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Womb, gravity, and space: shifting towards the cerebellum-basal ganglia paradigm in dystonia

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Introduction

Do we all experience a phase of dystonia in our lives? Surprisingly, yes. Based on the current classification, dystonia is defined as "*a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both*" [1, 2]. Based on this definition, it appears that we all pass through a physiological dystonia phase, at least early in life [3]. Indeed, movements typically considered dystonic (abnormal) in pediatric and adult stages [1, 4] are not phenotypically dissimilar from those observed in healthy neonates and infants [5, 6]. For example, newborns and infants display involuntary paroxysmal behaviors - movements that are non-epileptic and arise from normal developmental trajectories and exploratory motor skills (e.g., arm rotations, oral-buccal-lingual movements, biking, and pacing) [7–10]. Standard electroencephalographic (EEG) or video-EEG recordings performed during these neonatal movements generally do not indicate seizure activity or other encephalopathic conditions [11–13].

Interestingly, even before birth, fetuses display dystonia-like stereotyped movements [14]. These movements occur in a unique environment, with the fetus fully immersed in a microgravity-like amniotic fluid environment [15]. Throughout gestation, fetal movements interact with increasing gravitational forces, a result of fetal growth and the gradual reduction of amniotic fluid volume [16–18]. Remarkably, these motor, neuromuscular, and brain developmental processes are finely regulated by specific genetic, molecular, and physiological mechanisms, many of which have only recently begun to be understood in terms of timing and their developmental (ontogenic) and evolutionary (phylogenic) roles [19–22].

At another end of life experiences, humans (and some animals) may spend time in space, either for occupational or recreational purposes [23]. In these conditions - ranging from hours to months - subjects encounter changes and adaptations in motor and non-motor functions due to weightlessness, or microgravity, which is a state of near or complete absence of the sensation of weight. Life on Earth, and animal life in general, has evolved to adapt motor and non-motor behaviors in response to gravity [24, 25]. Through

various sensory and motor adaptations, humans and land animals maintain postural equilibrium, coordinating agonist-antagonist muscle processing to survive [26]. This coordination involves complex integration of visual, vestibular, and somatosensory inputs to counteract gravity's effects [27].

Cerebellum and gravity adaptation

Neuroanatomically, the cerebellum (CRB) is a central hub for gravity response and adaptation, primarily due to its direct connections with both ocular- and gravity-sensing vestibular receptors [28]. The CRB is integral to spatial orientation and gait regulation via the spino-cerebellum and ponto-cerebellum systems, which are essential for motor control, coordination, and learning, making it the main center for anti-gravity processes [29–32]. Both on Earth and in space, dystonic movements disrupt gravity perception, affecting posture, gait, and fine motor coordination [33]. In space, where gravitational forces are reduced, the vestibulocerebellar system rapidly adapts, recalibrating its responses to accommodate the altered gravitational environment [34]. This adaptation occurs almost instantly, similar to the adjustment newborns make at birth when transitioning from microgravity in the womb to Earth's full gravity [19, 35].

