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# The intrinsic mechanisms underlying the maturation of programming sequential spikes at cerebellar Purkinje cells

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**Abstract**

Cerebellum is involved in the motion coordination and working memory, to which the programming of sequential spikes at Purkinje cells is essential. It is not clear about the intrinsic mechanisms underlying spike capacity and timing precision as well as their postnatal maturation. We investigated the programming and intrinsic property of *sequential* spikes at Purkinje neurons during postnatal development by whole-cell recording in cerebellar slices. Cerebellar Purkinje neurons demonstrate the increasing of spike capacity and timing precision, as well as the lowering of refractory periods and threshold potentials during the postnatal maturation. In addition, the correlation between spike parameters and intrinsic properties converts to be more linear. This postnatal plasticity of neuronal intrinsic properties improves the timing precision and capacity of spike programming at cerebellar Purkinje neurons.


*Keywords:* Refractory periods; Threshold potentials; Action potentials; Cerebellar Purkinje cells and development

The cerebellum regulates fine-tuning movement and balance, as well as plays a critical role in working memory and cognition, in which GABAergic Purkinje cells are presumably involved [14,17,21,25]. Purkinje cells integrate the synaptic signals from glutamatergic inferior olivary-granule cells and GABAergic stellate-basket cells with their intrinsic property to encode sequential spikes precisely and loyally, which control the activities of deep nuclei. The fulfilling of this process requires cerebellar Purkinje cells to be well developed and matured.

The cerebellum achieves its matured configuration a few months after birth in spite of an early differentiation. Purkinje neurons are born at embryonic day 13 and migrate along radial glial fiber to cerebellar anlage, which depends on reelin pathway. Their maturation needs extensive interactions with the neighbors through eliminating supernumerary synapses from climbing fibers, developing extensive dendritic arbors, and making synapses onto granule neurons and deep cerebellar nuclei in late stage [3,25].

Less attention has been paid to studying the intrinsic mechanisms underlying the maturation of spike programming at cerebellar Purkinje cells, except for development profiles in spike patterns [18], calcium storage [11,15], $Ca^{2+}$ channels [9], and $Ca^{2+}$-dependent potassium channels [6,19]. Neuronal intrinsic properties influence the analysis of synaptic inputs and programming of spike patterns. Therefore, we investigated the spike programming and intrinsic properties at Purkinje cells during the postnatal development with whole-cell recording in cerebellar slices.

## Methods and materials

*Brain slices and neurons studied.* Cerebellar slices (400 μm) were prepared from Sprague–Dawley rats with either eyes-opened or eyes-unopened. Rats in postnatal day (PND) 7–10 and 15–18 were anesthetized by inhaling isoflurane and decapitated with a guillotine. Sagital cerebellar

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slices were cut with a Vibratome in the oxygenated (95% $O_2$ and 5% $CO_2$) artificial cerebrospinal fluid (ACSF) in the concentration of mM (124 NaCl, 3 KCl, 1.2 $NaH_2PO_4$, 26 $NaHCO_3$, 0.5 $CaCl_2$, 4 $MgSO_4$, 10 dextrose, and 5 Hepes; pH 7.35) at 4 °C. The slices were held in (95% $O_2$ and 5% $CO_2$) ACSF (124 NaCl, 3 KCl, 1.2 $NaH_2PO_4$, 26 $NaHCO_3$, 2.4 $CaCl_2$, 1.3 $MgSO_4$, 10 dextrose, and 5 Hepes; pH 7.35) at 25 °C for 2 h. A slice was transferred to a submersion chamber (Warner RC-26G) that was perfused with the oxygenated ACSF at 31 °C for whole-cell recording [23,24]. Chemicals were from Sigma. The procedures were approved by IACUC in Anhui, China.

Purkinje cells in the cerebellar cortex, which show a round or ovary-like soma and tree branch-like dendrites under DIC optics (Nikon FN-600), were recorded. Purkinje cells show responses to hyper- and depolarization pulses similar to previous report [1,23].

