release [76, 77]. Our model does not capture the effect of spatial distribution of VGCCs
598 on synaptic transmission, neither does it incorporate other mechanisms for paired-pulse
599 modulation expressed at putative single hippocampal synapses—lateral inhibition and release
600 inactivation [23, 24]. Thus, despite reproducing the observed inverse relationship between
601 paired-pulse facilitation and initial Pr, our model falls short of the measured values, suggesting
602 that we cannot eliminate additional mechanisms when investigating the interplay between
603 residual Ca^{2+} , facilitation, and depression. Although IP_3R -dependent modulation of cytosolic
604 Ca^{2+} is usually adequate for explaining the critical aspects of ER Ca^{2+} release and regulation
605 of neurotransmission, the upregulation of RyR expression and modulation of IP_3Rs ' gating due
606 to Ca^{2+} release through RyRs (and vice versa) are also thought to play a key role in the aberrant
607 Ca^{2+} release from the ER, as well as propagation of presynaptic signals [16, 17, 79, 94—100,
608 127—129]. It has been suggested that at the hippocampal Schaffer-collateral pathway,
609 presynaptic presenilin inactivation perturbs STP and facilitation via impaired RyR function
610 [80, 81]. Furthermore, in 3xTg-AD mice, deviant RyR activity triggers Ca^{2+} signalling
611 alterations that promote synaptic depression [82]. However, our model does not describe the
612 contribution of presynaptic RyRs to vesicular release, as the biophysical properties of these
613 receptors yield a distinct temporal range of Ca^{2+} transients that can modulate LTP/LTD [83,
614 84]. Another key factor missing from our model is synaptic mitochondria. Mitochondria play
615 a key role in shaping Ca^{2+} gradients in synaptic terminals. Synaptic mitochondria are among
616 the earliest targets in AD. Among other things, the ATP production and Ca^{2+} buffering
617 capacities of mitochondria are severely disrupted [140, 141]. All these issues are the subjects
618 of our future research.

619

620 In summary, we have leveraged diverse experimental data to model Ca^{2+} homeostasis in axonal
621 terminal and how exocytosis is affected in AD. Motivated by the difficulty in probing signalling
622 cascades at the AZ of small hippocampal synapses, our main goal was to build a comprehensive
623 but simple framework for unravelling the role of enhanced Ca^{2+} release from the ER in SVR

624 during AD pathology. In addition to agreeing closely with several observations about the
625 kinetics of IP₃Rs, SVR, and synaptic plasticity in both WT and diseased synapses, our
626 modelling work provides key insights into impaired presynaptic function in AD. Specifically,
627 we make five key predictions: (1) the overall Pr in response to a single AP is upregulated in
628 AD-affected synapses, (2) short-lived low-frequency stimuli promotes potentiation in AD-
629 affected synapses, (3) during sustained high-frequency stimulation, AD-affected terminals
630 exhibit enhanced depression, (4) AD-affected synapses operate less reliably, and (5) the effect
631 of AD pathology is exacerbated in synapses with low to intermediate Pr. Taken together with
632 the aforementioned limitations, our analysis highlights the need for further studies on
633 investigating the role of perturbed Ca²⁺ signalling due to intracellular organelles such as the ER
634 and mitochondria in cognitive deficits associated with AD and other neurodegenerative
635 diseases.

636

637 **Materials and Methods**

638 *Calcium model*

639 Building on extensive literature, we capture intracellular Ca²⁺ dynamics by first developing a
640 compartmental model of a hippocampal CA3 axonal bouton, which includes main fluxes that
641 invade the bulk cytosol as well as regulatory mechanisms present in the ER [67, 109—111]
642 (*Fig. 7*). Our canonical synaptic bouton is modelled as a sphere with fixed volume $V_{bouton} =$
643 $0.122 \mu\text{m}^3$, in agreement with findings from ultrastructural analysis of hippocampal synapses
644 [2, 78]. We consider an average of 1.3 AZs in small hippocampal boutons implemented in a
645 spherical AZ (with area = $0.04 \mu\text{m}^2$) [2, 78]. Although we assume a well-mixed cytoplasm, we
646 next incorporate two microdomains of sharp Ca²⁺ transients produced by clusters of IP₃R and
647 VGCCs proximal to the ER and plasma membrane respectively. Because the VGCCs (P/Q-
648 type Cav2.1 channels) implemented here are spatially distributed in small clusters within the
649 AZ, we implemented a characteristic 25 nm cluster [6, 78]. To account for the spatial extent of
650 the Ca²⁺ domain in the vicinity of the VGCCs cluster, we use the findings in cortical pyramidal
651 terminals that show that low mM concentrations of the slow Ca²⁺ buffer ethylene glycol
652 tetraacetic acid potently attenuates transmitter release [46, 115, 116] for guidance. We consider
653 a cytosol-to-VGCCs microdomain ratio of 60, assuming a domain of elevated [Ca²⁺] that
654 extends over more than 100 nm [46, 66]. As a result of these considerations, the Ca²⁺ dynamics

655 in the respective compartments as well as the entire bouton ($[Ca_{total}^{2+}]$) is described by four
 656 couple non-linear ODEs (*Eqs. 1-4*). *Tables 1* defines the fluxes (J) in terms of various Ca^{2+}
 657 concentrations, along with volume fractions. The parameters used are listed in *Tables 2* and *3*.
 658 As a critical second messenger, the pathways for IP_3 metabolism are succinctly described in
 659 *Eq. 5* [112, 114], with further details in *Table 4*. Inhomogeneity of ligands persists throughout
 660 the bouton; however, we assume spatially homogenous compartments, and only track temporal
 661 evolution of ligands.

