Jia *et al. Ageing Neur Dis.* 2025;5:3
DOI: 10.20517/and.2024.26

Ageing and Neurodegenerative Diseases

Commentary

Open Access

The cerebellum: a newly discovered circuitry basis for cognitive pain modulation

Qiqi Jia[1,#], Lihong Chen[2,#], Tianbai Li[1,*]

[1]Key Laboratory of Liaoning Province for Research on the Pathogenic Mechanisms of Neurological Diseases, the First Affiliated Hospital, Dalian Medical University, Dalian 116021, Liaoning, China.
[2]Department of Neurology, the First Affiliated Hospital, Dalian Medical University, Dalian 116021, Liaoning, China.
[#]Authors contributed equally.

[*]**Correspondence to:** Dr. Tianbai Li, Key Laboratory of Liaoning Province for Research on the Pathogenic Mechanisms of Neurological Diseases, the First Affiliated Hospital, Dalian Medical University, 193 Lianhe Road, Dalian 116021, Liaoning, China. E-mail: litianbai1@sina.com

How to cite this article: Jia Q, Chen L, Li T. The cerebellum: a newly discovered circuitry basis for cognitive pain modulation. *Ageing Neur Dis.* 2025;5:3. https://dx.doi.org/10.20517/and.2024.26

Received: 29 Aug 2024 **First Decision:** 20 Jan 2025 **Revised:** 31 Jan 2025 **Accepted:** 18 Feb 2025 **Published:** 21 Feb 2025

Academic Editor: Xiaojiang Li **Copy Editor:** Pei-Yun Wang **Production Editor:** Pei-Yun Wang

Abstract

Chen *et al.* investigate the neural basis of placebo analgesia in their recent *Nature* study, revealing the role of the cortico-ponto-cerebellar pathway. Using a placebo analgesia condition animal model, they show that expectations of pain relief are encoded through direct connections from the rostral anterior cingulate cortex (rACC) to the pontine nucleus (PN) and subsequently affect cerebellar regions linked to cognition. The study finds that placebo analgesia enhances rACC neuron activity and boosts calcium signaling in cerebellar Purkinje cells via *Oprd1*-expressing PN neurons. These results underscore the cerebellum's involvement in cognitive pain modulation and suggest that targeting this pathway could offer new approaches for pain relief, including advanced neurostimulation and tailored cognitive therapies.

Keywords: Cognitive pain, placebo analgesia, cerebellum, rostral anterior cingulate cortex, pontine nucleus

What underpins the neural circuitry of placebo pain relief? Recent research published in *Nature* (DOI: 10.1038/s41586-024-07816-z) by Chen *et al.* provides novel insights into the role of the cortico-ponto-

cerebellar pathway in modulating cognitive aspects of pain [Figure 1A][1]. Their findings suggest that targeting cerebellar circuitry with neurostimulation could pave the way for new pain management approaches.

Cognitive modulation of pain involves the influence of mental and cognitive processes - such as expectation, attention, and appraisal - on pain perception and experience[2]. The placebo effect, a phenomenon where pain relief is achieved through expectation rather than actual treatment, exemplifies this cognitive influence[3]. The neural mechanisms underlying placebo analgesia remain largely elusive, with most insights derived from human brain imaging and electrophysiological studies. These studies have identified altered activity in key brain regions, including the rostral anterior cingulate cortex (rACC), prefrontal cortex (PFC), medial thalamus, and nucleus accumbens, in association with placebo analgesia[3,4]. However, the precise neural circuits mediating these effects remain unclear. While pain modulation engages multiple brain systems, ranging from the spinal cord and cerebellum to the PFC, existing research has largely focused on these pathways without fully accounting for the cognitive, emotional, and sensory components underlying placebo analgesia. A key limitation in advancing this field is the lack of an ideal animal model for studying placebo effects. To address this gap, Chen et al. developed an animal model of placebo analgesia and utilized optogenetics, calcium imaging, and electrophysiology to investigate its neural mechanisms[1]. Their findings identify the cortico-ponto-cerebellar circuitry as a key pathway in placebo analgesia, providing novel insights into how this circuit contributes to placebo-induced pain relief.

