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EDITORIAL

Beyond motor control: cerebellar contributions to pain modulation

Além do controle motor: contribuições do cerebelo para a modulação da dor

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For many years, pain was understood as arising solely from nociceptor activation, with the nociceptive signal assumed to ascend in an uninterrupted manner to the brain. Research inspired by the Gate Control Theory later showed that transmission of nociceptive signals is not purely linear but is shaped by endogenous modulatory systems that can either enhance or suppress their transmission, ultimately shaping pain perception. Following research has demonstrated that pain perception is also shaped by dynamic interactions between biological, psychological, and social factors, with the latter two doing so through biological and neurophysiological mechanisms. For instance, expectations (a psychological factor that can also be shaped socially) can influence the experience of pain through placebo and nocebo effects, which operate via biological mechanisms.

Placebo analgesia refers to a reduction in pain driven by positive treatment expectations, whereas nocebo-induced hyperalgesia corresponds to an increase in pain arising from anticipatory negative beliefs. As previously noted, these effects are underpinned by genuine neurobiological mechanisms: placebo analgesia has for instance been associated with the activation of endogenous opioid and cannabinoid systems, while nocebo hyperalgesia has been shown to be mediated by anti-opioid peptides such as cholecystokinin. Other neuromodulators – including dopamine, oxytocin and vasopressin – can also shape pain experience through expectations. These processes engage a network of cortical and subcortical regions, such as the prefrontal cortex, anterior cingulate cortex, insula, amygdala, thalamus and periaqueductal gray, as well as the spinal circuits that modulate nociceptive processing (see Rossettini et al.[1] for a review).

Despite substantial developments in pain science, the notion that pain is primarily rooted in the somatosensory system has persisted, historically overshadowing contributions from other brain regions. One such region is the cerebellum; although cerebellar activation is frequently reported in pain neuroimaging research, this region remains largely absent from dominant pain models, presumably due to its primary association with motor functions. This motor-centric view of the cerebellum is reductive, considering early findings from the 19th century that suggest its involvement in emotional, cognitive and executive processes.

One of the earliest clues to cerebellar involvement in non-motor functions came in 1831, with the case report of a young girl with cerebellar agenesis who presented striking deficits in cognitive and emotional domains[2]. Despite this, a meaningful shift in the understanding of cerebellar function did not occur until the late 20th century, when Schmahmann described the Cerebellar Cognitive Affective Syndrome (CCAS), demonstrating that cerebellar lesions can impair executive functions, language, visuospatial processing, and emotional regulation. Today, the cerebellum's contribution to a wide range of non-motor functions (including emotion, perceptual processing and higher cognitive abilities) is well documented and increasingly recognized.

Accumulating evidence also suggests that the cerebellum could play a role in pain processing. One of the earliest demonstrations came in 1994, when positron emission tomography revealed cerebellar activation in response to painful stimulations. A few years later, a functional magnetic resonance imaging (fMRI) study revealed that the cerebellum plays distinct functional roles in pain processing, with posterior cerebellar activation during pain anticipation, and anterior activation during pain experience[3]. These findings paved the way for research showing that cerebellar engagement occurs early in nociception, beginning at the stage of pain anticipation[4]. Together, these observations indicate that the cerebellum could be involved not only in the experience of pain but also in its anticipation, suggesting a key role in expectation-driven modulations such as placebo and nocebo effects.

Although evidence continues to emerge, the cerebellum's contribution to pain perception and modulation remains largely underexplored, and neuroimaging findings of cerebellar activation in pain studies are still often dismissed as artifacts. A recent meta-analysis[5] provided new insights into the role of the cerebellum in pain perception and modulation, showing that the dorsomedial cerebellum exhibits a distinct activation pattern in response to painful stimuli, marked by reduced activity under placebo conditions and associations with the magnitude of placebo analgesia. The authors also noted decreased activity within the ventrolateral thalamic nucleus – a key relay of cerebellar output – suggesting that fronto-cerebellar connectivity could be central to processes underlying placebo analgesia.