$$662 \quad \frac{d}{dt} [Ca_{cyt}^{2+}] = J_{in} + J_{IPR-diff} - J_{PMCA} + J_{ER-leak} + J_{VGCC-diff} - J_{SERCA}, \quad (1)$$

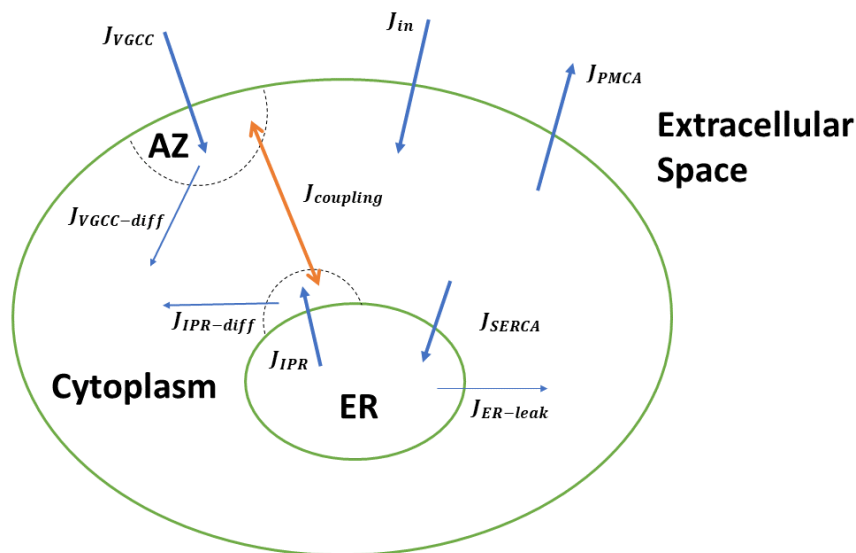
$$663 \quad \frac{d}{dt} [Ca_{IPR_n}^{2+}] = \delta_1 (J_{IPR} - J_{IPR-diff}) + J_{coupling}, \quad (2)$$

$$664 \quad \frac{d}{dt} [Ca_{AZ}^{2+}] = \delta_3 (J_{VGCC} - J_{VGCC-diff}) - \frac{1}{\delta_1} J_{coupling}, \quad (3)$$

$$665 \quad \frac{d}{dt} [Ca_{total}^{2+}] = J_{in} - J_{PMCA} + J_{VGCC}, \quad (4)$$

$$666 \quad \frac{d}{dt} [IP_3] = \frac{1}{\tau_{IP_3}} (J_{PLC} - J_{deg}), \quad (5)$$

667 where $[Ca_{cyt}^{2+}]$ is the Ca^{2+} concentration in the cytosol, $[Ca_{IPR_n}^{2+}]$ is the Ca^{2+} concentration in
 668 the microdomain surrounding the IP_3 Rs, and $[Ca_{AZ}^{2+}]$ represents the Ca^{2+} concentration
 669 surrounding the small cluster of VGCCs in the AZ.



670

671 **Figure 7.** Schematic of the overall multi-compartmental Ca^{2+} model. The arrowheads show the
 672 direction of the fluxes involved and the dotted half circles signify the Ca^{2+} domains around the
 673 IP₃Rs and VGCCS clusters.

674

675 The Ca^{2+} concentration in the ER is given by $[Ca_{ER}^{2+}] = \delta_2(Ca_{total}^{2+} - Ca_{cyt}^{2+} + Ca_{IP_3R_n}^{2+}/\delta_1 -$
 676 $Ca_{AZ}^{2+})$. δ_1 , δ_2 , and δ_3 represent the volume ratios of the intracellular compartments and are
 677 explained in *Table 4*. Fluxes in our model were selected to account for the essential regulating
 678 components of intracellular Ca^{2+} signalling. J_{in} represents the Ca^{2+} entry through plasma
 679 membrane channels such as store operated Ca^{2+} channels (SOCC) and basal plasma membrane
 680 leak. J_{IPR} represents release from the ER through IP₃Rs, whereas Ca^{2+} diffusion from the
 681 microdomain around IP₃Rs cluster to the bulk cytosol is modelled by $J_{IPR-diff}$. Likewise,
 682 $J_{VGCC-diff}$ and J_{VGCC} are included to account for Ca^{2+} diffusion from the AZ to the bulk
 683 cytoplasm and influx through VGCCs respectively. Ca^{2+} efflux from the intracellular
 684 compartment by plasma membrane Ca^{2+} ATPase (PMCA) is captured by J_{PMCA} , and $J_{ER-leak}$
 685 is the Ca^{2+} leak from the ER. Sequestering of Ca^{2+} from the cytoplasm into the ER through
 686 Sarco/Endoplasmic Reticulum Ca^{2+} ATPase (SERCA) is represented by J_{SERCA} .