*Whole-cell recordings.* The recordings were conducted in current-clamp model with an Axoclamp-2B amplifier (Axon Instrument Inc., Foster CA, USA); and electrical signals were inputted into pClamp 9 (Axon Instrument Inc.) for data acquisition and analysis. Output bandwidth in amplifiers was 3 kHz. The spike patterns were evoked by depolarization current pulses, in which the amplitude and duration were based on the aim of experiments. Pipettes for whole-cell recordings were filled with the standard solution that contained (mM) 150 K-gluconate, 5 NaCl, 5 Hepes, 0.4 EGTA, 4 Mg-ATP, 0.5 Tris-GTP, and 5 phosphocreatine (pH 7.35 adjusted by 2 M KOH). Fresh pipette solution was filtered with centrifuge filters (0.1 μm pores) before use, and the osmolarity was 295–305 mOsmol. Pipette resistance was 5–6 MΩ.

*The intrinsic properties* of cerebellar Purkinje cells in our investigation include the threshold potentials of firing spikes and refractory periods following each spike. The *threshold potentials* are a start point of the rising phase of spikes [5,26]. The absolute refractory periods (ARP) of sequential spikes are measured by injecting multiple depolarization-current pulses (3 ms) into Purkinje cells following each of spikes (see Fig. 2). By changing inter-pulse intervals, we define ARP as a duration from a complete spike to a subsequent spike at 50% probability [5]. Spike programming (capacity and timing precision) is represented as inter-spike interval (ISI) and standard deviation of spike timing (SDST), respectively.

*Data* were analyzed if the recorded neurons had the resting membrane potentials negatively more than −55 mV. The criteria for the acceptation of each experiment also included less than 5% changes in resting membrane potential, spike magnitude, and input resistance throughout each of experiments. Input resistance was monitored by measuring cell responses to the hyperpolarization pulses at the same values as the depolarization that evoked spikes. Vts, ARP, ISI, and SDST are presented as mean ± SE. The comparisons before and after eyes-opened are done by *t*-test.

## Results

### *Postnatal change in spike capacity and timing precision*

Spike capacity, manifesting the neuronal ability of firing spikes or encoding digital signals, is presented as ISI. Spike timing precision, the temporal precision of spike patterns, is presented as SDST. If the programming of patterned sequential spikes is the basis of cerebellar functions, the improvement of spike capacity and timing precision should be associated with the postnatal development of fine-tuning movement and balance, which we investigated by measuring ISI and SDST at cerebellar Purkinje neurons from eyes-opened and eyes-unopened rats.

Fig. 1A and B show sequential spikes evoked by depolarization currents at Purkinje neurons from eyes-unopened (A) and eyes-opened (B) rats, in which the matured Purkinje cells appear to fire more spikes with precise locking-phase. To quantify the differences in spike capacity, we measured ISI between spikes one and two ($ISI_{1–2}$) up to four and five ($ISI_{4–5}$). The values of $ISI_{1–2}$ to $ISI_{4–5}$ at Purkinje cells in eyes-unopened rats are $22.71 \pm 1.44$, $25.35 \pm 1.34$, $25.05 \pm 1.45$, and $25.24 \pm 1.25$ ms (filled circles in Fig. 1C, $n = 27$); whereas the values from $ISI_{1–2}$ to $ISI_{4–5}$ at Purkinje cells in eyes-opened rats are $12.01 \pm 0.72$, $16.02 \pm 0.93$, $16.99 \pm 0.95$, and $17.67 \pm 0.68$ ms (open circles in Fig. 1C, $n = 30$), respectively. ISI values relevant to the same number in sequential spikes between eyes-unopened and eyes-opened rats are statistically different ($p < 0.01$).

