

Cerebellar circuits in autism-linked social behavior

Shaofei Jiang^{1,2}, Yingping Ma³, Xiangjun Hu², and Haitao Wu^{1,3,4,5} (✉)

¹ Department of Neurobiology, Beijing Institute of Basic Medical Sciences, Beijing 100850, China

² Laboratory of Experimental Pathology, Beijing Institute of Radiation Medicine, Beijing 100850, China

³ School of Basic Medical Sciences, Anhui Medical University, Hefei 230032, China

⁴ Key Laboratory of Neuroregeneration, Co-innovation Center of Neuroregeneration, Nantong University, Nantong 226019, China

⁵ Chinese Institute for Brain Research, Beijing 102206, China

ARTICLE INFO

Received: 27 December 2022 / **Revised:** 5 January 2023 / **Accepted:** 10 January 2023

© The Author(s) 2023



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<http://www.creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission.

1 Introduction

Autism spectrum disorder (ASD), a neurodevelopmental disorder, characterized by social impairment, repetitive, and inflexible behaviors, puts a heavy burden on families and society with regard to the increased number of autistic patients. Recently, the cerebellum has been highly implicated in the pathogenesis of ASD patients, such as decreased Purkinje cell (PC) number and size, altered size and number of cerebellar output nuclear neurons, as well as changes in volumes and cerebellar activation, highlighting the posterior vermis and lobule VII [1]. And many autism-related susceptibility genes are expressed in the cerebellum, including *Tsc1/2*, *PTEN*, and *Shank2*. However, many issues concerning how cerebellum plays a role in ASD remained elusive. Hence, we reviewed the latest research progress on the involvement of the

cerebellum in the regulation of ASD-linked social functions from the perspective of neural circuits and dopamine receptors.

2 Cerebellar predictive and adaptive model in social behavior

Social behaviors are particularly complex. Stoodley and Tsai summarized that social behaviors require neural correlates not only of emotion, mentalizing, and reward networks, but also of the accurate and specific predictions, which integrates diverse processes, including the ability to understand the consequences of one's own actions while anticipating the state, needs, and meaning of other's actions, all in real time [1]. A core principle underlying this understanding and anticipation is the ability to generate rapid, well-timed, and accurate predictions and seamlessly adapt those predictions to the dynamic behavioral landscape

Address correspondence to wuht@bmi.ac.cn

that makes up a social interaction. Cerebellum is a critical neural substrate of predictive processing and meets the criteria for the representation of adaptive internal models that enable automatic, rapid, and well-calibrated behaviors. When an error signal was received, the climbing fiber (CF) from the inferior olive generates a large dendritic calcium spike-complex spike (CSp) at PCs, inducing the heterosynaptic plasticity at the parallel fiber–PC synapse by long-term depression (LTD).

The cerebellum provides the circuit properties to generate, update, and automatize predictions using both supervised and reinforcement learning. These predictive and adaptive internal models enable precise performance, timing, and learning of complex behaviors, including those relevant to social interactions. Cerebellar circuits, acting at the implicit level and using social information conveyed through extensive cerebro–cerebellar connections, could build and hone internal models of complex behaviors. Moreover, the cerebellar circuits allow for automatic information processing and appropriate behaviors in a range of socially relevant processes ranging from perception of biological motion to the understanding of mental states of others.

Consistent with disrupted cerebellar predictive modeling, the ability to make accurate predictions in both social and nonsocial domains is impacted in ASD, which was seemingly incapable of adapting those predictions consistent with the insistence on sameness and cognitive inflexibility. Thus, the growing evidence for cerebellar dysfunction in autism is not coincidental but rather provides a parsimonious explanation for both the circuit dysfunction and behavioral challenges observed in ASD. The fundamental cerebellar-mediated functions—implicit prediction and adaptation—provide a core mechanism that ties together the apparently disparate behavioral categories impacted in ASD, from sensorimotor

challenges to social impairment and inflexible behaviors. Based on the abovementioned cerebellar predictive and adaptive model in social behavior, some recent interesting studies demonstrated the involvement as well as the cellular and neural circuits mechanisms of cerebellum in the regulation of ASD-related social behaviors.