687

688 To investigate the effect of altered ER Ca^{2+} handling on vesicular fusion situated in the AZ, we
 689 incorporate a flux ($J_{coupling}$) intended to mimic the close association of the ER with the nerve
 690 terminal of CA3 pyramidal neurons [101—103]. Based on evidence of the existence of a
 691 feedback loop between synaptic function and ER Ca^{2+} content, we build a bidirectional model
 692 of Ca^{2+} exchange. We assume a simple transfer of Ca^{2+} between the two microdomains,
 693 potentially mediated by Ca^{2+} buffering and enzymatic proteins. This coupling is modelled by
 694 an equation analogous to bidirectional models of SERCA flux (*Eq. 6*) [111], which where V_c is
 695 the maximum flux from the AZ to the microdomain around IP₃R cluster and K_c determines the
 696 half-maximal transfer rate.

$$697 \quad J_{coupling} = V_c \frac{([Ca_{AZ}^{2+}]^2 - \bar{k}([Ca_{IP_3R_n}^{2+}]^2))}{[Ca_{AZ}^{2+}]^2 - K_c^2} \quad (6)$$

698 There is strong evidence that the expression of Ca^{2+} buffering proteins in AD affected neurons
 699 is significantly lower than WT neurons [133—135]. We incorporate these observations in our
 700 model by using parameter values that results in a stronger coupling in AD-affected bouton as

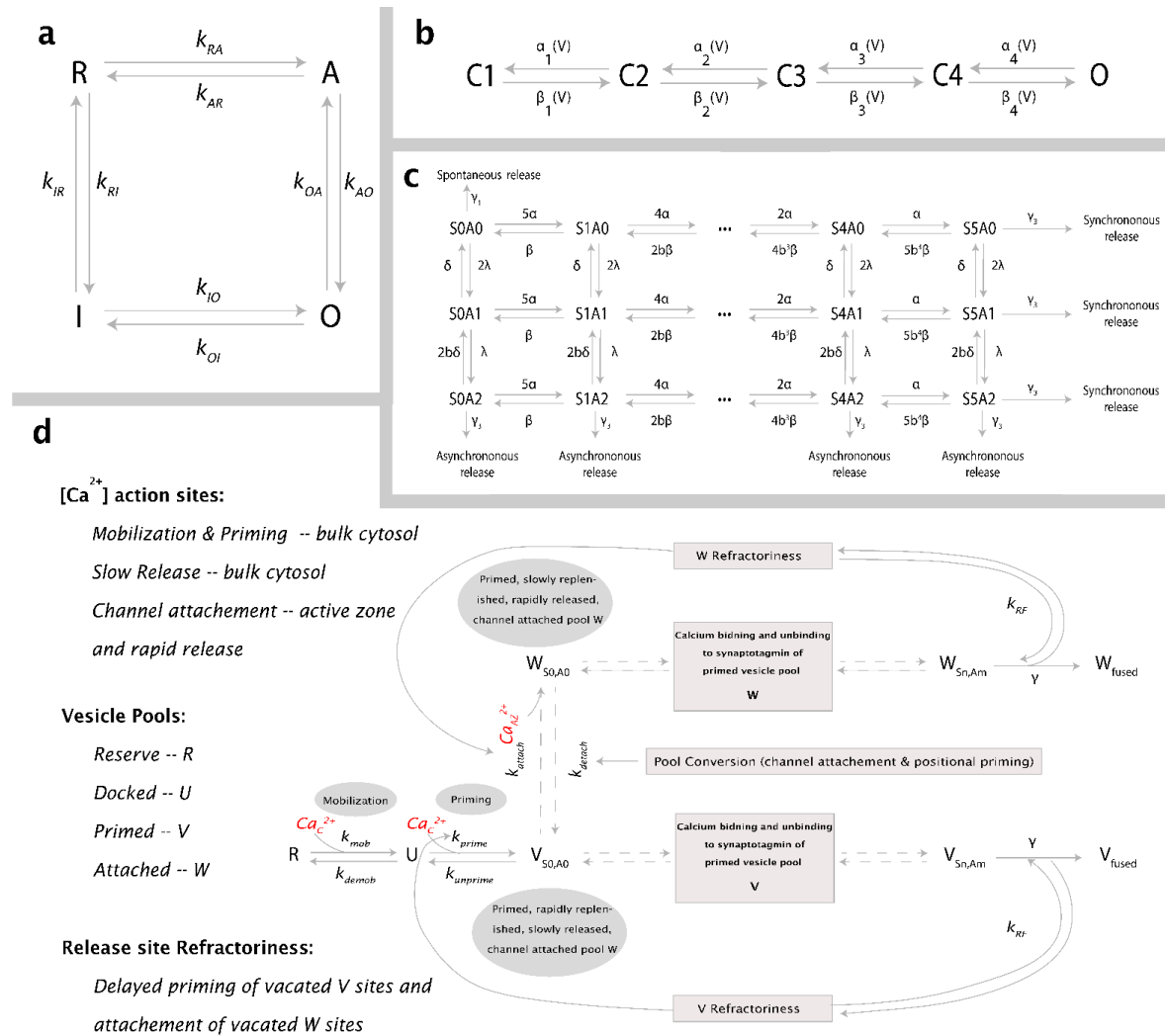
701 compared to WT bouton. Although the choice of the model has its limitations, using a model
702 that captures buffered Ca^{2+} diffusion becomes numerically intractable quickly as distances
703 approach physiologically reasonable order of nanometres. Thus, this approach provides an
704 extremely useful method to account for the interplay of $[\text{Ca}_{AZ}^{2+}]$ and $[\text{Ca}_{IPR_n}^{2+}]$.

