Regulating Temporal Neural Coding via Fast and Slow Synaptic Dynamics

Yuanhong Tang, Lingling An, Xingyu Zhang, Huiling Huang, Zhaofei Yu

Abstract—The NMDAR, as a ubiquitous type of synapse in neural systems of the brain, presents slow dynamics to modulate neural spiking activity. For the cerebellum, NMDARs have been suggested for contributing complex spikes in Purkinje cells (PCs) as a mechanism for cognitive activity, learning, and memory. Recent experimental studies are debating the role of NMDAR in PC dendritic input, yet it remains unclear how the distribution of NMDARs in PC dendrites can affect their neural spiking coding properties. In this work, a detailed multiple-compartment PC model was used to study how slow-scale NMDARs together with fast-scale AMPA, regulate neural coding. We find that NMDARs act as a band-pass filter, increasing the excitability of PC firing under low-frequency input while reducing it under high frequency. This effect is positively related to the strength of NMDARs. For a response sequence containing a large number of regular and irregular spiking patterns, NMDARs reduce the overall regularity under high-frequency input while increasing the local regularity under low-frequency. Moreover, the inhibitory effect of NMDA receptors during high-frequency stimulation is associated with a reduced conductance of large conductance calcium-activated potassium (BK) channel. Taken together, our results suggest that NMDAR plays an important role in the regulation of neural coding strategies by utilizing its complex dendritic structure.

Index Terms—Purkinje cell; NMDA; Spiking coding; Temporal coding; Neuronal morphology

I. Introduction

NMDA receptor (NMDAR) is a glutamate-gated ion channel that plays a crucial role in excitatory synaptic transmission, which has several unique properties compared to other receptors, including voltage-dependent block by extracellular Mg^{2+} and ligand-gated [1]. These characteristics have a profound impact on the physiological functions of NMDA, including information processing, synaptic plasticity, learning, and memory, as well as many neurological diseases [2]–[6]. Consequently, the exploration of the role of NMDA in different brain regions remains a prominent area of research due to its unique functions and structure.

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The cerebellum has the most neurons in the brain and is responsible for movement and cognitive behavior [7]–[9]. Purkinje cells (PCs), as the only output neurons of the cerebellum, receive excitatory inputs from parallel fibers (PFs) and climbing fibers (CFs) and inhibition from intermediate molecular neurons [9]–[14] and rely on its complex dendritic morphological structure for synaptic integration. Studies in rodents indicate that NMDA plays an important role in triggering PC responses [15]–[17]. First, functional NMDA receptors in the CF-PC synapses are minimally detectable in mice during the first month of life, achieving mature expression at approximately 2 months old [18]. This expression is pivotal in synaptic gain control in the mature cerebellum [19] and regulates the complex spike waveform associated with cerebellar learning [18], [20], [21]. Secondly, physiological experiments revealed NMDAR expression at PF-PC synapses through NMDA reagent injection [22], [23] and transgenic expression of NMDA [24]. This NMDA expression primarily influences the plasticity of synapses formed between PF and PC, implying a role for NMDA in cerebellar learning [19], [25]–[28]. Furthermore, the long-term properties of NMDA allow it to be used as a storage device, facilitating the association of rapid presynaptic signals with more extended postsynaptic signals [29], which is considered to play an important role in the information transmission process [30]. Likewise, the tetanic activation of NMDA receptors will reduce intrinsic excitability and promote bistable activity, and ultimately impact neuron discharge [31].

NMDA receptors play a pivotal role in temporal coding by orchestrating the timing of synaptic inputs and neuronal firing. This process is essential for the brain's ability to decode and anticipate sequences, supporting essential behaviors such as speech and movement, as well as various cognitive functions that depend on understanding time [32]–[34]. Additionally, NMDA receptors significantly enhance the encoding of auditory stimuli in the inferior colliculus (IC) by facilitating the temporal integration of synaptic inputs [35], [36]. In neocortical pyramidal neurons, NMDA receptor-mediated peaks in basal dendrites mediate the detection and generation of burst firing through postsynaptic mechanisms [37]. Moreover, model studies indicate that the short-term dynamics influenced by NMDA receptors can improve the processing of temporal information [38]. Nevertheless, current research primarily focuses on understanding the role of these receptors in cerebellar functions, yet studies

on their impact on temporal encoding in Purkinje cells remain relatively scarce. This gap highlights a critical area for future investigations, potentially revealing new insights into how these cells contribute to spatial navigation and motor coordination through synaptic mechanisms modulated by NMDA receptors.

In this study, we employ a detailed dendritic morphology Purkinje cell model to investigate the impact of NMDA on PC encoding, with the aim of gaining a deeper understanding of the role of NMDA in the information transmission process. Our findings reveal that NMDA receptors function as a band-pass filter, allowing Purkinje cells to generate an impulse response within a specific frequency range. Additionally, NMDA exhibits varying effects on the regularity of PC spike trains, decreasing overall regularity under high-frequency stimulation while enhancing local regularity under low-frequency stimulation. Similarly, we also confirmed that NMDA plays a negative role in phase reversal learning. Furthermore, the inhibitory effect of NMDA receptors during high-frequency stimulation correlates with decreased conductance in large conductance calcium-activated potassium (BK) channel. In summary, NMDA significantly modulates PC spike coding, and the extent of this modulation is contingent on its intensity.

II. Methods

A. Detailed compartment model of Purkinje cell

To ensure a representative range of morphological properties, we used the 3D reconstruction of PC from guinea-pig available on the public archive www.neuromorpho.org, consisting of a somatic compartment, and 941 dendritic sections. The neuronal model has following passive parameters: membrane resistance $R_m = 5000\Omega/cm^2$, axial resistance $R_i = 250\Omega/cm$. membrane capacitance C_m was set to $0.8F/cm^2$ in the soma, trunk dendrites and smooth dendrites, and $1.5F/cm^2$ in spiny dendrites. There are 13 different types of voltage-gated ion channels modeled, eight of which (P-type Ca^{2+} channel, T-type Ca^{2+} channel, class-E Ca^{2+} channel, persistent K^+ channel, A-type K^+ channel, D-type K^+ channel, delayed rectifier, decay of sub-membrane Ca^{2+}) were inserted into the soma and dendrites. In addition, three ion channels (fast sodium channel, persistent sodium channel, anomalous rectifier channel) were solely added to the soma, and two ion channels (high-threshold calcium-activated potassium channel, low-threshold calcium-activated potassium channel) were solely added to the dendrites [39]. These channels used standard Hodgkin-Huxley equations or a modified version of the Hodgkin-Huxley formulation. The resting potential of the neuron was set at -65mV and the temperature was set at 37C.

B. Synaptic model

In our model, we randomly distributed 1000 synapses on the spiny dendrites to receive stimulus input from PF, including three types of receptor models, namely AMPA, NMDA, and AMPA+NMDA. And in the third receptor model, the AMPA and NMDA channels were co-localized one-to-one in each synapse and received the same inputs [40]. AMPA and NMDA receptors are two excitatory receptors, which can mediate excitatory postsynaptic currents and have complex dynamics. Synapse of two-state kinetic scheme described by rise time constant τ_{rise}, and decay time constant τ_{decay}. Accordingly, the mathematical model of AMPA/NMDA receptor is

$$I_r = g_r \times (V - E_r)$$

$$g_r = g_{\max\_r} \times weight \times factor \times Q_r$$

where, $r \in \{\text{AMPA}, \text{NMDA}\}$, I_r is the receptor current, g_r is the receptor conductance, V is the synaptic membrane potential, E_r is the receptor reversal potential, $g_{\max\_r}$ is the maximum synaptic conductance, weight is the connection weight between the synaptic stimulus and the neuron, factor is to make the normalized peak of the conductance 1. Since NMDA-mediated currents often require AMPA-mediated depolarization to remove extracellular Mg^{2+} blockade of NMDA-associated channels [41], the associated channels open only when magnesium ions are blocked and NMDA receptors are activated. Therefore, the configuration parameter Q_r of different types of receptor models is

$$Q_{AMPA} = e^{-(t-t^f)/\tau_{decay}} - e^{-(t-t^f)/\tau_{rise}}$$

$$Q_{NMDA} = [e^{-(t-t^f)/\tau_{decay}} - e^{-(t-t^f)/\tau_{rise}}] \times g_{Mg^{2+}}$$

where, t^f is the moment when the stimulus arrives, $g_{Mg^{2+}} = 1/(1 + 0.24 * \exp(-154 * v/0.027))$ represents the channel controlled by Mg^{2+}. Both AMPA and NMDA receptors were double exponential models, and the NMDA receptor model was more complex and had more dynamic behaviors than the AMPA receptor model. Detailed AMPA model parameters are g=0.8nS, E=0, $\tau_{rise} = 0.5$ms, $\tau_{decay} = 5$ms. NMDA parameters are g=0.96nS, E=0, $\tau_{rise} = 8$ms, $\tau_{decay} = 30$ms. Both receptors are distributed on spiny dendrites.