3 Cerebellar cortex and cerebellar–prefrontal circuits modulate the autism-like behaviors

Cerebellar right Crus I (RCrus I) abnormalities are consistently reported in human imaging and animal studies of ASD, the contribution of RCrus I dysfunction to ASD remains unclear. The Tsai’ lab conducts a series of studies around RCrus I and ASD [2, 3]. The earlier study reported the critical roles of RCrus I and RCrus I–cerebral circuit in ASD-related behaviors in both ASD children and PCs-specific *Tsc1* mutant ASD mouse model [2]. They reported that modulation of RCrus I altered functional connectivity with the inferior parietal lobule (IPL), and identified disrupted RCrus I–left IPL functional connectivity in children with ASD and structural connectivity in the ASD mouse model. Further, social impairments and repetitive behaviors appeared after chemogenetically mediated silencing of RCrus I, while social function was not impaired by inhibition of left Crus I (LCrus I). Such findings are consistent with the results of human studies, indicating that RCrus I, but not LCrus I, shows converging structural differences in ASD. Moreover, RCrus I (but not LCrus I) activation only rescued social impairments but failed to mitigate repetitive or inflexible behaviors. Notably, several issues are not discussed by this article, such as whether the ASD-related behavioral changes observed in mice following neuromodulation of RCrus I are mediated by RCrus I–IPL connections, and

whether the specific cerebellar subregions control social and/or repetitive/inflexible behaviors, which have already been carefully addressed by Tsai's lab [3].

The recent study demonstrated that cerebellar-medial prefrontal cortex (mPFC) connections play an important role in the regulation of ASD-relevant behaviors [3]. In this study, the researchers delineated a circuit from cerebellar cortical areas RCrus I and posterior vermis through the cerebellar nuclei and ventromedial thalamus (VM) and culminating in the left prelimbic cortex (PrL). And inhibition of this circuit induced social deficits and repetitive behaviors, whereas activation of PCs in RCrus I and posterior vermis improved social preference impairments and repetitive/inflexible behaviors, respectively, in PCs-specific *Tsc1* mutant male ASD mice. Therefore, distinct cerebellar regions control particular behaviors, with RCrus I stimulation sufficient to ameliorate social behaviors, whereas posterior vermis stimulation is sufficient to improve repetitive/inflexibility behaviors.

Together, the results highlighted the key roles of the cerebellum in modulation and execution of social behaviors and further support functional connections of cerebro-cerebellum in the regulation of complex non-motor behavior [2, 3]. In parallel, these insights show the potential in the development of cerebellum-related therapeutic avenues for as the treatment of ASD.

4 Cerebellar nuclei-ventral tegmental area (VTA) pathway modulates the social and reward behavior

In addition to the cerebellar cortex and their downstream nuclei culminated in VM circuits in the regulation of mPFC neurons, there are some other cortical and sub-cortical regions might also be regulated by the cerebellum to contribute to

ASD-relevant behaviors, such as the mediodorsal thalamus, striatum, and VTA. By coincidence, Carta et al. found that monosynaptic excitatory projections from the deep cerebellar nuclei to the VTA (DCN-VTA) powerfully activate the reward circuitry and contribute to social behavior [4]. They reported that the DCN-VTA pathway was more active when the mouse explored the social chamber in a three-chamber social task. Furthermore, optically silenced cerebellar axons in the VTA-impaired mice exhibited a preference for the social chamber, while optogenetic activation of the DCN-VTA inputs was not prosocial. These results indicate that the DCN-VTA input may be a necessary, but not sufficient component for social behavior.

The abovementioned study opens a new avenue for interpreting the function of the cerebellum and also for understanding social behavior and related pathologies, with the potential to discover novel therapies to treat these diseases. It should be noted that in this study, they treated all cerebellar nuclei projections to VTA as a single unit. However, it is likely that the DCN-VTA projection neurons originate from different parts of cerebellum. The distinct types of neurons within the cerebellar nuclei follow a specific connectivity pattern with the VTA neurons, and convey different information. Interestingly, in addition to the function of DCN-VTA circuit in regulation of sociability and reward, the other physiological and cognitive functions of this circuit need further studies.

5 Cerebellar dopamine D2 receptors regulate social behaviors

Cerebellar contributions to higher cognitive functions including reward and social interaction has been ascribed to monoaminergic system in limbic regions or cerebellar-cerebral circuits, such as previously described DCN-VTA circuit [4].

However, the contribution of cerebellar dopamine signaling in the modulation of these functions remains largely unknown. Recently, Cutando et al. combined cell-type-specific molecular and imaging analysis, together with electrophysiology and mouse behavior to parse the role of cerebellar dopamine D2 receptors (D2Rs) [5]. They demonstrated that in mice cerebellar D2Rs are preferentially expressed in PCs, being particularly abundant in Crus I/II and lobules VI/VII, and regulate synaptic efficacy. Moreover, they revealed that cerebellar D2Rs play a key role in modulating sociability and preference for social novelty without affecting the motor functions specifically in PCs during adulthood.

Overall, their findings unveiled novel roles of D2R in PCs in the regulation of social interaction and may have important implications in understanding the etiology of socially related neurological and psychiatric disorders. Further studies may clarify the source of dopamine in the cerebellar from the VTA or the locus coeruleus. In addition, it is still unclear whether D2R in PCs participates in the reward processing through the modulation of the DCN–VTA pathway. Further research is still needed to be done on these issues.