705

706 ***IP₃R model***

707 In the past, several models for IP₃Rs have been developed in WT and AD-affected cells [16,
708 137—139]. All these models are based on data obtained from non-neuronal cells. While these
709 models can be used to make reliable qualitative predictions, our goal here is to quantify the
710 effect of upregulated Ca^{2+} signalling on neurotransmitter release where a small difference in
711 the open probability of the channel or dwell times can result in a significant change due to the
712 small volume of the synaptic terminal. Thus, we developed a new four-state model to
713 implement the kinetics of IP₃Rs (*Fig. 8A*). The channel has zero, two, two, and five Ca^{2+} bound
714 when in the Resting (R), Active (A), Open (O), and Inactive (I) states, respectively. The
715 transition rates between different states and the corresponding parameters are reported in
716 *Tables 5* and *6* respectively. As shown in *Fig. 1*, the model closely fits the kinetics of IP₃R in
717 neurons from WT and 3xTg AD mice observed in [127]. In the cluster, the gating of each IP₃R
718 is regulated by the Ca^{2+} concentration in the microdomain around the cluster.

719



720

721 **Figure 8.** Kinetic schemes used in the model. (A) Gating kinetics of IP₃R. Four-state model

722 representing the possible states along with corresponding transition rates. (B) Model for VGCC

723 gating with four closed states (C1 - C4) and one open Ca²⁺ conducting state (O). (C) Scheme

724 for Ca²⁺ binding to Synaptotagmin with dual Ca²⁺ sensors for fast synchronous (S with five

725 Ca²⁺-binding sites), slow asynchronous (A with two Ca²⁺-binding sites), and spontaneous

726 exocytosis. (D) Modified from [27], the overall release scheme which includes vesicle

727 mobilization from a reserve pool (R) to docked, unprimed pool (U), molecular priming to

728 vesicles unattached to a Ca²⁺ channel (V), and conversion to vesicles coupled to a VGCCs

729 cluster (W). Both vesicle pools are released through the dual sensor release model. Channel

730 attached vesicles are steeply dependent on [Ca²⁺]_{AZ}, whereas [Ca²⁺]_{cyt} governs the release of

731 detached vesicles. Reaction rates along with respective references are listed in Tables 6, 8, and

732 9.

733

734 **Membrane voltage dynamics**

735 The basic equations for the membrane potential used in our model are adopted from Ref. [125].
736 Membrane potential (V) is governed by primary Na^+ (I_{Na}), K^+ (I_K), Cl^- (I_{Cl}), and Ca^{2+} (I_{Ca}),
737 currents, as well as current due applied stimulation (I_{app}), and is given as,

$$738 \quad C_m \frac{dV}{dt} = I_{app} + I_{Na} + I_K + I_{Cl} + \left(\frac{I_{Ca}}{Area} \right),$$

739 where we assumed standard membrane capacitance C_m of $1\mu\text{F}/\text{cm}^2$. The Na^+ and K^+
740 concentrations were assumed to be fixed, with corresponding currents consisting of active and
741 passive leak components given by

$$742 \quad I_{Na} = -(g_{Na} m_{\infty}^3 h)(V - E_{Na}) - g_{Na_{leak}}(V - E_{Na}),$$

$$743 \quad I_K = -\left(g_K n^4 + \frac{g_{AHP}[Ca^{2+}]_{cyt}}{1+[Ca^{2+}]_{cyt}} \right) (V - E_K) - g_{K_{leak}}(V - E_K).$$

744 Chloride currents only consist of passive leak contribution, defined by $I_{Cl} = -g_{Cl_{leak}}(V -$
745 $E_{Cl})$.

746 The steady state gating activation and inactivation variables, as well as associated channel
747 forward and reverse rates were calculated using the equations in *Table 7*. Various parameters
748 used in the membrane potential equations are listed in *Table 8*.

749

750 **Voltage gated Ca^{2+} channels**

751 Consistent with findings in [75], we implement only the predominant high-threshold Cav2.1
752 (P/Q-type) channels present at presynaptic nerve terminals using a five-state kinetic scheme
753 (see *Fig. 7B*). Voltage-dependent activation and deactivation rates for each closed state ($i = 1,$
754 $2, 3, 4$) were respectively calculated as follows: $\alpha_i(V) = \alpha_{i0} \exp(V/k_i)$, $\beta_i(V) =$
755 $\beta_{i0} \exp(V/k_i)$, where values for activation and deactivation rates at 0 mV, α_{i0} and β_{i0} , and for
756 slope factor k_i were taken from [75] and listed in *Table 8*. As with the IP₃Rs, we model VGCC
757 gating stochastically as a discrete-time Markov Chain (DTMC) (see “*Numerical Methods*”
758 section below). Single channel Ca^{2+} currents were calculated using $I_s = gP_o(V - E_{Ca^{2+}})$,
759 where values for conductance g , extracellular Ca^{2+} concentration and Nernst potential $E_{Ca^{2+}}$
760 were obtained from [6] and are reported in *Table 8*.