C. Stimulus sequence model

Synaptic inputs were modeled using a modified version of the NetStim object provided in the NEURON package. Each synapse (AMPA, NMDA) received an independent spike train generated simultaneously [40]. A single stimulation consists of a sequence of spikes containing spike times and inter-spike intervals (ISI), so we can generate a successive spike train by the previous spike plus the regular or irregular time intervals. Each spike train was generated using the same algorithm as in [39], [42]–[44]. To study PC's phase information modulation ability, we used the Modulated Renewal Process to generate stimulus sequences with phase information. It was described by:

$$F(t) = A * sin(2 * f * \pi * t + \theta)$$

where A, f and θ control the amplitude, frequency, and phase of the stimulus respectively.

D. Data Analysis

After the theoretical model was established, we simulated the PC morphology model in NEURON 7.6 and used MATLAB 2020 for data analysis. The time step of all simulation experiments was set at 0.025ms. A simple spike (SS) is considered to occur when the membrane potential at its location crosses a threshold voltage (-10mV) in the positive direction. For effective data analysis, we used three measures to characterize the effect of NMDA on PC response: rate coding, time coding, and phase modulation capabilities.

Rate coding: The firing spikes of neurons contain abundant neural information. Therefore, we used rate coding to analyze and study the response characteristics of neurons. We evaluated the rate coding of the stimulus and response sequences by considering the number of discharge spikes within 1s, The calculation formula is:

$$PCrate=\frac{N_{t_{end}}-N_{t=1100ms}}{t_{end}-t_{1100ms}}$$

where, t_{end} is the end time of the stimulus. $N_{t_{end}}$ is the number of SS extracted from the start to end of the stimulus. $N_{t=1100ms}$ is the number of SS extracted in the first 1100ms. We investigated the effects of NMDA receptors on synaptic integration by giving the different Poisson stimulus sequences from PF to PC and measuring the mean output firing rate with or without NMDA/AMPA. Further, multiplicative and additive transformations of the input-output relation were quantified by fitting the data to Hill-like equations and measuring the gain under slope change (ΔGain) and the shift in the half-maximal frequency (ΔOffset). In addition, we observe how changes in NMDA strength affect input-output relationships, gains, and offsets by changing the NMDA connection weight, number, and rate of NMDA/AMPA.

Time coding: The cerebellum can accurately control motion-related tasks and conditional behaviors, not only related to the average discharge frequency of SS, but also related to the precise time structure. We investigated the effect of NMDA on the fine temporal structure of PC from the perspective of the dispersion and regularity of the response sequence. The coefficient of variation (CV) of the ISI can characterize the dispersion of an impulse train. The calculation formula of CV is:

$$CV=\frac{\sqrt{\sigma_{ISI}}}{\langle n\rangle_{ISI}}$$

where, σ_{ISI} is the variance of the ISI sequence, and $\langle n\rangle_{ISI}$ is the mean value of the ISI sequence. To understand the influence of NMDA on the time structure of SS in more detail, we focused on analyzing the short-term variability of the response sequence using the local regularity of the pulse sequence. It was described by:

$$(CV_2)_n=2\left|\frac{ISI_{n+1}-ISI_n}{ISI_{n+1}+ISI_n}\right|$$

where, CV_2 varies from 0 to 2. The number of regular patterns was measured using 0.2 as the threshold value for CV_2.

Phase modulation: Another feature of PCs response is phase modulation capabilities. NMDA has been found to impair vestibular oculomotor reflex behavior [24]. Thus, based on the Modulated Renewal Process stimulus sequence constructed as sinusoidal stimulus input, we investigated the influence of NMDA on PC phase modulation by changing sinusoidal input parameters and NMDA receptor intensity. This process used the control variable method to fit the response sequence under different phases, frequencies, and amplitudes. In the process of obtaining the PC response sequence information, firstly, we recorded the simple peak moments extracted within 4s and set a time window of 30ms. Subsequently, the histogram after stimulation was obtained by calculating the instantaneous discharge frequency of each window. Ultimately, the response potential was obtained by sinusoidal function fitting according to the instantaneous discharge frequency.

Gain and offset of the I-O function: PC firing rates (F) as a function of PF inputs were fitted with the following Hill function as previously [45]:

$$\mathrm{F(PF)}=\frac{\mathrm{F_{max}}}{1+(\mathrm{PF_{50}/PF})^{\mathrm{n}}}+\mathrm{F_0} \tag{1}$$

where n is the exponent factor, F_0 the firing rate offset, and F_{max} the maximum firing rate. PF_{50} is the value of PF at which F reaches half maximum. To investigate changes in the input-output relationship of PC firing caused by NMDA, the change of PC response was quantified by ΔGain calculated as follows [45]:

$$\Delta\mathrm{Gain}=(\frac{\mathrm{F'_{+x}}-\mathrm{F'_{-x}}}{\mathrm{F'_{-x}}}) \tag{2}$$

where F' is the average slope of the fits between 5% and 75% its maximum value. +x and −x denote different conditions of with/without NMDA, e.g. ±NMDA. A shift along the input axis corresponds to an additive operation, while a change in slope corresponds to a multiplicative operation, or gain change. Offset shifts (ΔOffset) were defined as the difference between the half-maximum values of the fits in the conditions +x and −x.

III. Results

A. NMDARs regulate somatic response to synaptic inputs

The way a neuron transfers information can be represented by its input-output relationship, which is affected by synaptic inputs. We first investigated the effect of NMDARs on PC membrane potential by considering three types of synaptic connections illustrated in Figure 1A. We measured the component of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) mediated excitatory post-synaptic currents (EPSCs) and NMDA-mediated EPSCs at the millisecond level. By comparing the time scale and current characteristics of three scenarios with the biological data, the usability of AMPA and NMDA receptor models was verified. The time process of AMPA lasts 20-30 milliseconds, while the time process of NMDA lasts tens to hundreds of milliseconds. In order to verify the temporal characteristics of the AMPA and NMDA