The researchers initially developed an animal model of placebo analgesia conditioning that successfully established pain relief expectations in mice [Figure 1B][1]. The placebo analgesia conditioning assay involves three phases: habituation (days 1-3), conditioning (days 4-6), and post-conditioning analgesia testing (day 7). During conditioning, mice learn to associate one chamber (set at 30 °C) with pain relief after experiencing noxious heat (48 °C) in another chamber. On the post-test day, both chambers are set to 48 °C, revealing that conditioned mice exhibit prolonged latencies to nocifensive behaviors (e.g., paw licking, rearing, and jumping), indicative of an analgesic effect driven by expectation [Figure 1B]. Although this model may not encompass all the complexities of human placebo analgesia, it captures several essential features, including dependence on the endogenous opioid system, the persistence of pain relief expectations, and variability in placebo responses.

The study provides compelling evidence of direct monosynaptic projections from the rACC to the pontine nucleus (PN), highlighting the involvement of the rACC-PN pathway in encoding pain relief expectations[1]. At the mesoscopic and cellular level, single-cell RNA sequencing identified neurons in the PN expressing *Oprd1*, which project to cerebellar lobules VI, crus I-II - regions associated with cognitive functions[1]. This study elucidates how the rACC mediates placebo analgesia via projections to the PN and subsequent cerebellar engagement in the circuit-level process [Figure 1A]. Furthermore, electrophysiological data demonstrated that placebo analgesia specifically enhances the activity of rACC neurons projecting to the PN and increases Ca^{2+} activity in cerebellar Purkinje cells within the VI lobule, mediated by *Oprd1*-expressing neurons in the PN[1].

At the synaptic level, the PN conveys pain relief expectations from the rACC to the cerebellum by amplifying the amplitude and frequency of Ca^{2+} spikes in the dendrites of Purkinje cells [Figure 1C]. The study also found feedforward inhibition and synaptic plasticity in the rACC → PN neurons and Purkinje cells under placebo analgesia[1]. Feedforward inhibition plays a crucial role in regulating burst firing, structuring network representations of behavioral events, and modulating Ca^{2+} signaling during learning processes. Therefore, it is proposed that reduced feedforward inhibition might serve as a common synaptic