761

762 ***Overall release model***

763 The complete release scheme has been adopted and modified from [27] (see *Fig. 7C & 7D*). In
764 addition to the Ca^{2+} —dependent vesicle mobilization and priming steps, we replace the
765 independence of Ca^{2+} binding to C2A and C2B domains of synaptotagmin with the dual sensor
766 model proposed in [1], where two independent Ca^{2+} sensors act in parallel to trigger distinct
767 pathways of exocytosis that lead to fast synchronous, slow asynchronous, and spontaneous
768 release. Synchronous release is mediated by the sensor S with 5 Ca^{2+} -binding sites and
769 cooperativity(b) incorporated to progressively decrease backward rates— Ca^{2+} unbinding.
770 Synchronous fusion occurs when all 5 binding sites are occupied. Likewise, the sensor A —
771 with 2 Ca^{2+} -binding sites—mediates asynchronous release with the same cooperativity
772 parameter b . Spontaneous release is also included and occurs at a much slower rate when the
773 sensors have no Ca^{2+} bound. As in [70], release rates and model parameters were obtained
774 according to fits to experimental data reported in [113]. Contrary to the dual sensor model of
775 [1], we do not assume the synchronous (γ_2) and asynchronous (γ_3) release rates to be the same.
776 This is because according to [70], hippocampal release rates from [113] could not be fitted
777 otherwise. Consequently, we use the release rate for the asynchronous release to be $a\gamma$ where
778 $a = 0.025$.

779

780 As described in [1] and shown in *Fig. 2*, compared to the Allosteric model, this model captures
781 the expected heterogeneity and latency of exocytosis more accurately at the Calyx of Held.
782 Apart from the intrinsic heterogeneity of release pathways, the model implemented here
783 captures the heterogeneity of vesicle pools—slow and fast—, where docking and priming are
784 part of the upstream processes for recruiting vesicles into the Slow-Releasing Pool (SRP) and
785 super-priming of vesicles in the SRP aids the conversion of SRP vesicles to those in the Fast-
786 Releasing Pool (FRP). The recruitment of vesicles into the SRP is dependent on the cytosolic
787 $[\text{Ca}_{\text{cyt}}^{2+}]$, whereas channel attachment is aided by Ca^{2+} influx. As described in *Fig 7*, the target
788 of Ca^{2+} mediating vesicle fusion depends on which pool the fusing vesicle belongs to; for
789 vesicles in the FRP, this is $[\text{Ca}_{\text{AZ}}^{2+}]$, while those in the SRP bind $[\text{Ca}_{\text{cyt}}^{2+}]$.

790

791 We also include release site refractoriness introduced in [27, 70] in order to simulate
792 experimental observations. In this context, a vesicle cannot be released from a vacated site for

793 a period determined by k_{RF} , such that sites—either Ca^{2+} -attached (W) or detached (V)—from
794 which vesicles had been released remain unable to accept a new primed vesicle for some time.
795 Phasic synapses are known to have briefer refractoriness compared to their tonic counterparts,
796 and as such, we choose k_{RF} to be 0.01 ms^{-1} , similar to values observed at hippocampal synapses
797 in [23]. Different parameters used in the release model are listed in *Table 9*.

798

799 ***Synchrony measure***

800 For a wide range of synaptic configurations with distinct intrinsic release probabilities, we
801 computed the synchrony of AP arrival times (estimated at peak) and release event times using
802 a modified version of the Pinsky-Rinzel measure of synchrony [121]. We transformed the
803 firing times $T(k)$ for every k^{th} event of the neuron into a set of corresponding vector phases
804 $\phi(k)$ using *Eq. 7*, where $T_{AP}(k)$ corresponds to all the AP events within the duration of
805 simulation. For each vector phase $\phi(k)$, we compute the synchrony $r(\phi(k))$ —numbers
806 between 0 and 1—using the complex order parameter defined by Strogatz and Mirollo averaged
807 across all events for a single synaptic configuration [123] (*Eq. 8*).

808

$$809 \quad \phi(k) = \frac{T_{AP}(k) - T(k)}{T(k+1) - T(k)} \quad (7)$$

$$810 \quad r(\phi(k)) = \frac{1}{N_K} \sum e^{(2\pi i \phi(k))} \quad (8)$$

811

812 ***Numerical Methods***

813 Deterministic equations (*Eqs. 1-4*) are solved using the fourth-order Runge-Kutta algorithm
814 (RK4) with a $1 \mu\text{s}$ time step, while the stochastic states of the IP_3Rs and VGCCs are determined
815 by the corresponding kinetic schemes were simulated using a procedure outline in [117], which
816 is equivalent to Gillespie algorithm with fixed time step. All numerical simulations were
817 performed in MATLAB (The MathWorks, Natick, MA) and data analysis was carried out using
818 custom Python scripts (version 3.9).

819 ***Code availability***

820 The complete model code as well as analysis scripts will be posted on our lab's webpage after
821 the manuscript is accepted for publication.

822

824 **Tables**

825 **Table 1.** Ca²⁺ fluxes in the model.

Flux (reference)	Equation
Basal leak and R/SOCC [110, 111]	$J_{in} = J_{leakin} + V_{leakin}IP_3$
Ca ²⁺ diffusion from the IP ₃ R cluster [67]	$J_{IPR-diff} = k_{IPR-diff}(Ca_{IPRn}^{2+} - Ca_{cyt}^{2+})$
PMCA [67]	$J_{PMCA} = V_{PMCA} \frac{(Ca_{cyt}^{2+})^n}{(Ca_{cyt}^{2+})^n + K_{PMCA}^n}$
SERCA [67]	$J_{SERCA} = V_{SERCA} \frac{(Ca_{cyt}^{2+})^n}{(Ca_{cyt}^{2+})^n + K_{SERCA}^n}$
ER-leak [67]	$J_{ER-leak} = k_{ER-leak}(Ca_{ER}^{2+} - Ca_{cyt}^{2+})$
IP ₃ Receptor [67]	$J_{IPR} = k_{IPR}P_o(Ca_{ER}^{2+} - Ca_{IPRn}^{2+})$ $P_o = N_{open}/N_{IP3R}$
Ca ²⁺ diffusion from the VGCC cluster	$J_{VGCC-diff} = k_{VGCC-diff}(Ca_{AZ}^{2+} - Ca_{cyt}^{2+})$
ER—AZ Coupling	$J_{coupling} = V_c \frac{(Ca_{AZ}^{2+} - \bar{k}(Ca_{IP3Rn}^{2+}))}{Ca_{AZ}^{2+} - K_c^2}$
VGCC [6]	$J_{VGCC} = \frac{-I_{Ca^{2+}}}{zFV_{cell}}$ $I_{Ca^{2+}} = channel\ density \cdot cluster\ area \cdot I_s$ $I_s = gP_o(V - E_{Ca^{2+}}), P_o = N_{open}/N_{VGCC}$ $channel\ density = \frac{N_{VGCC}}{(AZ_{area} \cdot N_{AZ})}$