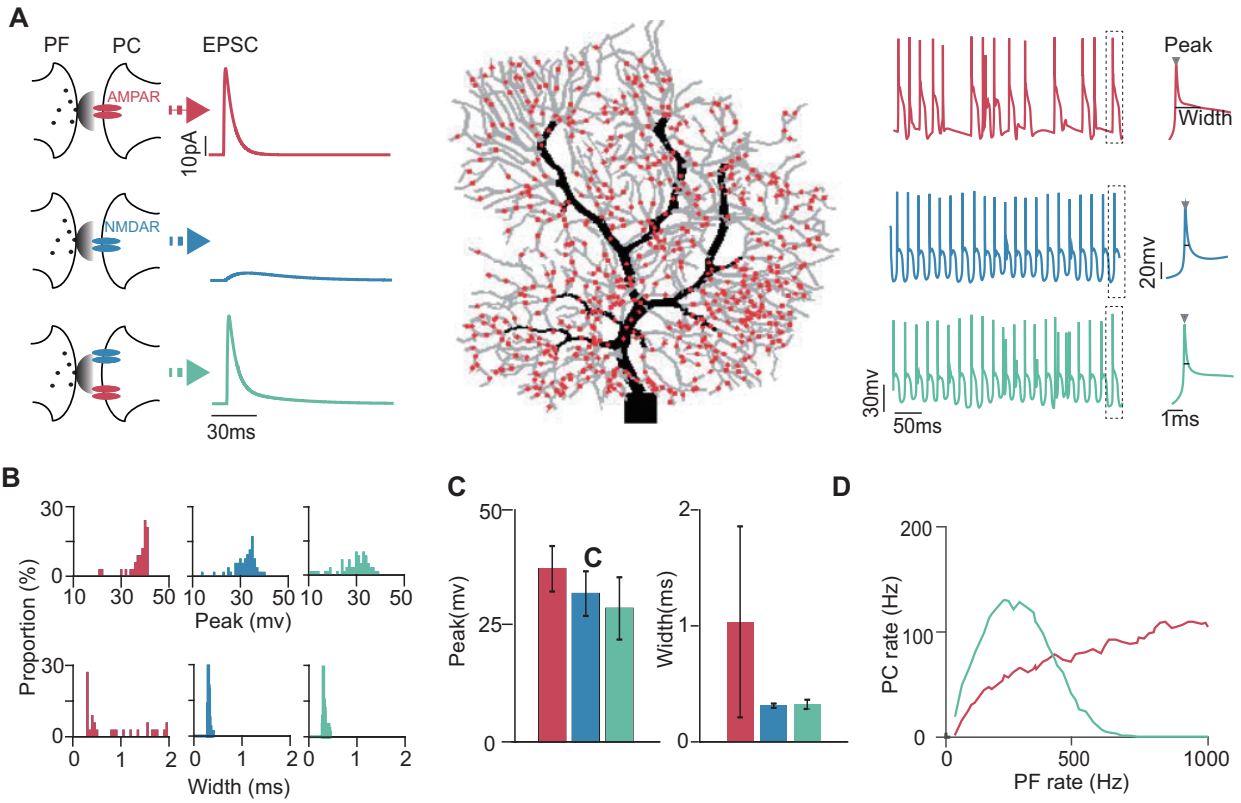

Fig. 1. PC somatic membrane potential regulated by three different receptor scenarios. (A) Three synaptic scenarios between a PF and a PC. The EPSC current is induced by a single spike input. PC somatic membrane potential traces induced by a sequence of 50 Hz Poisson spikes with 1000 synapses (red dots) randomly on the entire dendritic tree. A zoom-in of a single spike response (black box) with two characteristics of peak and width. (B) Histograms of membrane potential characteristics of the peak (top), and width (bottom). (C) Statistics of peaks and widths (mean±STD) computed using a 1-second of PC spikes. (D) Input-output relation for two scenarios (AMPA: red, AMPA+NMDA: green).

receptor models, we stimulated PC with 1Hz pulses, and clamped the voltages of AMPA and NMDA at -70mV.

Figure 1A shows that the AMPA component responds rapidly to the presynaptic spike and produces a rapidly decaying excitatory postsynaptic current. The NMDA component is much slower, mediates persistent slow post-synaptic current, and expresses at relatively low levels in amplitude for a single stimulation. The AMPA duration was about 25 milliseconds, while the NMDA duration was about 100 milliseconds, which are consistent with biological data of AMPA as 20-30ms and NMDA as tens to hundreds.

we will further verify the effectiveness of the model. Physiological studies have shown that AMPA and NMDA receptors are involved in the formation of excitatory post-synaptic currents in different stages of EPSC. Therefore, in the early and late phases, the EPSC values in the three synaptic models were recorded in Table I. The corresponding P value was measured using the t-test, and the effects of AMPA and NMDA on excitatory postsynaptic current were analyzed. $P1\,(\mathrm{I},\mathrm{III}) = 0.0059$, indicating that AMPA-mediated current is not significantly different from that mediated by both AMPA and NMDA, and AMPA receptors are mainly involved in the formation of the early peak of EPSC. $P2\,(\mathrm{II},\mathrm{III}) = 0.0125$, indicating that

TABLE I
P values of EPSCs in three synaptic scenarios at different temporal phases.

Receptor type	I (AMPA)	II (NMDA)	III (AMPA+NMDA)
I(pA)(early phase)	43	3.7	43.8
P1(I, III)	\	0.0059	\
P1(II, III)	\	0.4463	\
I(pA)(late phase)	0.1	2.5	2.6
P2(I, III)	\	0.4755	\
P2(II, III)	\	0.0125	\

NMDA is mainly involved in the formation of the late peak of EPSC. The temporal process of the NMDA-mediated EPSC is controlled by subunit composition. Long-term dynamics are not only biophysical, but also critical to synaptic function as a memory device that connects fast presynaptic signals with longer postsynaptic signals. Our models reproduce well the temporal characteristics of AMPA and NMDA receptors shown in experiments, so the accuracy of subsequent simulations can be guaranteed.

After the EPSC reaches the soma, it causes a change in the somatic membrane potential. The effects of NMDA on

the peak and width of membrane potential were analyzed by using a 50 Hz Poisson spike train input with 1000 synapses randomly distributed across the entire dendritic tree. Figure 1A (right) shows the membrane potential of the PC triggered by three synaptic scenarios. We use two indicators peak (triangle) and width (solid line) to further analyze the membrane potential. The peak and width distribution of the membrane potential (Figure 1B), as well as their mean values (Figure 1C) were shown. It can be seen that the peak and width distribution of the membrane potential generated by the three models varied (Figure 1 B). However, when NMDA was used alone or in cooperation with AMPA, the width distribution was concentrated around 0.3 ms. The width (1ms) and peak (37mV) of AP with the AMPA are consistent with all types of PCs [39], confirming the availability of the PC model. As shown in Figure 1 C, the maximum membrane potential mediated by NMDA is lower than that mediated by AMPA. When AMPA and NMDA were present simultaneously, the peak value decreased further. The width values are uniform and similar when the NMDA alone or coexists with the AMPA. Interestingly, NMDA has the function of band-pass filtering, increasing PC excitability at low frequencies, but inhibiting PC excitability at high frequencies in Figure 1D. The above results suggest that NMDA receptors play a key role in shaping the PC response, especially in reducing PC response to excitatory inputs.

B. PC rate coding in response to synaptic inputs

It is generally believed that the number of response spikes per unit of time carries the signal about the stimulus sequence and affects the ability of the PC to transmit the signal downstream. Therefore, the PC rate code to excitation of 1000 PF synapses firing at the different average frequencies with the range from 10 to 250 Hz was studied to analyze the effect of NMDA on PC discharge. It can be seen that the range of response frequency in the presence of AMPA only was 10~70Hz (Figure 2A left), which is consistent with previous results [39]. It can be seen from the Hill fitting curve that there is an approximate linear relationship between PC rate and PF rate when there is NMDA only. In the presence of AMPA and NMDA, the response frequency curve is similar to that in the presence of AMPA only, but the response frequency values are higher. These results show that NMDA can promote the frequency of PC discharge.

The effect of NMDA on multiplicative gain and offset during synaptic integration was analyzed by a Hill function fitting stimulus frequencies and response frequencies. The movement of the fitting function along the input axis corresponds to the addition operation(+), while the change in slope corresponds to the multiplication operation or the gain change(×). The effects of AMPA and NMDA on the offset and gain are shown in Figure 2A right. AMPA±NMDA represents the AMPA as the driver and the NMDA as the modulator. The representation in NMDA±AMPA is the opposite. It can be seen that NMDA plays a major role in gain modulation and has little effect on additive offset. The effect of APMA is mainly reflected in the additive offset, and mainly causes the fitting curve to shift to the left, and plays a small role in the gain modulation. The simulation results indicate that NMDA can act as amplifying modulators of neuronal gain and play a multiplicative role in synaptic integration.