In the quantification of differences in spike timing precision, we measured SDST from spike one ($SDST_1$) up to five ($SDST_5$). The values of $SDST_1$ to $SDST_5$ at Purkinje cells in eyes-unopened rats are $0.67 \pm 0.07$, $1.6 \pm 0.19$, $1.95 \pm 0.19$, $2.46 \pm 0.21$, and $2.78 \pm 0.22$ ms (filled circles in Fig. 1D, $n = 27$); and the values from $SDST_1$ to $SDST_5$ at Purkinje cells in eyes-opened rats are $0.73 \pm 0.08$, $0.9 \pm 0.08$, $1.37 \pm 0.15$, $1.92 \pm 0.22$, and $2.1 \pm 0.24$ ms (open circles in Fig. 1D, $n = 30$), respectively. SDST values relevant to the same number in sequential spikes between two ages of rats are statistically different ($p < 0.01$).

The results in Fig. 1 imply that excitatory inputs on cerebellar Purkinje cells are able to drive them to fire more spikes with temporal precision after rat's eyes open. In other words, rat's eyes-opening during postnatal period is critical for cerebellar Purkinje cells to be matured in firing sequential spikes. We investigated intrinsic mechanisms underlying the postnatal improvement of firing sequential spikes.

### *Postnatal change in threshold potentials and refractory periods*

The threshold potentials and refractory periods of sequential spikes are linearly correlated with spike parameters [5]. We examined whether the plasticity of threshold potentials and refractory periods underlies the improvement of spike timing precision and capacity during postnatal development.

ARP of sequential spikes at cerebellar Purkinje cells appear longer in eyes-unopened rats (Fig. 2A) than eyes-opened rats (Fig. 2B). Fig. 2C shows the comparisons of ARP at cerebellar Purkinje cells from these two ages of rats. ARP values of spikes 1–4 are $4.53 \pm 0.2$, $5.19 \pm 0.27$, $5.53 \pm 0.32$, and $6.49 \pm 0.67$ ms in eyes-opened rats (open circles, $n = 16$); and the values are $5.71 \pm 0.34$, $6.82 \pm 0.49$, $7.81 \pm 0.59$, and $9.1 \pm 0.99$ ms in eyes-unopened rats (filled circles, $n = 18$). ARP values relevant to the same number in sequential spikes at Purkinje neurons of these two ages of rats are statistically different ($p < 0.01$). Refractory periods subsequent to each of spikes are shortening during postnatal period.

Threshold potentials are presented as a gap between resting membrane potential ($V_r$) and threshold potential ($V_{ts}$). The reasons to use $V_{ts}$–$V_r$ include followings. The values of $V_r$ and $V_{ts}$ vary among cortical neurons [26];