826

827

828

829 **Table 2.** Parameter values for the Ca^{2+} dynamics.

Parameters	Description	Value/Units	Notes
Cellular			
J_{leakin}	Plasma membrane leak influx	$0.03115 \mu\text{M}\cdot\text{ms}^{-1}$	From [67]
V_{leakin}	R/SOCC flux coefficient	0.2 ms^{-1}	From [67]
$k_{IPR-diff}$	$Ca_{IP_3R_n}^{2+}$ diffusional flux coefficient	10 ms^{-1}	From [67]
k_{IPR}	IP ₃ R flux coefficient	5 ms^{-1}	Modified from [67]
N_{IPR}	Total number of IP ₃ R channels	10	
$k_{ER-leak}$	ER-leak flux coefficient	0.0022 ms^{-1}	Modified from [67]
PMCA			
V_{PMCA}	Maximum capacity of PMCA	$3.195 \mu\text{M}\cdot\text{ms}^{-1}$	Modified from [67]
K_{PMCA}	Half activation PMCA constant	$0.5 \mu\text{M}$	From [67]
n_P	Hill coefficient of PMCA	2	From [67]
SERCA			
V_{SERCA}	Maximum capacity of SERCA	$10 \mu\text{M}\cdot\text{ms}^{-1}$	From [67]
K_{SERCA}	Half maximal activation SERCA constant	$0.26 \mu\text{M}$	From [67]
n_S	Hill coefficient of SERCA	1.75	From [67]
VGCC and Coupling			
$k_{VGCC-diff}$	Ca_{AZ}^{2+} diffusional flux coefficient	0.071 ms^{-1}	
V_{cell}	Terminal volume	$1.22 \times 10^{-6} \text{ L}$	Modified from [6]
$cluster\ area$	Area of VGCC cluster	$0.001963 \mu\text{m}^2$	Modified from [6]
AZ_{area}	Active zone area	$0.04 \mu\text{m}^2$	Modified from [2, 6]
N_{AZ}	Active zone number	1.3	Modified from [6]
V_c	Maximum capacity of transfer component	$118 \mu\text{M}\cdot\text{ms}^{-1}$	
\bar{k}	Concentrating power of the transfer components.	High coupling: $15 \mu\text{M}$ Low coupling: $5 \mu\text{M}$	
K_c	Half-maximal transfer rate	High coupling: $10 \mu\text{M}$ Low coupling: $20 \mu\text{M}$	

830

831

832 **Table 3.** Additional parameters used in the Ca^{2+} dynamics.

Parameter	Value / Units	Notes
Resting cytosol [Ca^{2+}]	0.1 μM	
Resting AZ [Ca^{2+}]	0.05 μM	
Resting Total [Ca^{2+}]	56 μM	
Resting [IP_3]	0.1 μM	
Extracellular [Ca^{2+}]	2.0 mM	
δ_1	100	Cytoplasmic to ER microdomain volume ratio
δ_2	10	Cytoplasmic to ER volume ratio
δ_3	60	Cytoplasmic to VGCC microdomain volume ratio

833

834

835 **Table 4.** IP₃ fluxes in the model.

Flux (reference)	Equation
PLC _δ [112, 114]	$J_{PLC} = \bar{V}_{PLC} \frac{(Ca_{cyt}^{2+})^2}{(Ca_{cyt}^{2+})^2 + K_{PLC}^2}$ $\bar{V}_{PLC} = V_{PLC} PLC$ $V_{PLC} = V_0 + V_Q \frac{q^2}{q^2 + K_Q^2}$ $q = H(t - t_1) * A\beta * e^{-r(t-t_1)H(t-t_1)}$ $\rho = V_R \frac{q}{q + K_R}$ $\frac{d}{dt} PLC = k_{f_{PLC}} G (PLC_{tot} - PLC) - k_{d_{PLC}} PLC$ $\frac{d}{dt} G = k_{f_G} (\rho + \delta) (G_{tot} - G) - k_{d_G} G$
IP ₃ Degradation [112]	$J_{deg} = \left(\eta \frac{(Ca_{cyt}^{2+})^2}{(Ca_{cyt}^{2+})^2 + K_{IP_3k}^2} + (1 - \eta) \right) IP_3$ $\eta = k_{3k} / (k_{3k} + k_{5p})$
Time constant of IP ₃ turnover	$\tau_{IP_3} = 1 / (k_{3k} + k_{5p})$