Further, we studied the influence of NMDAR intensity on output frequencies (Figure 2B-D) with the influence of NMDA intensity on the gain and offset of the frequency curve. The black curves of Figure 2B-D are the rate curves with only AMPA, which is taken as the control group. The offset and gain changes of the frequency curve for different NMDAR intensities are shown on the right. By combining the effects of the three components, it can be seen that the increase of NMDA will decrease the offset value, but increase the gain effect. NMDA-mediated gain modulation allows a modulatory of NMDA strengths to scale a neuron's sensitivity to all of its driving inputs.

C. PC temporal coding in response to synaptic inputs

The cerebellum can precisely control motion-related tasks and behaviors [46]. It is thought that the spike timing may encode additional information. Here, the effects of NMDA on the fine temporal structure of PC were studied by using synapses with or without NMDA from the perspective of simple spike dispersion and regularity.

Figure 3A shows the PF spike sequence and the membrane potential traces generated by the different synaptic models, under the stimulation protocols of the Poisson spikes. Two common ways to characterize the temporal structure of the spike sequence is to use CV and CV_2 of ISI sequence. Firstly, we used the CV, which can represent the dispersion of a spike sequence. The larger CV is, the more discrete the spike train is. Figure 3B left shows the ISI and CV distributions of PC response sequence with and without NMDA. The results indicate that the spike sequences generated by the PC are significantly less discrete than those of PF. It is further found that the presence of NMDA in the model can reduce the dispersion of PC spike trains.

CV can only be used to analyze the overall dispersion of the time structure of a spike sequence. To describe the influence of NMDA on the temporal structure of a spike sequence in more detail, CV_2 was used to characterize the local regularity of a spike sequence. Figure 3B right shows the CV_2 distributions of PC spike sequence in different conditions. The CV_2 of PC spike sequence without NMDA has a wide distribution with a peak around 0.25. However, the CV_2 of PC spike sequence with NMDA has a concentrated distribution with peaks around 0.05 and 1.05. Obviously, the PC spike sequence is more regular when NMDA receptors are present.

To verify our simulations, the effects of NMDAR on the dispersion and regularity of spike sequence were further observed by changing the stimulus frequencies and the

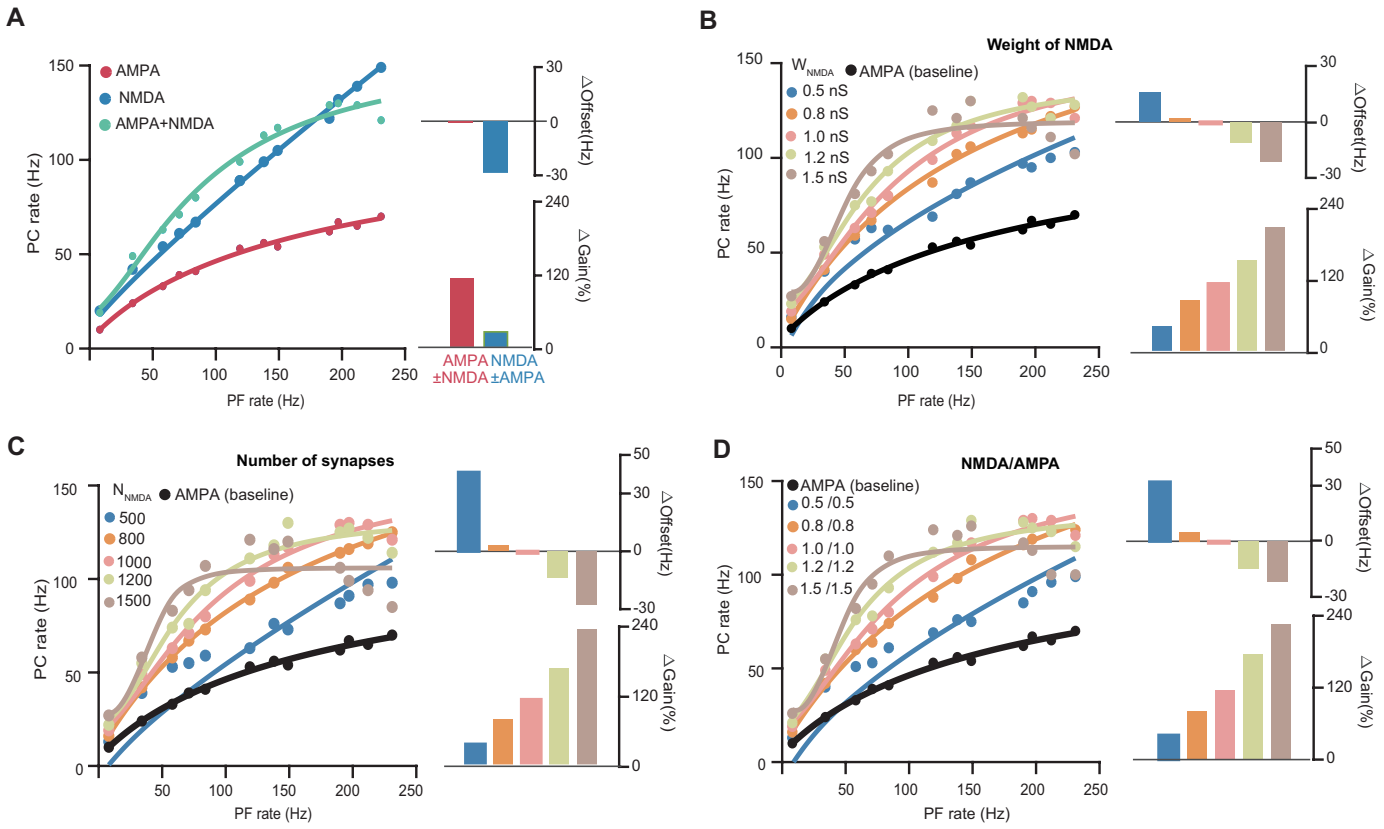

Fig. 2. Gain and offset modulation by NMDA during synaptic integration. (A) Left: the input-output relation for three scenarios (AMPA, NMDA, and AMPA+NMDA) with Hill fits. Right: gain (bottom) and offset (top) changes due to AMPA or NMDA regulation. (B) Left: the input-output relation for baseline conditions (AMPA, black symbols) and various connection weights of NMDA together with Hill fits. Right: gain (bottom) and offset (top) changes due to the different weights of NMDA. (C) As for B, but varying the number of NMDA. (D) As for B, but varying the rate of NMDA and AMPA.

intensity of NMDA. Figure 3C shows the CV values of the PC spike sequence at different Poisson frequencies of 10-250 Hz. We found that PC spike sequences with NMDA are less discrete with the only exception in a low stimulus frequency (10 Hz) and a high stimulus frequency (230 and 250Hz). Interestingly, at various stimulus frequencies, the dispersion of PC spike sequence increases with the intensity of the stimulus when NMDA receptors are present. Figure 3D shows the average values of CV_2 under the same experimental conditions as in Figure 3C. Not surprisingly, the PC spike sequences with NMDA are more regular, except at 90 Hz and 130 Hz (p=9.8927e-4 for PC without NMDA versus with NMDA). However, the effect of NMDA intensity on the mean average of CV_2 is not regular.

Cerebellar Purkinje cells are commonly reported to generate regular spike trains. To see this effect, regular patterns and irregular patterns were extracted from the PC spike sequences according to a threshold of 0.2 on the measured CV_2 values. As shown in Figure 4A, when PC spike sequence fragments of 500 ms are extracted under Poisson stimulation at 50 Hz, it is found that NMDA can increase the number of regular patterns. Figure 4B shows that ISI distribution of regular patterns with NMDA is more concentrated than that without NMDA, and the peak appears around ISI =20ms. Figure 4C shows that the relationship between ISI of regular patterns and NMDA intensity, with the increase of NMDA, a small part of ISI concentrates around ISI=5ms, while most of ISI concentrates around ISI=20ms. Regular patterns can be characterized by two parameters: patterns rate and patterns mean ISI. As can be seen from Figure 4D, when NMDA is present, the patterns rate is doubled and the patterns mean ISI is halved, indicating that NMDA increases the ISI quantity of regular patterns.

Thus, we conclude that NMDA can change the PC timing coding by reducing the discreteness of the PC spike sequence and increasing its regularity. If the regular spike patterns is a specific signal through which the PC transmits information [46], then NMDA can be used to control signal transmission.