In the sensorimotor domain, the cerebellum is thought to operate through internal models that allow the brain to predict the sensory consequences of actions as they unfold[6]. These predictions shape and influence perception according to their certainty; the more confident the brain is in its predictions, the more perception is skewed toward these expectations. In this framework, the brain continuously updates internal models by

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treating prediction errors as learning signals, aiming to increase the certainty of future predictions. When applied to pain, this process may contribute to the development and maintenance of chronic pain, as the brain "learns" to anticipate pain even in the absence of actual nociceptive signals. This could be the case, for example, of individuals experiencing chronic pain linked to functional neurological disorders (FND). Another intriguing possibility is that the cerebellum could participate in placebo analgesia and nocebo hyperalgesia by predicting the consequences of painful stimuli, similar to what it does in the context of motor control. Two studies appear to support this hypothesis:

- One of these studies focused on the rostral anterior cingulate cortex (rACC), a structure involved in pain modulation, by mapping its cellular circuits in rodents[7]. Using a contextual conditioning paradigm linking environmental cues to pain relief, the authors showed that rACC neurons projecting directly to the pontine nucleus (Pn) – a major gateway to the cerebellum – increased their activity as mice learned to expect analgesia; a pattern that was also seen in a cluster of cerebellar Purkinje cells. Interestingly, optogenetic inhibition of the rACC neurons abolished pain relief, while its activation enhanced pain thresholds, suggesting that neurons projecting from the rACC to the Pn could causally mediate placebo analgesia. As additional support, a specific population of Oprd1+ pontine neurons, projecting to the cerebellum, proved necessary for placebo analgesia to occur. Within the internal model framework, these observations suggest that the cerebellum could integrate rACC inputs to "learn" predictions of forthcoming pain relief and apply these predictions to influence pain perception.
- A complementary fMRI study in humans examined how the brain adapts its activity when pain expectations are either confirmed or violated[8]. After visual cues were paired with low or high pain, participants were presented with mismatched cues, resulting in either placebo-like effects (a low-pain cue causing analgesia despite a high pain stimulus), nocebo-like effects (a high-pain cue causing hyperalgesia despite a low pain stimulus), or expectation violation (cue exerting no influence on pain ratings). Compared to correctly cued trials, cerebellar activity was greater during nocebo trials and reduced during placebo trials, mirroring both cue type and subjective pain ratings. Activity was also greater in expectation violation trials, reflecting a mismatch between expected and experienced pain. Together, these findings suggest that the cerebellum not only biases perception towards predictions but also encodes pain-related prediction errors, reinforcing its proposed role in maintaining internal pain models akin to those in the motor domain.

The two studies discussed above suggest that the cerebellum may harbor internal models that can be used to predict and modulate pain. However, additional research employing causal approaches are required to validate this hypothesis in human populations. Early causal findings derived from patients with cerebellar lesions already support this view[9]. In this latter study, researchers assessed pain thresholds and endogenous pain modulation in patients with prior (> 1 year) cerebellar infarction. Heat and pressure pain thresholds were measured, followed by a conditioning paradigm to test expectation-driven analgesia. While pain thresholds did not differ between groups, patients exhibited reduced placebo analgesia and greater heat pain intensity, indicating that the cerebellum, while not involved in baseline pain sensitivity, likely contributes to supra-threshold pain perception and placebo effects.

Collectively, these findings indicate that the cerebellum not only receives nociceptive inputs but also *encodes expectations related to pain* and dynamically responds when there is a mismatch between expected and experienced pain. This aligns with the predictive coding framework, in which pain perception reflects the brain's ongoing comparison between expected and actual nociceptive input[10]. Placebo and nocebo effects may represent clinical manifestations of this framework, reflecting the brain's continuous control over pain modulation pathways, themselves shaped by prior experience and expectations. Together, these findings provide strong support for the idea that cerebellar internal models extend beyond motor control and could play a key role in pain modulation[11].