836

837 **Table 5.** Transition rates used in the IP₃R model

Rate/parameter	Equation
Transition rates	$k_{RA} = \left[1 \times \left(\frac{1}{j_{01}[Ca^{2+}]_c} + \frac{1}{j_{12}([Ca^{2+}]_c)^2} \right) \right]^{-1}$ $k_{AR} = \left[K_A([Ca^{2+}]_c)^2 \times \left(\frac{1}{j_{01}[Ca^{2+}]_c} + \frac{1}{j_{12}([Ca^{2+}]_c)^2} \right) \right]^{-1}$ $k_{AO} = \left[K_A([Ca^{2+}]_c)^2 \times \left(\frac{1}{j_{22}([Ca^{2+}]_c)^2} \right) \right]^{-1}$ $k_{OA} = \left[K_O([Ca^{2+}]_c)^2 \times \left(\frac{1}{j_{22}([Ca^{2+}]_c)^2} \right) \right]^{-1}$ $k_{OI} = \left[K_O([Ca^{2+}]_c)^2 \times \left(\frac{1}{j_{23}([Ca^{2+}]_c)^3} + \frac{1}{j_{45}([Ca^{2+}]_c)^5} \right) \right]^{-1}$ $k_{IO} = \left[K_I([Ca^{2+}]_c)^5 \times \left(\frac{1}{j_{23}([Ca^{2+}]_c)^3} + \frac{1}{j_{45}([Ca^{2+}]_c)^5} \right) \right]^{-1}$ $k_{RI} = \left[1 \times \left(\frac{1}{\tilde{j}_{01}[Ca^{2+}]_c} + \frac{1}{\tilde{j}_{45}([Ca^{2+}]_c)^5} \right) \right]^{-1}$ $k_{IR} = \left[K_I([Ca^{2+}]_c)^5 \times \left(\frac{1}{\tilde{j}_{01}[Ca^{2+}]_c} + \frac{1}{\tilde{j}_{45}([Ca^{2+}]_c)^5} \right) \right]^{-1}$
Occupancy parameters	$K_O = a_1 \frac{[IP_3]^{n_O}}{[IP_3]^{n_O} + K_{Od}^{n_O}}$ $K_A = a_2 \frac{[IP_3]^{n_A}}{[IP_3]^{n_A} + K_{Ad}^{n_A}}$ $K_I = a_2 \frac{[IP_3]^{n_I}}{[IP_3]^{n_I} + K_{Id}^{n_I}}$

838

839 **Table 6.** Parameter values for the IP₃ dynamics and IP₃R

Parameter	Description	WT	AD	Notes
IP₃ Model				
V_0	PLC-mediated IP ₃ production	0.15 μM	0.19 μM	From [114]
V_Q	Control parameter for influence of A β on IP ₃	7.82 μM	380 μM	From [114]
K_Q	PLC dissociation constant	0.0086 $\mu\text{g/mL}$	0.0086 $\mu\text{g/mL}$	From [114]
K_{IP_3k}	Half-activation for 3-kinase	0.6 μM	1.6 μM	From [114]
K_{PLC}	PLC sensitivity to Ca ²⁺	0.01 μM	0.016 μM	From [114]
k_{3k}	IP ₃ phosphorylation rate	1.5 μs^{-1}	0.7 μs^{-1}	From [114]
k_{5p}	IP ₃ dephosphorylation rate	0.01 μs^{-1}	0.005 μs^{-1}	From [114]
PLC				
k_{fPLC}	PLC-protein activation rate	0.35 μs^{-1}	0.75 μs^{-1}	From [114]
k_{bPLC}	PLC-protein deactivation rate	22 μs^{-1}	200 μs^{-1}	Modified from [114]
PLC_{tot}	Scaled total number of PLC	1	1	From [114]
G-Protein				
k_{fG}	G-protein activation rate	0.33 μs^{-1}	0.047 μs^{-1}	From [114]
k_{bG}	G-protein deactivation rate	2.17 μs^{-1}	4.7 μs^{-1}	From [114]
δ	G-protein intrinsic activity	0.01	0.012	From [114]
V_R	Maximal G-protein activation	7.4	10	From [114]
K_R	A β producing half-activation	4467 $\mu\text{g/mL}$	2000 $\mu\text{g/mL}$	From [114]
G_{tot}	Scaled total number of G-protein	1	1	From [114]
IP₃R				
a_1		17.05043 μM^{-2}	1.108278 $\times 10^2$ μM^{-2}	Fit
n_O		2.473407	2.473407	Fit
K_{Od}		0.909078 μM	0.909078 μM	Fit
a_2		18.49186 μM^{-2}	18.49186 μM^{-2}	Fit
n_A		0.093452	0.093452	Fit
K_{Ad}		1.955650 μM	1.955650 μM	Fit
a_3		2.340259 $\times 10^2$ μM^{-5}	1.4041556 $\times 10^2$ μM^{-5}	Fit
n_I		56.84823	56.84823	Fit
K_{Id}		0.089938 μM	0.089938 μM	Fit
j_{01}		3.031635 $\times 10^2$ $\mu\text{M}^{-1}\text{ms}^{-1}$	3.031635 $\times 10^2$ $\mu\text{M}^{-1}\text{ms}^{-1}$	Fit
j_{12}		3.230063 $\times 10^2$ $\mu\text{M}^{-2}\text{ms}^{-1}$	3.230063 $\times 10^2$ $\mu\text{M}^{-2}\text{ms}^{-1}$	Fit
j_{22}		4.814111 $\mu\text{M}^{-2}\text{ms}^{-1}$	5.3978052 $\mu\text{M}^{-2}\text{ms}^{-1}$	Fit
j_{23}		5.356155 $\mu\text{M}^{-3}\text{ms}^{-1}$	2.0652269 $\times 10^3$ $\mu\text{M}^{-3}\text{ms}^{-1}$	Fit
j_{45}		5.625616 $\mu\text{M}^{-5}\text{ms}^{-1}$	5.4319289 $\mu\text{M}^{-5}\text{ms}^{-1}$	Fit
\tilde{j}_{01}		3.013284 $\times 10^2$ $\mu\text{M}^{-1}\text{ms}^{-1}$	3.013284 $\times 10^2$ $\mu\text{M}^{-1}\text{ms}^{-1}$	Fit
\tilde{j}_{45}		2.648741 $\mu\text{M}^{-5}\text{ms}^{-1}$	8.512829 $\times 10^{-8}$ $\mu\text{M}^{-5}\text{ms}^{-1}$	Fit