D. PC phase modulation under synaptic inputs

A recent study [24] found that introducing NMDA-mediated currents damaged vestibular-ocular reflex (VOR) behavior, i.e. phase-reversal learning. In order to elucidate PC firing modulation with NMDA, we constructed the PF inputs through the sinusoidal modulation function. By varying the phase, amplitude, and frequency

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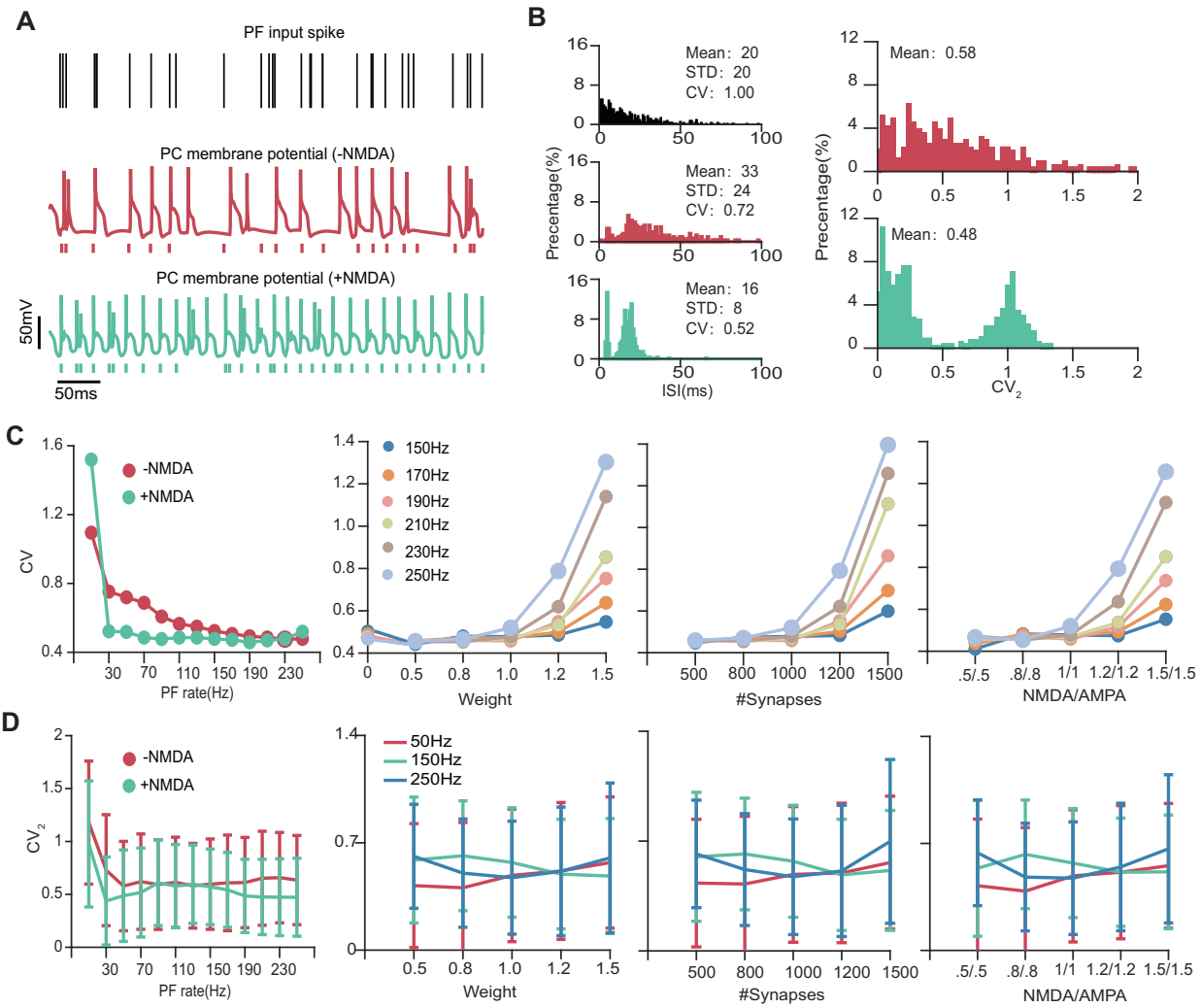

Fig. 3. The effect of NMDA on the dispersion of response sequence. (A) The response potentials of two PC models under Poisson stimulation at 50 Hz. (B) ISI and CV_2 distribution of PC response sequences under different receptor conditions as in (A). (C) The CV values at different frequencies and NMDA receptor intensities. (D) The CV_2 values at different frequencies and NMDA receptor intensities. T-test: p=9.8927e-4 for PC without NMDA versus with NMDA.

of sinusoidal input [47], we investigated the ability of phase modulation of PC with or without NMDA.

We first analyzed the phase modulation ability of PC by changing the sinusoidal input phase, where the amplitude and frequency of the sinusoidal input are 50 and 1. Figure 5A shows the histogram with a 30-ms time window of PF and PC spike sequences as well as the sinusoidal function after fitting. The maximum value of the fitted sinusoidal function of the PC spike sequence is the same as that of the PF spike sequence when NMDA is present, but the values are smaller when the NMDA is absent. Figure 5D left shows the phases extracted from the fitted sinusoids. It can be seen that the PC modulation phases without NMDA are identical to the PF input phases, except when the input phase was $3\pi/4$. However, the introduction of NMDA caused the PC modulation phases to delay to the PF input phases. In addition, it can be seen that the PC modulation phases with NMDA are delayed compared with the case without NMDA.

The same experiment was performed but the sinusoidal input frequency was changed to study the effect of NMDA on PC firing modulation, and the given amplitude and phase of the sinusoidal inputs were 50 and 0 respectively. We found that the maximum variation of the fitting sinusoidal function of PC and PF spike sequences is the same as the experimental results mentioned above (Figure 5B). Compared to the PF input phases, the PC modulated phases without NMDA are leaded at low input frequencies but delayed at high input frequencies (Figure 5D middle). The presence of NMDA causes the PC modulation phases to be delayed of the PF input phases and the PC modulation phases without NMDA.

The amplitude of sinusoidal input is also an important parameter affecting PF inputs. The phase and frequency of the sinusoidal input in this section were set to 0 and 1, respectively. Figure 5C shows that the PC modulation amplitude without NMDA is smaller than the PC input amplitude, but it is the same when the amplitude is 25