Understanding cerebellar responses to altered gravity in both space and prenatal environments could deepen insights into gravity-related consequences for astronauts, fetuses, infants, and patients with dystonia [36]. Gravity shifts, such as weightlessness, trigger neuromuscular, sensory, and vestibular changes that may contribute to distinct syndromic features, particularly in astronauts [37, 38]. Among these phenomena, dystonia-like movements stand out [39–41]. Notably, though similar dystonia-like movements appear in healthy individuals on Earth (pre- and post-birth), in microgravity, and in patients with dystonia, the underlying causes may differ. However, phenotypic, pathogenetic and adaptive similarities and differences across different dystonia-appearing phenomena could still provide meaningful and possibly unexpected tools for the treatment of dystonia in general or specific forms of it [42]. For example, it is expected that hypergravity environments exacerbate symptoms or lead to different manifestations of muscle control challenges. Increased gravitational forces may amplify muscle rigidity or spasms in those with dystonia. On the other hand, for individuals with dystonia, exposure to microgravity (like fetuses) could have therapeutic effects. More specifically, microgravity environments tend to decrease overall muscle tone and reduce physical resistance and consequently, people with dystonia could ease some symptoms related to muscle contractions and spasms. Moreover, microgravity may offer temporary relief from the continuous muscle firing and rigidity that characterizes dystonia. In addition, microgravity could set changes in neurocircuits feedback loops, and specifically in the BG-CRB inputs since it alters proprioception and how the brain interprets muscle feedback and so potentially modifying movement patterns. We hypothesize that the same adaptive phenomena are actually present in the opposite direction at the passage from in-utero (microgravity) to extra-utero (at birth). A better understanding of the genetic or metabolic causes and processes of these BG-CRB mechanisms at birth could actually provide new rehabilitative approaches for dystonia patients in general or for those type of dystonia (isolated dystonia) that appear physiopathological closer to the neonatal events. Importantly, this hypothesis, while still speculative, seems to be supported by studies using animals in a microgravitational environment during and after pregnancy [43, 44]. Furthermore, microgravity leads to muscle atrophy over time, and without gravity as resistance, muscles lose strength. For someone with dystonia, muscle weakening might temporarily lessen spastic contractions but could also lead to long-term challenges in muscle control. In general, microgravity effects exploration has expanded our understanding of neurological conditions by showing how the absence of gravity affects motor control and muscle function [45, 46]. This knowledge might inform treatments that mimic the effects of microgravity to help manage dystonia symptoms on Earth, such as specialized anti-gravity rehabilitation apparatuses.

In general, we propose that motor phenomena in space and the womb may be more accurately linked to cerebellar mechanisms rather than primarily to basal ganglia (BG) dysfunction, as seen in many dystonia cases [47, 48]. In particular, cerebellar injury *in utero* have been recently the focus of various studies that have applied non-invasive imaging techniques (i.e., MRI, ultrasound) to analyze in more detail, especially in neuroanatomical terms, cerebellar lesions *in utero* and their clinical consequences during gestation and after birth [49]. Cerebellar injury *in utero* are associated to both motor and non-motor consequences and among the motor abnormalities alterations of fine motor skills have been described and some of them have dystonia-like features. Moreover, the biological and neurophysiological aspects of the synchronization between vestibular system development and microgravity-to-gravity passage started to offer more specific notions about the possibility of cerebellar injury and their consequence on the motor and vestibular system [50]. Furthermore, study of hypergravity (in animals) have shown that hypergravity exposure during different period of gestation deeply alter cerebellar development and Purkinje cells in particular [51, 52]. Purkinje cells have been shown to be affected by subtle changes in dystonia human cases [48, 53] and specific genes have been involved in paroxysmal dystonia episodes in mice [54]. Moreover, a study by Dooley JC [55] described, in an animal model, how the brain develops internal models for tracking limb movements in real-time, even without visual cues, to avoid delays from sensory feedback. These