6 Conclusions and prospectives

The cerebellum has initially been considered to be involved in the coordination of voluntary movements, while increasing evidence indicates that it might also take part in cognitive and emotional abilities as well as social interactions. Here, we summarized the cerebellar predictive and adaptive model in social behavior, followed by outlining social functions of three cerebral-cerebellar circuits, including RCrus I–lateral nucleus (LN)–VM–PrL, posterior vermis–fastigial nucleus (FN)/medial nucleus (MN)–VM–PrL, and DCN–VTA, respectively. And, the novel roles for D2Rs in PCs in social behaviors have also

been introduced, which has been summarized and illustrated in Fig. 1. The latest studies raised the possibility that cerebellum and cerebellar circuits might be the potential neuromodulation targets for the treatment of ASD. More intensive studies should be conducted to further explore the neural mechanisms underlying cerebellar circuits-mediated ASD and social behaviors in the future.

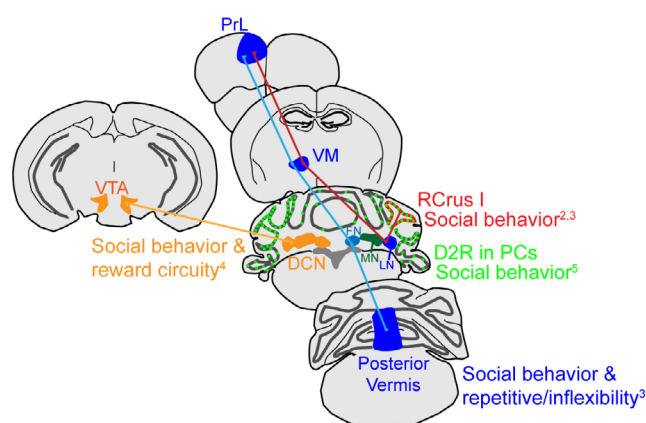


Figure 1 Cerebellar circuits modulate ASD-linked behaviors. Illustration of the cerebral-cerebellar circuits regulating social functions, including RCrus I–LN–VM–PrL, posterior vermis–FN/MN–VM–PrL, and DCN–VTA, and the novel roles for D2Rs in PCs in modulating social function were also included.

Acknowledgements

This work is supported by the National Natural Science Foundation of China (Nos. 32171148 and 31770929) and the National Key Research and Development Program of China (Nos. 2021ZD0202500 and 2021YFA1101801).

Author contributions

The manuscript was initiated and written by S.J., Y.M., X.H., and H.W.

Declaration of conflicting interests

The authors declare no competing interests regarding the content of this article.

References

- [1] Stoodley, C. J., Tsai, P. T. Adaptive prediction for social contexts: The cerebellar contribution to typical and atypical social behaviors. *Annual Review of Neuroscience*, **2021**, 44: 475–493.
- [2] Stoodley, C. J., D'Mello, A. M., Ellegood, J., Jakkamsetti, V., Liu, P., Nebel, M. B., Gibson, J. M., Kelly, E., Meng, F. T., Cano, C. A. et al. Altered cerebellar connectivity in autism and cerebellar-mediated rescue of autism-related behaviors in mice. *Nature Neuroscience*, **2017**, 20(12): 1744–1751.
- [3] Kelly, E., Meng, F. T., Fujita, H., Morgado, F., Kazemi, Y., Rice, L. C., Ren, C. Y., Escamilla, C. O., Gibson, J. M., Sajadi, S. et al. Regulation of autism-relevant behaviors by cerebellar-prefrontal cortical circuits. *Nature Neuroscience*, **2020**, 23(9): 1102–1110.
- [4] Carta, I., Chen, C. H., Schott, A. L., Dorizan, S., Khodakhah, K. Cerebellar modulation of the reward circuitry and social behavior. *Science*, **2019**, 363(6424): eaav0581.
- [5] Cutando, L., Puighermanal, E., Castell, L., Tarot, P., Belle, M., Bertaso, F., Arango-Lievano, M., Ango, F., Rubinstein, M., Quintana, A. et al. Cerebellar dopamine D2 receptors regulate social behaviors. *Nature Neuroscience*, **2022**, 25(7): 900–911.



Haitao Wu received his Ph.D. degree from the Academy of Military Medical Sciences, China (2007), and then received his postdoctoral training in Medical College of Georgia, USA (2008–2012). He is a professor and the Department Head in Beijing Institute of Basic Medical Sciences since 2015, and was awarded NSFC Excellent Young Scholar in 2015. Now he is also the Guest Professor and CIBR scholar in Chinese Institute for Brain Research, Beijing (2020). He has published many high-quality papers in journals including *Neurons*, *PNAS*, *Science Advances*, *Cell Reports*, and *eLife*.

His current research interests are focused on the cellular and molecular mechanisms underlying cortical development as well as stress-induced psychiatric and cognitive disorders. E-mail: wuht@bmi.ac.cn.