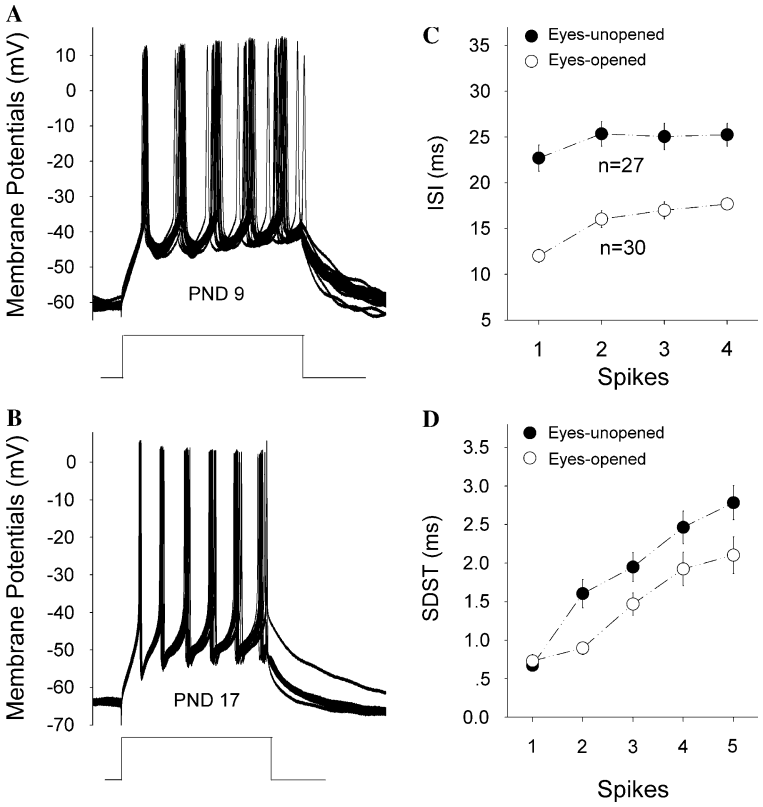


Fig. 1. Postnatal maturation of spike capacity and timing precision at cerebellar Purkinje cell (CPC). (A) The superimposed waveforms of sequential spikes are evoked by depolarization current pulses (110 ms) at CPC from eyes-unopened rats. (B) The superimposed waveforms of sequential spikes are evoked by depolarization currents (80 ms) at CPC from eyes-opened rats. (C) The comparisons of inter-spike intervals (ISI) of sequential spikes at Purkinje cells between eye-opened (open symbols, $n = 30$) and eye-unopened rats (filled symbols, $n = 27$). (D) The comparisons of the standard deviation of spike timing (SDST) at CPC between eye-opened (open symbols) and eye-unopened rats (filled symbols).

$V_{ts}$–$V_r$ is an energy barrier to lift $V_r$ toward $V_{ts}$; and $V_{ts}$–$V_r$ is better to show how easily synaptic inputs drive neurons to fire spikes. Fig. 1D shows the comparison of $V_r$–$V_{ts}$ values at Purkinje cells from eyes-opened and eyes-unopened rats. $V_{ts}$–$V_r$ values of spikes 1–5 are $25.36 \pm 1.14$, $28.51 \pm 1.17$, $28.81 \pm 1.14$, $29.27 \pm 1.11$, and $30.23 \pm 1.66$ ms in eyes-unopened rats (filled circles, $n = 25$); and the values are $18.8 \pm 0.85$, $22.64 \pm 0.96$, $23.56 \pm 0.94$, $23.87 \pm 0.93$, and $24.19 \pm 0.94$ ms in eyes-opened rats (open circles, $n = 30$). $V_{ts}$–$V_r$ values relevant to the same number in sequential spikes at Purkinje neurons from these two ages of rats are statistically different ($p < 0.01$). Threshold potentials are lowering during postnatal development.

The results above indicate that the lowering of threshold potentials at cerebellar Purkinje cells in eyes-opened rats allows them being more sensitive to the excitatory synaptic inputs and firing spikes with higher capacity, as well as that the shortening of refractory periods permits Purkinje cells firing sequential spikes with high capacity and temporal precision. Therefore, the plasticity in shortening $V_{ts}$–$V_r$ and ARP underlies the maturation of spike capacity and timing precision during the postnatal period. It is noteworthy that the correlations between ARP and $V_{ts}$–$V_r$ are linear in both eyes-unopened ($r^2 = 0.95$, filled circles in Fig. 2E) and opened rats ($r^2 = 0.88$, open circles, $p < 0.01$), indicating such two intrinsic properties are controlled by a single mechanism.

### *Developmental change in the correlation between intrinsic properties and spike programming*

The threshold potentials and refractory periods are linearly correlated with spike capacity and timing precision [5] and we examined whether the linear correlations are established during the postnatal period. If their linear correlations are present in entire postnatal period, refractory periods and threshold potentials underlie spike programming. If the linear correlations establish postnatally, what mechanisms control spike programming in early stage? We investigated these issues at Purkinje cells from eyes-opened and -unopened rats.