At present, additional studies are essential to clarify how the cerebellum contributes to pain modulation, particularly through fronto-cerebellar loops involving the prefrontal cortex. Future research should investigate cerebellar activity patterns across different populations, including those suffering from persistent pain and FND. The particularly high prevalence of FND in chronic pain settings (17% versus 0.05% in the general population), and its association with predictive processing suggests that cerebellar mechanisms and alterations may constitute a central hallmark underlying both conditions. Future research should test these hypotheses, and investigate the impact of cerebellar modulation, for instance through neurostimulation, in paradigms that induce expectation violations. Applying inhibitory stimulation when predicted and actual pain diverge would test whether the cerebellum is necessary for detecting and correcting pain-related prediction errors – a process that may be disrupted in patients with FND and chronic pain. From a clinical perspective, these insights could open promising therapeutic avenues, where cerebellar modulation through stimulation techniques (such as transcranial direct current stimulation or repetitive transcranial magnetic stimulation), alongside pain reprocessing therapy, could help to recalibrate maladaptive predictive processes.

Overall, although research remains limited, the evidence reviewed in this editorial supports the hypothesis that the cerebellum may contribute to pain perception and modulation, likely through internal models that predict and regulate pain, similar to its role in motor control. Placebo analgesia and nocebo hyperalgesia may reflect the clinical manifestation of these cerebellar processes, with the cerebellum dynamically responding to mismatches between expected and actual pain. Further exploration of cerebellar internal models in pain could not only deepen our understanding of the neural mechanisms underlying placebo and nocebo effects, but also guide new therapeutic strategies, including targeted neuromodulation and pain reprocessing interventions.

REFERENCES

1. Rossettini G, Campaci F, Bialosky J, Huysmans E, Vase L, Carlino E. The biology of placebo and nocebo effects on experimental and chronic pain: state of the art. J Clin Med. 2023;12(12):4113. https://doi.org/10.3390/jcm12124113. PMid:37373806.
2. Ashraf O, Jabeen S, Khan A, Shaheen F. Primary cerebellar agenesis presenting as isolated cognitive impairment. J Pediatr Neurosci. 2016;11(2):150-2. https://doi.org/10.4103/1817-1745.187646. PMid:27606028.
3. Ploghaus A, Tracey I, Gati JS, Clare S, Menon RS, Matthews PM, Rawlins JN. Dissociating pain from its anticipation in the human brain. Science. 1999;284(5422):1979-81. https://doi.org/10.1126/science.284.5422.1979. PMid:10373114.
4. Moulton EA, Schmahmann JD, Becerra L, Borsook D. The cerebellum and pain: passive integrator or active participator? Brain Res Brain Res Rev. 2010;65(1):14-27. https://doi.org/10.1016/j.brainresrev.2010.05.005. PMid:20553761.
5. Zunhammer M, Spisák T, Wager TD, Bingel U, Placebo Imaging Consortium. Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data. Nat Commun. 2021;12(1):1391. https://doi.org/10.1038/s41467-021-21179-3. PMid:33654105.
6. Popa LS, Ebner TJ. Cerebellum, Predictions and Errors. Front Cell Neurosci. 2019;12:524. https://doi.org/10.3389/fncel.2018.00524. PMid:30697149.
7. Chen C, Niehaus JK, Dinc F, Huang KL, Barnette AL, Tassou A, Shuster SA, Wang L, Lemire A, Menon V, Ritola K, Hantman AW, Zeng H, Schnitzer MJ, Scherrer G. Neural circuit basis of placebo pain relief. Nature. 2024;632(8027):1092-100. https://doi.org/10.1038/s41586-024-07816-z. PMid:39048016.
8. Zeidan F, Lobanov OV, Kraft RA, Coghill RC. Brain mechanisms supporting violated expectations of pain. Pain. 2015;156(9):1772-85. https://doi.org/10.1097/j.pain.0000000000000231. PMid:26083664.
9. Ruscheweyh R, Kühnel M, Filippopulos F, Blum B, Eggert T, Straube A. Altered experimental pain perception after cerebellar infarction. Pain. 2014;155(7):1303-12. https://doi.org/10.1016/j.pain.2014.04.006. PMid:24721690.
10 Chen ZS. Hierarchical predictive coding in distributed pain circuits. Front Neural Circuits. 2023;17:1073537. https://doi.org/10.3389/fncir.2023.1073537. PMid:36937818.
11. Gatti D, Rinaldi L, Ferreri L, Vecchi T. The human cerebellum as a hub of the predictive brain. Brain Sci. 2021;11(11):1492. https://doi.org/10.3390/brainsci11111492. PMid:34827491.