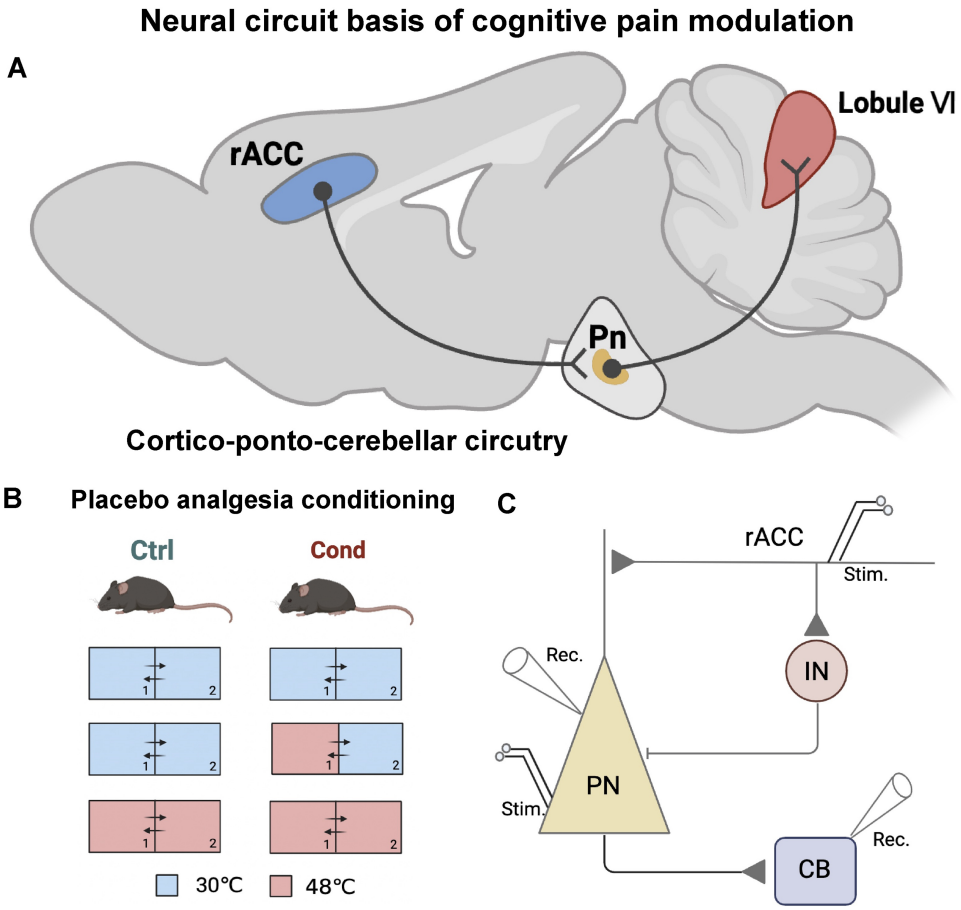

Figure 1. Neural circuit basis of cognitive pain modulation. (A) Recent research published in *Nature* by Chen *et al.* identified the cortico-ponto-cerebellar pathway in the regulation of cognitive aspects of pain[1];(B) A placebo analgesia conditioning assay designed for rodents to generate placebo-like anticipatory pain relief, allowing for the evaluation of the resulting analgesic effect. Ctrl, the control group; Cond, placebo analgesia condition group; (C) Schematic of the recording configuration for rACC → PN → Purkinje circuitry. rACC: Rostral anterior cingulate cortex; PN: pontine nucleus; IN: local interneurons.

mechanism for mediating pain relief expectations in both the cerebral and cerebellar cortices.

It has been shown that feedforward inhibition refines pain-related neural processing by enhancing signal precision and preventing excessive excitatory activity[5]. This inhibitory mechanism is crucial for filtering nociceptive inputs and modulating pain perception based on cognitive and emotional context. Meanwhile, synaptic plasticity, including long-term potentiation and long-term depression, underpins experience-dependent changes in pain sensitivity and placebo analgesia[6]. The cerebellum is increasingly recognized for its role in pain modulation through cortico-cerebellar interactions, integrating cognitive and affective signals to regulate pain responses via the cortico-ponto-cerebellar circuitry and influencing synaptic plasticity in cognitive pain modulation-related pathways.

The authors' findings expand on previous research by highlighting the cerebellum's role not only in motor control but also in a range of cognitive functions, including attention, memory, language, social interactions, emotional regulation[7], and now, cognitive pain modulation. There is broad agreement on the cerebellum's critical role in cognitive modulation, with evidence suggesting that damage to cerebellar

regions associated with cognitive and affective processes can lead to "dysmetria of thought" symptoms[7]. Current understanding emphasizes that the cerebellum regulates cognitive processing through its interactions with various cortical regions and its involvement in different intrinsic connectivity networks[7]. Recent studies have revealed the cerebellum's influence on cognitive and decision-making processes and have linked cerebellar dysfunction to numerous psychiatric and neurodegenerative disorders, including Alzheimer's disease[8-10]. Advances in neuropathology and neuroimaging have further highlighted the cerebellum's role in cognitive impairment and disease progression in Alzheimer's disease[8]. Remarkably, the cerebellum has emerged as a promising target for neurostimulation therapies aimed at enhancing cognitive function across multiple domains[9]. A recent randomized clinical trial demonstrated that repetitive transcranial magnetic stimulation (TMS) of the cerebellum significantly improved cognitive recovery and altered specific cerebellar-thalamic-cerebral functional connectivity in patients with Alzheimer's disease[11].

Expanding on these insights, researchers suggest that novel analgesic drugs and neurostimulation techniques, such as TMS or deep brain stimulation, could be developed specifically to target cerebellar pathways, aiming to alter pain processing at its source. However, cerebellar neurostimulation for pain management remains challenging due to individual variability in response to stimulation, as well as the difficulty of achieving precise targeting within complex cerebellar circuits to ensure effective and consistent analgesic outcomes. Furthermore, cognitive behavioral therapies could be adapted to incorporate cerebellum-focused strategies, enabling patients to better manage pain through integrated multimodal interventions. By combining pharmacological approaches with cognitive behavioral therapy that leverages the cerebellum's role in cognitive and sensory processing, a more comprehensive framework for pain management may be developed[12].