With the measured intrinsic properties (ARP and $V_{ts}$–$V_r$) and parameters (ISI and SDST) of sequential spikes at cerebellar Purkinje cells, we plotted ARP vs. SDST and ISI, as well as $V_{ts}$–$V_r$ vs. SDST and ISI. The correlations between ARP and SDST are linear in eyes-unopened rats ($r^2 = 0.95$, filled circles in Fig. 3A) and eyes-opened rats ($r^2 = 0.93$, open circles; $p < 0.01$). The relationship between ARP and ISI changes to be linear from eyes-unopened rats

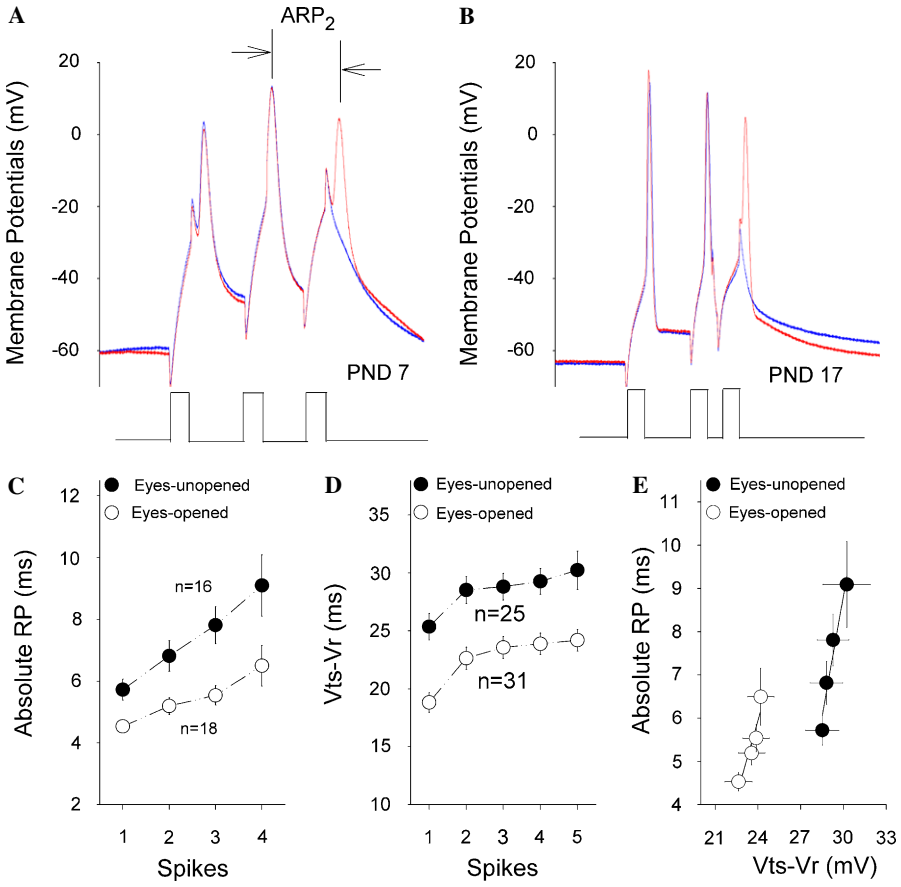


Fig. 2. The postnatal changes in the refractory periods and threshold potentials of sequential spikes at cerebellar Purkinje cell (CPC). (A) The superimposed waveforms show the measurement of ARP by giving depolarization current pulses (3 ms) at CPC from eyes-unopened rats. (B) The superimposed waveforms show the measurement of ARP by giving depolarization current pulses (3 ms) at CPC from eyes-opened rats. (C) The comparisons of ARP of sequential spikes at CPC between eye-opened (open symbols, $n = 18$) and eye-unopened rats (filled symbols, $n = 16$). (D) The comparisons of threshold potentials ($V_{ts}$–$V_r$) of sequential spikes at CPC between eye-opened (open symbols, $n = 31$) and eye-unopened rats (filled symbols, $n = 25$). (E) The relationship between ARP and $V_{ts}$–$V_r$ is linearly correlated ($r^2 = 0.89$–$0.95$).