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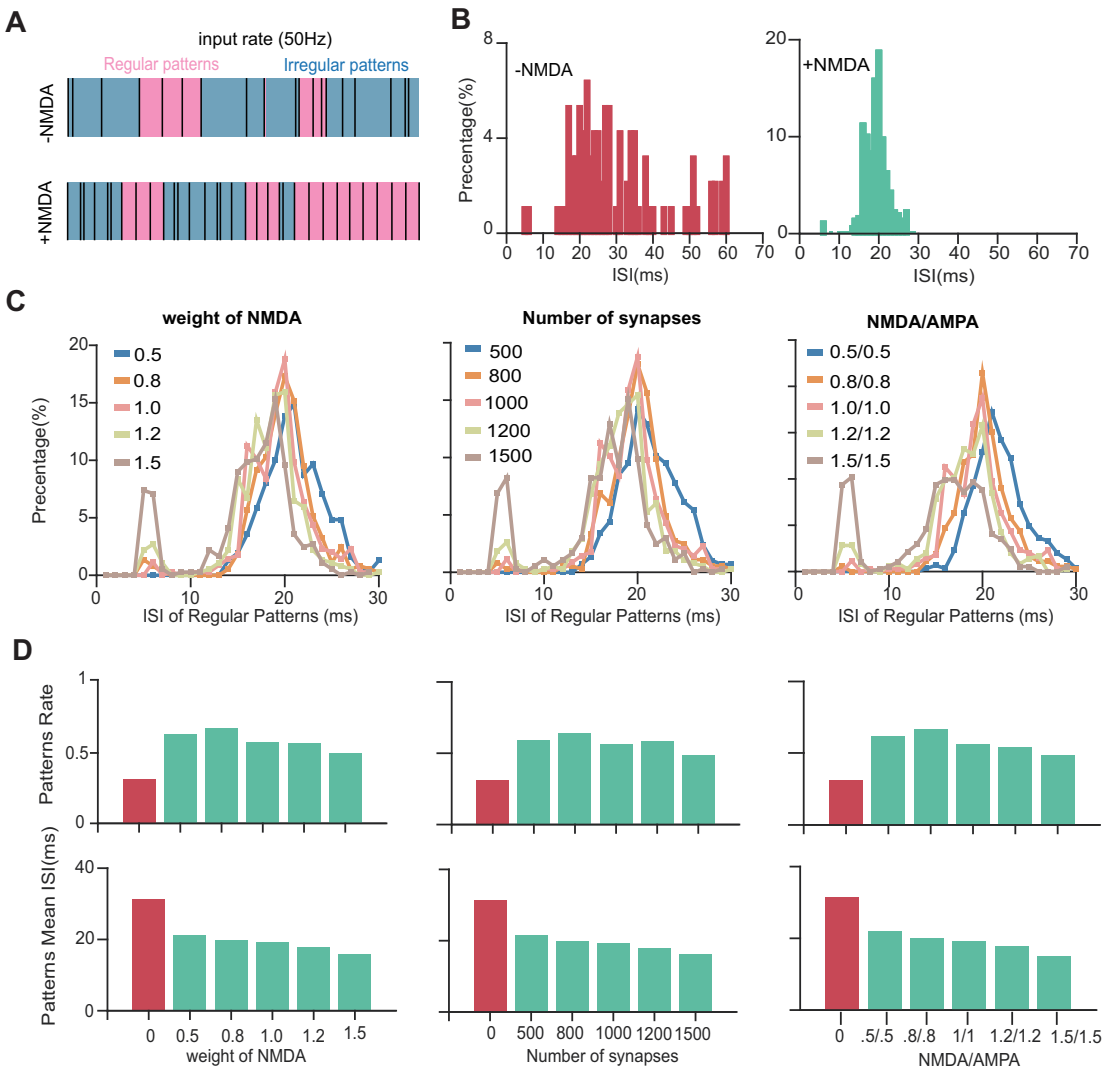

Fig. 4. The effect of NMDA on the regularity of spiking response sequence. (A) Spike trains with regular and irregular patterns. (B) Distribution of ISI under different models. (C) The relationship between ISI of regular patterns and different NMDA receptor intensities: synaptic weight, number, and ratio between AMPA and NMDA. (D) The rate and mean of regular patterns under different NMDA receptor intensities.

and 50. The introduction of NMDA resulted in higher modulation amplitudes in Purkinje cells (PCs) than those induced by parallel fiber (PF) inputs. Figure 5D right illustrates that, in the absence of NMDA, the modulation phases of PCs align with the PF input phases for most input amplitudes. However, with NMDA, the PC modulation phases are delayed relative to both the PF input phases and the PC modulation phases without NMDA.

At the same time, we studied the effect of NMDA intensity on PC phase modulation. Figure 5E shows the difference between the PC modulation phases and the PF input phases when the connection weight and number of NMDA and the ratio of NMDA to AMPA change. It can be seen that the difference mainly exists in the fourth quadrant, indicating that the NMDA receptors make the PC modulation phase more delayed than the PF input phase under different intensities. These results, together with experiments [24], indicate that NMDA is essential for modulating VOR learning.

E. The effects of dendritic intrinsic properties on NMDA inhibitory expression

Different ion channels have an important role in regulating cerebellar neural firing properties [48]. PCs are endowed with different types of voltage-dependent channels due to their rich dendrite structure, which enables them to actively transmit postsynaptic currents. The external input can stimulate the local potential of dendrites and trigger the selective opening of ion channels, and then induce the change of dendritic ion current and affect somatic membrane potential. To explore the regulation mechanism of NMDA receptor expression by the active characteristics (ion channels) of dendrites, PC was subjected to 10 Hz low-frequency stimulation and 450 Hz high-frequency stimulation, and the currents and membrane potential on

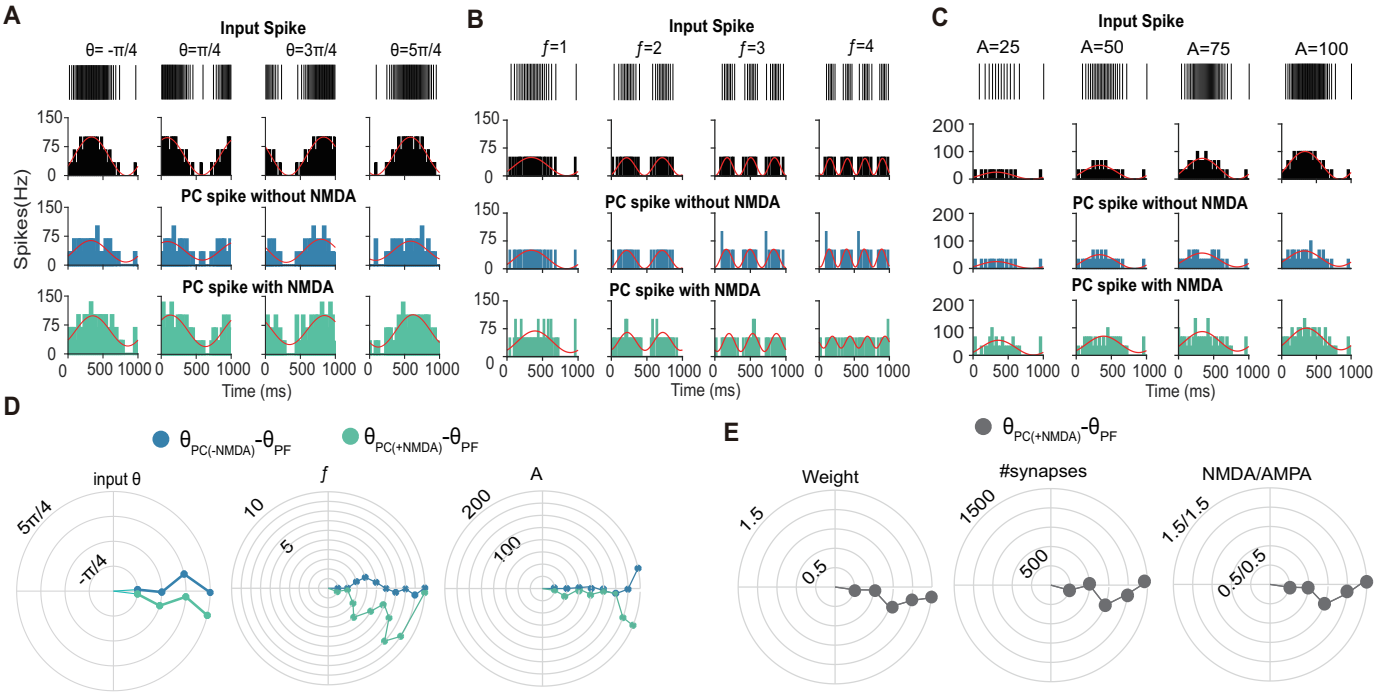

Fig. 5. The effect of NMDA on the PC phase modulation ability. (A) Stimulus and response sequence fitting curves at different input phases. (B) Similar to (A) but at different frequencies. (C) Similar to (A) but at different amplitudes. (D) The effects of NMDA receptors on phase changes in response sequences at different phases, frequencies, and amplitudes. (E) The effect of NMDA receptor intensity on PC phase modulation. The stimulus is a modulated renewal process, with the default amplitude A=50, frequency f=1, and phase θ= 0.

the dendrites (Figure 6A) and soma (Figure 6B) were extracted as the output analysis values.