This study also raises important questions about the direct applicability of findings from mouse models to the complexity of human physiology in placebo analgesia. The identified neural pathway, while providing valuable insights, may oversimplify the multifaceted nature of pain perception and modulation in living organisms. Additionally, although the study highlights specific neural circuits, it may not fully account for the contributions of various neurotransmitter systems that play a role in placebo analgesia.

Building on the findings of Chen *et al.*, future research should explore several key areas to further understand the neural mechanisms of placebo analgesia[1]. First, bridging the gap between animal models and human studies is essential. Utilizing non-invasive neuroimaging techniques, such as functional magnetic resonance imaging or positron emission tomography, could help validate these neural circuits in humans and assess their clinical significance. Second, the influence of psychological and environmental factors on placebo analgesia warrants further investigation. Exploring how individual differences in expectancy, emotional states, and past experiences shape these neural circuits could offer a more comprehensive perspective. Third, beyond the opioid system, future studies should examine the potential contributions of other neurotransmitter systems, such as serotonin, norepinephrine, and endocannabinoids, to placebo-induced analgesia. Addressing these aspects will contribute to a more nuanced understanding of placebo mechanisms and their potential clinical applications.

In summary, Chen *et al.* have significantly advanced our understanding of the circuit, cellular, and synaptic mechanisms behind placebo-induced pain relief[1]. Their research underscores the potential of targeting cerebellar pathways with pharmacological and neurostimulation approaches as a promising strategy for pain relief and managing related cognitive dysfunctions.

DECLARATIONS

Authors' contributions

Wrote the first draft of the commentary: Jia Q, Chen L
Edited and contributed to the final draft: Li T

Availability of data and materials

Not applicable.

Financial support and sponsorship

This work was supported by the Natural Science Foundation of Liaoning Province, China (2023-MSLH-029, TL).

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

REFERENCES

1. Chen C, Niehaus JK, Dinc F, et al. Neural circuit basis of placebo pain relief. *Nature.* 2024;632:1092-100. DOI PubMed PMC
2. Atlas LY. How instructions, learning, and expectations shape pain and neurobiological responses. *Annu Rev Neurosci.* 2023;46:167-89. DOI PubMed PMC
3. Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. *Nat Rev Neurosci.* 2015;16:403-18. DOI PubMed PMC
4. Wang Y, Wang Q, Tang L, Zhang X. Cannabinoid modulations of pain- and stress-related circuits. *Ageing Neur Dis.* 2023;3:16. DOI
5. Bissière S, Humeau Y, Lüthi A. Dopamine gates LTP induction in lateral amygdala by suppressing feedforward inhibition. *Nat Neurosci.* 2003;6:587-92. DOI PubMed
6. Owen SF, Berke JD, Kreitzer AC. Fast-spiking interneurons supply feedforward control of bursting, calcium, and plasticity for efficient learning. *Cell.* 2018;172:683-95.e15. DOI PubMed PMC
7. Devita M, Alberti F, Fagnani M, et al. Novel insights into the relationship between cerebellum and dementia: a narrative review as a toolkit for clinicians. *Ageing Res Rev.* 2021;70:101389. DOI
8. Jacobs HIL, Hopkins DA, Mayrhofer HC, et al. The cerebellum in Alzheimer's disease: evaluating its role in cognitive decline. *Brain.* 2018;141:37-47. DOI PubMed
9. Yang C, Liu G, Chen X, Le W. Cerebellum in Alzheimer's disease and other neurodegenerative diseases: an emerging research frontier. *MedComm.* 2024;5:e638. DOI PubMed PMC
10. Li T, Le W, Jankovic J. Linking the cerebellum to Parkinson disease: an update. *Nat Rev Neurol.* 2023;19:645-54. DOI
11. Yao Q, Tang F, Wang Y, et al. Effect of cerebellum stimulation on cognitive recovery in patients with Alzheimer disease: a randomized clinical trial. *Brain Stimul.* 2022;15:910-20. DOI
12. Moody TD, Morfini F, Cheng G, et al. Mechanisms of cognitive-behavioral therapy for obsessive-compulsive disorder involve robust and extensive increases in brain network connectivity. *Transl Psychiatry.* 2017;7:e1230. DOI PubMed PMC