($r^2 = 0.54$, filled circles in Fig. 3B) to eyes-opened rats ($r^2 = 0.78$, open circles; $p < 0.01$). The linear correlation between $V_{ts}$–$V_r$ and SDST in eyes-unopened rats ($r^2 = 0.93$, filled circles in Fig. 3C) converts to less linear in eyes-opened rats ($r^2 = 0.69$, open circles). The correlations between $V_{ts}$–$V_r$ and ISI are linear in eyes-unopened rats ($r^2 = 0.95$, filled circles) and eyes-opened rats ($r^2 = 0.99$, open circles in Fig. 3D; $p < 0.01$). These results imply that refractory periods become a major factor to control spike timing precision and capacity during postnatal maturation, whereas threshold potentials seem to be more critical to navigate spike programming during early development of cerebellar Purkinje cells.

## Discussion

With quantifying sequential spikes and their intrinsic properties at Purkinje cells in cerebellar slices from the postnatal rats, we first document their maturation in spike programming. The capacity and timing precision of sequential spikes are improved dramatically during the postnatal period, especially the eyes-opening is critical. In the meanwhile, spike threshold potentials shift toward lower and refractory periods are shortened. These together with the linear correlations between intrinsic properties and spike parameters make cerebellar Purkinje cells to be sensitive to excitatory inputs and enhanced in the ability of programming sequential spikes after rats' eyes open.

The activities of potassium channels are thought to influence neuronal excitability and spike timing [8,10,12,20,22]. Voltage-gated sodium channels mechanistically underlie the threshold potentials and refractory periods [2,4,7,13]; also our data submitted), which influence spike programming [5]. With such postnatal changes in spike firing and intrinsic properties, we propose that the kinetics of voltage-gated ion channels undergoes plastic change during postnatal maturation, which is under study.

ARP reduction occurs predominantly in the late phase of sequential spikes (Fig. 2), which allows the late phase of spikes moving closely toward initial ones. If spikes represent digital "1" and inter-spike interval denotes digital "0" [16], the reduction of ARP and ISI will mainly lower