840 **Table 7.** Parameter values for membrane potential equations.

Parameter	Value / Units	Description
C_m	1 $\mu\text{F}/\text{cm}^2$	Membrane Capacitance
g_{Na}	120 mS/cm^2	Maximum Conductance for active Na^+ channels
$g_{Na_{leak}}$	0.0175 mS/cm^2	Conductance for Na^+ passive leak channels
g_K	36 mS/cm^2	Maximum Conductance for active K^+ channels
$g_{K_{leak}}$	0.05 mS/cm^2	Conductance for K^+ passive leak channels
$g_{Cl_{leak}}$	0.05 mS/cm^2	Conductance for Cl^- passive leak channels
ϕ	5.0	
g_{AHP}	0.01	
α_n	$\frac{0.01(V + 34)}{1 - \exp(-\frac{V + 34}{10})}$	Forward rate for K^+ current activation gating variable
β_n	$0.125 \exp(-\frac{V + 44}{80})$	Backward rate for K^+ current activation gating variable
α_h	$0.07 \exp(-\frac{V + 44}{20})$	Forward rate for Na^+ current inactivation gating variable
β_h	$\frac{1}{1 + \exp(-\frac{V + 14}{10})}$	Backward rate for Na^+ current inactivation gating variable
α_m	$\frac{0.1(V + 30)}{1 - \exp(-\frac{V + 30}{10})}$	Forward rate for Na^+ current activation gating variable
β_m	$4 \exp(-\frac{V + 55}{18})$	Backward rate for Na^+ current activation gating variable
m_∞	$\frac{\alpha_m}{\alpha_m + \beta_m}$	Occupancy of Na^+ activation gating variable
	$\frac{dn}{dt} = \phi(\alpha_n(1 - n) - \beta_n n)$	Evolution occupancy of gating K^+ current gating variable
	$\frac{dh}{dt} = \phi(\alpha_h(1 - h) - \beta_h h)$	Evolution occupancy of gating Na^+ current inactivation gating variable

841

842 **Table 8.** Reaction rates for kinetic schemes for VGCC

Parameter	Value / Units	Notes
$\alpha_{10}, \alpha_{20}, \alpha_{30}, \alpha_{40}$	4.04, 6.70, 4.39, 17.33 ms ⁻¹	From [70, 75]
$\beta_{10}, \beta_{20}, \beta_{30}, \beta_{40}$	2.88, 6.30, 8.16, 1.84 ms ⁻¹	From [70, 75]
k_1, k_2, k_3, k_4	49.14, 42.08, 55.31, 26.55 mV	From [70, 75]

843

844

845 **Table 9.** Reaction rates for kinetic schemes for Exocytosis

Parameter	Description	Value / Units	Notes
Vesicle Recruitment			
k_{mob}	Mobilization rate	$5.0 \times 10^{-5} \mu\text{M}^{-1}\text{ms}^{-1}$	From [27]
k_{demob}	Demobilization rate	0.0022ms^{-1}	From [27]
$k_{priming}$	Priming rate	$0.027990 \mu\text{M}^{-1}\text{ms}^{-1}$	From [27]
k_{unpr}	Unpriming rate	0.005356ms^{-1}	From [27]
k_{attach}	Attachment rate	$0.0015 \mu\text{M}^{-1}\text{ms}^{-1}$	Fit
k_{detach}	Detachment rate	0.001158ms^{-1}	Fit
k_{RF}	Refractoriness	$10.34^{-1} \text{ms}^{-1}$	Fit
Calcium sensor			
α	Association rate for synchronous release	$0.061200 \mu\text{M}^{-1}\text{ms}^{-1}$	From [70]
β	Dissociation rate, synchronous release	2.32ms^{-1}	From [70]
λ	Association rate for Asynchronous release	$0.002933 \mu\text{M}^{-1}\text{ms}^{-1}$	Fit
δ	Dissociation rate for Asynchronous release	0.014829ms^{-1}	Fit
γ_1	Spontaneous release rate	$9 \times 10^{-6} \text{ms}^{-1}$	Fit
γ_2	Synchronous release rate	2.000008ms^{-1}	From [70]
γ_3	Asynchronous release rate	$a \cdot \gamma_2 \text{ms}^{-1}$	From [70]
b	Cooperativity factor	0.250007	From [70]
a		0.025007	From [70]

846

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850

851 **Competing Interests**

852 The authors declare no conflict of interest. The funders had no role in the design of the study;
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