Under the low-frequency stimulation, KA, cad and CaP2 ion channels of dendrites (Figure 6C) and Khh ion channel of soma (Figure 6E) are critical for the action potential (AP) generation. After stable input, adding NMDA receptor significantly increased the AHP of BK channel (Figure 6C) and Khh channel (Figure 6E) current. The BK ion current of dendrites and Khh ion current of soma accumulated and remained at a high level (Figure 6D and F), which affected the normal repolarization process of AP, inhibited the generation of SS, and led to the decrease of response frequency.

To verify the mediating effect of BK and other ion channels in dendrites for EPSCs, using the control variable method, different ion channels on PC dendrites were blocked one by one (by setting the conductivity value of each ion channel as 0) to observe the influence of different ion channels on NMDA receptor-mediated PC membrane potential (Figure 7A) and response frequency (Figure 7B). The BK ion current is the main component that mediates the membrane potential of PC, and is independent of the presence of NMDA receptor (Figure 7A). In the absence of NMDA receptors, a single blocking of each ion channel had little effect on the response frequency of PC (Figure 7A and B). In the case of NMDA receptor, these ion channel blocks can reduce the PC response frequency mediated by NMDA receptor to different degrees, especially Khh and K2 ion channels (red arrow, Figure 7B). Furthermore, the inhibitory effect of NMDA was observed under high-frequency stimulation only in the presence of BK channels (Figure 7B). As shown in Figure 7C, the PC response potential after blocking Khh (yellow box) and K2 (black box) ion channels is compared with the normal PC response potential (control). It is found that Khh ion channel is mainly involved in the repolarization of AP, while K2 channel mainly affects the AHP.

To further explore how BK ion channel regulates PC discharge mediated by NMDA, we recorded and analyzed APs, the BK current and Khh current under different conductivity of BK ion channel at 350 Hz. As can be seen from Figure 7D, when g_{BK} = 0.02nS, PC can not generate AP normally regardless of the presence or absence of NMDA, and the membrane potential eventually oscillated around -30mV. When g_{BK} = 0.04nS, PC without NMDA can generate normal APs, while PC mediated by NMDA receptor still can not generate APs (Figure 7E). When g_{BK} = 0.2nS, both of them can generate APs normally (Figure 7F). Additionally, our research on the input-output relationships under various BK conductances revealed that a BK conductance of 0.02 did not induce Purkinje cell (PC) firing. However, at a conductance of 0.04, NMDA exhibited an inhibitory effect under high-frequency stimulation, whereas at a conductance of 0.2, NMDA displayed excitatory behavior (Figure 7G). These results suggest that the inhibition of NMDA under high-frequency stimulation is mainly regulated by BK ion channels. Specifically, the low conductivity of BK activated the BK channel, which further affected the Khh ion current on soma. However, the slow deactivation of Khh ion channel

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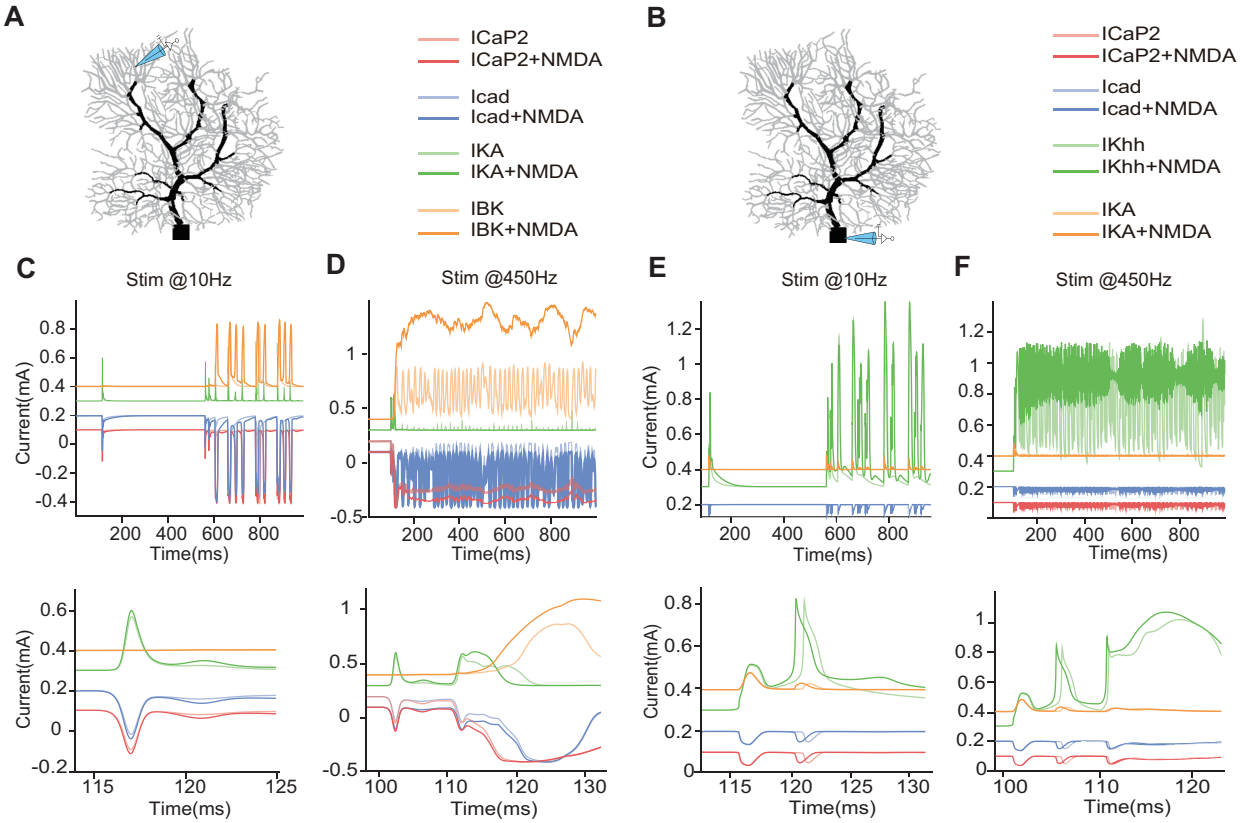

Fig. 6. The effect of NMDA on different ion channel mediated currents. (A) Four key ion currents (CaP2, cad, KA, BK) were recorded on dendrites at different stimulus frequencies and synaptic receptors. (B) Similar to (A), but the four ion currents (CaP2, cad, KA, Khh) recording site is soma. (C) The changes of four ion currents on dendrites when the input stimulus was 10Hz. The initial current values of different ions were translated for the convenience of observation. Ion currents in 115-125 ms are magnified (middle, bottom). (D) The input stimulus is 450 Hz, and the ion current magnified time window was 100-130 ms. (E, F) The ion current enlarged at 115-130 ms and 100-120 ms, other parameter settings are similar to those in C and D, respectively. Obviously, the input stimulus has the greatest influence on the ion current of Khh channel on soma.

can affect the repolarization process of AP and inhibit PC discharge. Therefore, controlling the conductance of BK channel can effectively regulate the inhibitory expression of NMDA receptors on PCs.