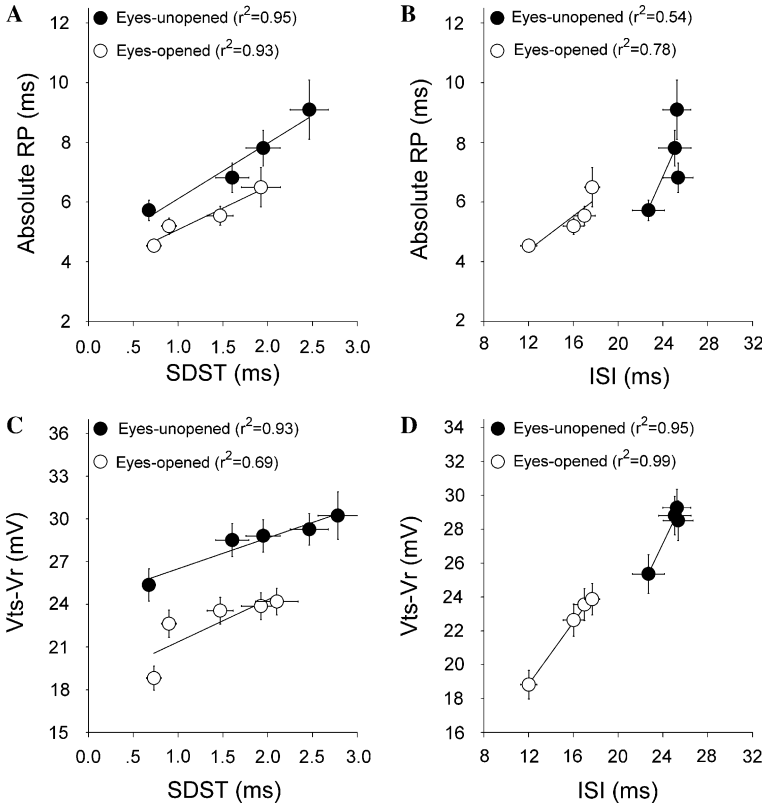


Fig. 3. Dynamic changes in the relationship between intrinsic properties (ARP and $V_{ts}$–$V_r$) and spike parameters (ISI and SDST) at cerebellar Purkinje cells. (A) ARP and SDST are linearly correlated in eyes-unopened rats ($r^2 = 0.95$, filled circles) and eyes-opened rats ($r^2 = 0.93$, open circles). (B) The relationship between ARP and ISI in eyes-unopened rats ($r^2 = 0.54$, filled circles) changes to be linear in eyes-opened rats ($r^2 = 0.78$, open circles; $p < 0.01$). (C) A linear correlation between $V_{ts}$–$V_r$ and SDST in eyes-unopened rats ($r^2 = 0.93$, filled circles) converts to less linear in eyes-opened rats ($r^2 = 0.69$, open circles). (D) $V_{ts}$–$V_r$ and ISI are linearly correlated in eye-unopened rats ($r^2 = 0.95$, filled circles) and eyes-opened rats ($r^2 = 0.99$, open circles; $p < 0.01$).

the number of digital "0" between "1" in the late phase of spike programming. Together these data with the developmental regulation in the plasticity of neuronal excitability [26], we suggest that the eyes-opened during postnatal development is a critical period for cerebellar Purkinje cells to be matured in the ability of firing spikes by expressing a low threshold and a short refractory periods in the response to excitatory synaptic inputs.

The advantages of approaches used in our studies are the followings. Instead of experimenting in cultured Purkinje cells [9,11,15,19], we studied the developmental profiles of the intrinsic properties of cerebellar Purkinje cells in acute isolated slices, in which a more natural environment is provided for cell survivals. We developed the approach to measure the refractory periods after each of spikes, which helps to address the mechanisms underlying quantitative spike capacity and timing precision.

Our study provides the developmental profiles of intrinsic properties at cerebellar Purkinje cells for understanding the maturation of the cerebellum in programming the sequential spikes, i.e., the spectrum of neural signals, to manage motion coordination, balance, working memory, and cognition as well.

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## References

[1] C. Aizenmann, D.J. Linden, Rapid, synaptically driven increases in the intrinsic excitability of cerebellar nuclear neurons, Nat. Neurosci. 3 (2000) 109–111.
[2] R. Azous, C.M. Gray, Dynamic spike threshold reveals a mechanism for synaptic coincidence detection in cortical neurons in vivo, Proc. Natl. Acad. Sci. USA 97 (2000) 8110–8115.
[3] M. Brown, R. Keynes, A. Lumsden, Development of cerebral cortex and cerebellar cortex, in: M.E.A. Brown (Ed.), The Development of Brain, Oxford University Press Inc., New York, 2001, pp. 169–193.
[4] A.R. Cantrell, W.A. Catterall, Neuromodulation of $Na^+$ channels: an unexpected form of cellular plasticity, Nat. Rev. Neurosci. 2 (2001) 397–407.
[5] N. Chen, S.L. Chen, Y.L. Wu, J.H. Wang, The measurement of threshold potentials and refractory periods of sequential spikes by whole-cell recordings, Biochem. Biophys. Res. Commun. 340 (2006) 151–157.

[6] L.A. Cingolani, M. Gymnopoulos, A. Boccaccio, M. Stocker, P. Pedarzani, Developmental regulation of small conductance $Ca^{2+}$-activated $K^+$ Channel expression and function in rat Purkinje neurons, J. Neurosci. 22 (2002) 4456–4467.
[7] C.M. Colbert, E. Pan, Ion channel properties underlying axonal action potential initiation in pyramidal neurons, Nat. Neurosci. 5 (2002) 533–538.
[8] P.A. Glazebrook, A.N. Ramirez, J.H. Schild, C.-C. Shieh, T. Doan, B.A. Wible, D.L. Kunze, Potassium channels Kv1.1, Kv1.2 and Kv1.6 influence excitatory of rat visceral sensory neurons, J. Physiol. (Lond.) 541 (2002) 467–482.
[9] D.L. Gruol, C.R. Deal, A.J. Yool, Developmental changes in calcium conductances contribute to the physiological maturation of cerebellar Purkinje neurons in culture, J. Neurosci. 12 (1992) 2838–2848.
[10] D. Hess, A.E. Manira, Characterization of a high-voltage-activated Ia current with a role in spike timing and locomotor pattern generation, Proc. Natl. Acad. Sci. USA 98 (2001) 5276–5281.
[11] P.E. Hockberger, H.-Y. Tseng, J.A. Connor, Development of rat cerebellar Purkinje cells: electrophysiological properties following acute isolation and in long-term culture, J. Neurosci. 9 (1989) 2258–2271.
[12] D. Johnston, D.A. Hoffman, J.C. Magee, N.P. Poolos, S. Watanabe, C.M. Colbert, M. Migliore, Dendritic potassium channels in hippocampal pyramidal neurons, J. Physiol. (Lond.) 525 (2000) 75–81.
[13] M.C. Kiernan, A.V. Kirshnan, C.S. Lin, D. Burkke, S.F. Berkovic, Mutation in the $Na^+$ channel subunit SCN1B produces paradoxical changes in peripheral nerve excitability, Brain 128 (2005) 1841–1846.
[14] J. Kleim, K. Vij, D. Ballard, W. Greenough, Learning-dependent synaptic modifications in the cerebellar cortex of the adult rat persist for at least four weeks, J. Neurosci. 17 (1997) 717–721.
[15] P. Liljelund, J.G. Netzeband, D.L. Gruol, L-Type calcium channels mediate calcium oscillations in early postnatal Purkinje neurons, J. Neurosci. 20 (2000) 7394–7403.
[16] M. London, A. Schreibman, M. Hausser, M.E. Larkum, I. Segev, The information efficacy of a synapse, Nat. Neurosci. 5 (2002) 332–340.
[17] M.D. Mauk, J.F. Medina, W.L. Nores, T. Ohyama, Cerebellar function: coordination, learning or timing? Curr. Biol. 10 (2000) R522–R525.
[18] B.E. McKay, R.W. Turner, Physiological and morphological development of the rat cerebellar Purkinje cell, J. Physiol. (Lond.) 567 (Pt3) (2005) 829–850.
[19] Y.L. Muller, R. Reitstetter, A.J. Yool, Regulation of $Ca^{2+}$-dependent K1 channel expression in rat cerebellum during postnatal development, J. Neurosci. 18 (1998) 16–25.
[20] S. Nedergarrd, Regulation of action potential size and excitability in substantia nigra compacta neurons: sensitivity to 4-aminopyridine, J. Neurophysiol. 82 (1999) 2903–2913.
[21] J.L. Roymond, S.G. Lisberger, M.D. Mauk, The cerebellum: a neuronal learning mechanize? Science 272 (1996) 1126–1130.
[22] B. Rudy, A. Chow, D. Lau, Y. Amarillo, A. Ozaita, M. Saganich, H. Moreno, M.S. Nadal, R. Hernandez-Pineda, A. Hernandez-Cruz, A. Erisir, C. Leonard, E. Vega-Sarnz de Miera, Contributions of Kv3 channels to neuronal excitability, Ann. N Y Acad. Sci. 868 (1999) 304–343.
[23] J.-H. Wang, Short-term cerebral ischemia causes the dysfunction of interneurons and more excitation of pyramidal neurons, Brain Res. Bull. 60 (2003) 53–58.
[24] J.-H. Wang, P.T. Kelly, $Ca^{2+}$/CaM signaling pathway up-regulates glutamatergic synaptic function in non-pyramidal fast-spiking neurons of hippocampal CA1, J. Physiol. (Lond.) 533 (2001) 407–422.
[25] V.Y. Wang, H.Y. Zoghbi, Genetic regulation of cerebellar development, Nat. Rev. Neurosci. 2 (2001) 484–491.
[26] M. Zhang, F. Hung, Y. Zhu, Z. Xie, J. Wang, Calcium signal-dependent plasticity of neuronal excitability developed postnatally, J. Neurobiol. 61 (2004) 277–287.