IV. Conclusion

It is still debated how NMDA receptors play their role on PCs via input fibers [49]–[51]. Studying the mechanism of NMDA on dendritic synapses is beneficial to enrich the information transmission mechanism between neurons and provide a reference for studying synaptic integration ability in cerebellar network models. In this study, similar to experiment [24] but with more detailed manipulations via a modeling approach, we integrated NMDA into a PC model and demonstrated how NMDA affects the PC responses of firing rate, spike timing, and phase modulation. Here we have used the input-output relationship to capture the information transmission between neurons. It was observed that NMDA-mediated excitatory input promoted PC discharge at low frequencies, but inhibited PC discharge at high frequencies. Our results suggest that the effect of NMDA on PC discharge depends on the input mode, which is due to the saturation of NMDA at high frequencies. This is consistent with the physiological experiment results [22], which showed that NMDA (5-200μM) perfusion on the brain surface could inhibit the discharge frequency of spontaneous SS of PC, and the effect was dose-dependent. The fine temporal structure of PC response sequence can carry rich neural information. In one view, the transmission of timing-sensitive information is performed by precisely timed PC spikes and their synchronized firing [52], [53]. Infrequent interspike intervals in the PC spike train are a well-known phenomenon in many contexts. Moreover, ISI irregularity in response sequence is the key to influencing the information transmission from PC to downstream neurons [54], [55]. Inspired by the effect of NMDA on the fine time structure of PC discharge proposed by [46], we studied the effect of NMDA on PC time coding from the perspective of time series dispersion and regularity by using the Coefficient of Variation of spike interval [56]. The results show that NMDA receptors can reduce the overall dispersion and increase the local regularity of the response sequence of PC. Thus, NMDA influences the time signal ISI of PC response sequence, which provides a time-reliable signal for saccades [57], classical conditioning [58], and other activities to achieve precise timing and continuous motion control. During the test for VOR phase-reversal adaptation, mice learn to

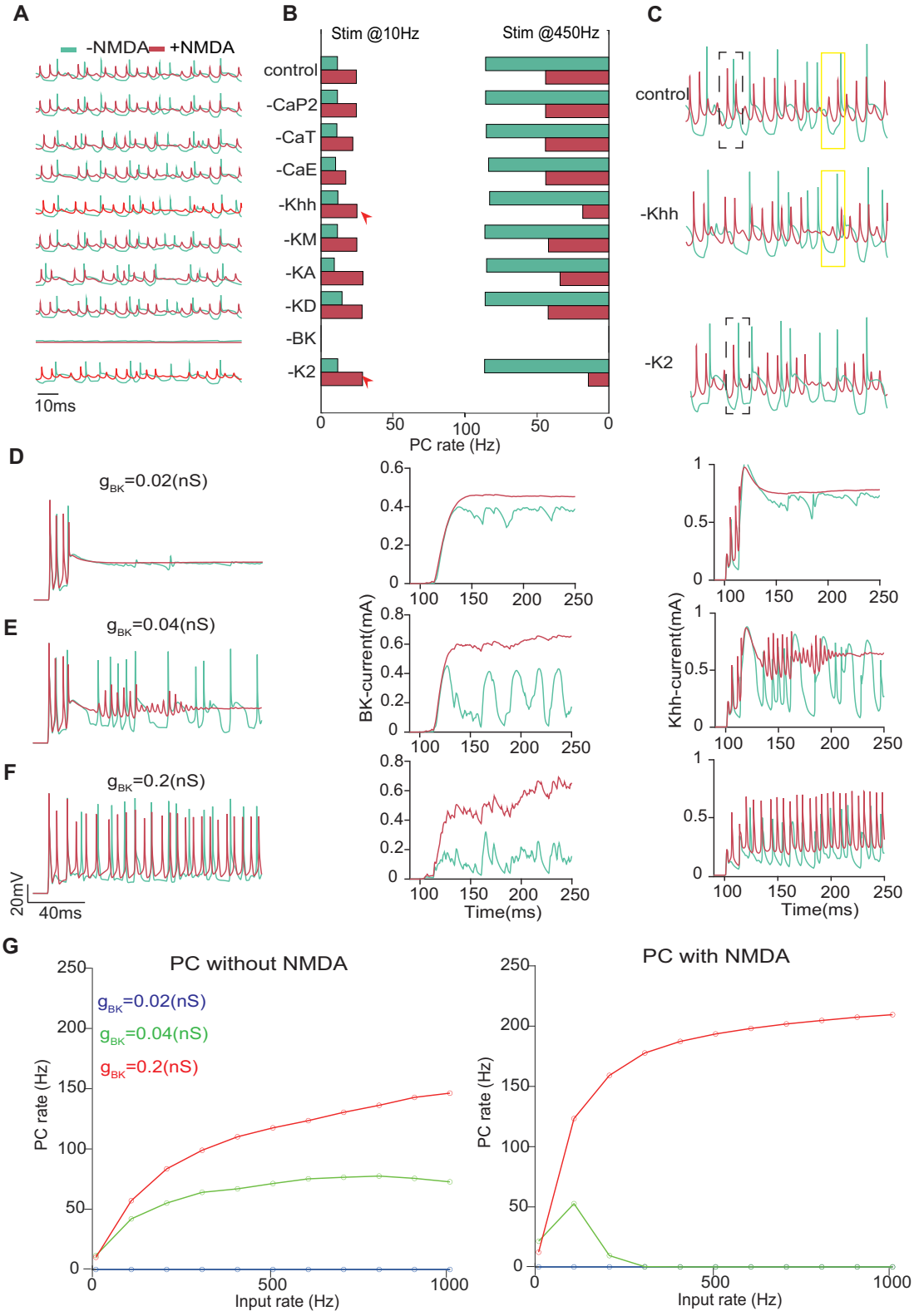

Fig. 7. Regulation of PC firing by different ion channels. (A) Dendrite response membrane potential after removal of an ion channel (two receptor conditions: with or without NMDA). (B) The corresponding PC firing frequency when the input stimulus frequency was 10Hz and 450Hz, respectively. (C) control: Normal PC response potential when all ion channels are present. -Khh: The response potential of PC when removing the Khh ion channel. -K2: similar to -Khh. (D) The changes of PC membrane potential, BK ion current and Khh ion current when the stimulation frequency was 350Hz and $g_{BK} = 0.02$nS. (E) Similar to (D) but $g_{BK} = 0.04$nS. (F) Similar to (D) but $g_{BK} = 0.2$nS. (G) Input-output relation for three scenarios ($g_{BK} = 0.02$nS: blue. $g_{BK} = 0.04$nS: green. $g_{BK} = 0.02$nS: red) in the absence (Left) and presence (Right) of NMDA .

shift the phase of their VOR following sinusoidal visual-vestibular mismatch stimulation, in which the visual stimulus moves in the same direction as the vestibular stimulus [59], [60]. Interestingly, [24] found that NMDA-mediated current abolishes the ability for LTP induction at mice PF-PC synapses and affects a demanding form of cerebellar-dependent motor learning, VOR phase-reversal learning. Consequently, comprehending the effect of NMDA on phase modulation of PC response will contribute to the design of drug therapy for abducens nerve palsy and other eye movement disorders [61]. Based on these findings, we investigated the effect of NMDA on the phase modulation ability of PC by changing the phase, frequency, and amplitude of the input stimulus from the perspective of cell discharge. The results show that under different sinusoidal input parameters and different intensities of NMDA, the introduction of NMDA-mediated current destroys the phase stability at different frequencies and delays the phase response of the response sequence. This phase modulation result further confirms that NMDA plays a negative role in phase-reversal learning [24].

The short-term synaptic changes mediated by NMDA receptors, influenced by the frequency and pattern of synaptic activity, are intricately linked to long-term synaptic plasticity [62]. Research in hippocampal studies has highlighted that presynaptic NMDA receptors significantly contribute to both short-term and long-term synaptic plasticity [63], [64]. Furthermore, model studies have demonstrated that short-term fluctuations in NMDA receptor activity can substantially enhance long-term synaptic plasticity, essential for processing temporal information [38]. This interplay between short-term synaptic modifications and long-term adaptations enables the brain to smoothly integrate immediate responses to stimuli with lasting changes, enhancing complex cognitive functions such as learning, memory, and decision-making. Additionally, this dynamic regulation also maintains neural efficiency, ensuring optimal brain function in response to various environmental demands.

Our research has found that NMDA receptors can modulate information across various time scales in cerebellar Purkinje cells. This has also been observed in the rat's primary somatosensory cortex, in which NMDARs are essential for handling both fast and slow sensory inputs [65]. However, in retinal ganglion cells, NMDARs and AMPARs collaboratively encode a broad spectrum of temporal frequencies, indicating that NMDARs in certain sensory neurons exhibit relatively fast kinetics [66]. Moreover, NMDARs in the CA1 area are essential for forming memories that associate events across time [67]. In the hippocampus, NMDA receptors play a crucial role in converting short-term memory into long-term memory [68], [69]. NMDA receptors specific roles can vary significantly, influenced by the local circuitry and the type of neurotransmission involved in each area. This diversity in function illustrates the complexity of NMDA receptor involvement in brain physiology and pathology.

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