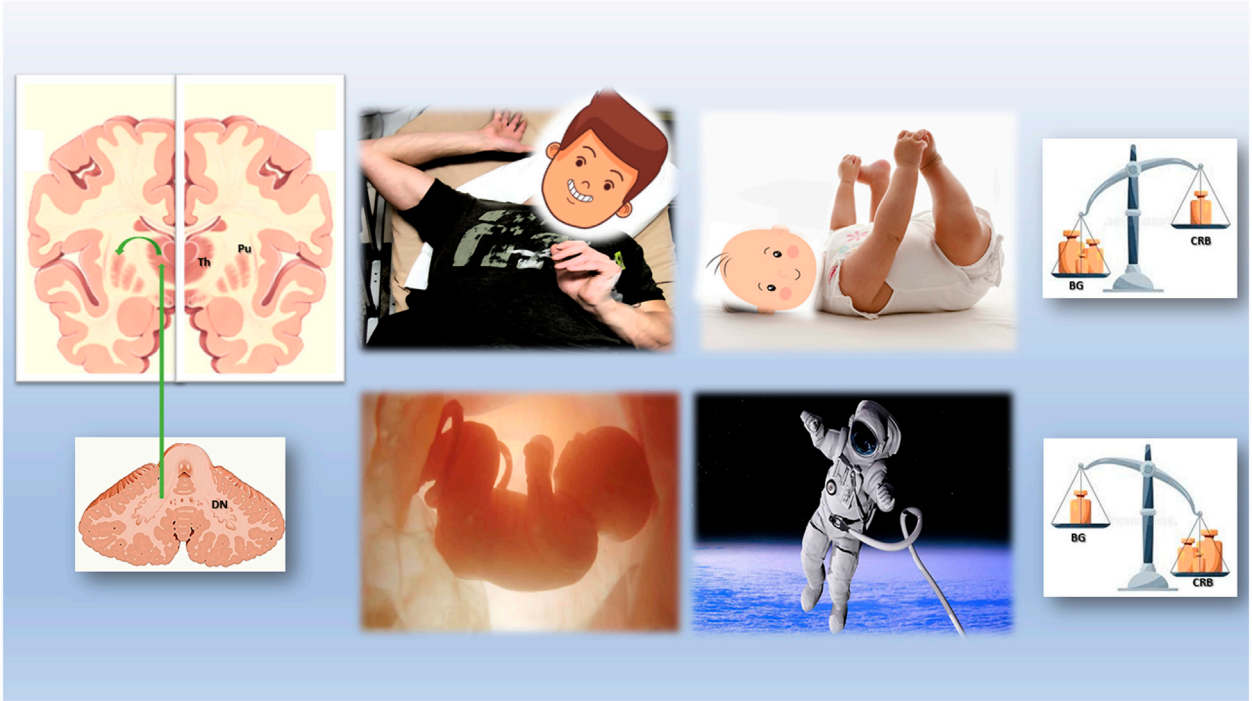

FIGURE 1
Physiological and Pathologic Cerebellum-Basal Ganglia Interactions from the womb to the space.

investigators found that, in rats, these cerebellum-dependent internal models begin forming by postnatal day 20 (P20), allowing the brain to predict and mirror movements rather than reacting to them after the fact. In particular, observing neural activity during spontaneous limb twitches in sleep, the study showed that only by P20 did a specific part of the thalamus (the ventral lateral nucleus, receiving cerebellar input) synchronize precisely with limb movement. These findings suggest that sleep twitches help develop and refine these internal movement models. These findings, if confirmed in newborns or in-utero babies, would support our hypothesis for which cerebellar-dependent internal movement modules could be associated to normal dystonic-like movement during normal development or if affected by different types of injury could be actually related to prolonged dystonic-like movements early in life and later.

The overlapping yet distinct causes of these motor phenomena, despite genetic or environmental differences, could illuminate previously unexplored brain mechanisms involved in dystonia and dystonia-like movements across various life stages. A valuable approach would be to examine these movements for neuroanatomical, neurophysiological, and neurotransmitter-based similarities and differences, from fetal life to life in space (see Figure 1). To test this hypothesis one of the possible analysis would be to systematically record (video-ultrasound) and score in-utero vs. extra-utero "*dystonia-like*" movements as related to specific cerebellar injury (vascular, developmental, metabolic). In addition, this set of data should be related to the specific timing and development of the vestibular system. These types of correlations if confirmed to be associated to an increase incidence of dystonia-like phenomena during the first month of life and later, could be an excellent clinicometrics tool to assess and mitigate the long-term effect of the cerebellar-vestibular dysfunction manifesting as a dystonic disorder. Moreover, a similar approach could be used to study the long-term effects of microgravity in astronauts exposed for a long period of time to a weightlessness environment and mitigate the serious effects described after a "quick" hypergravity change when back on Earth [56–58].

Clinically, the CRB's role in dystonia has often been overlooked in favor of BG involvement. However, recent debates have increasingly recognized the CRB's influence, challenging the idea that dystonia is solely a BG-driven condition [59–61]. Evidence now suggests that both BG and CRB, along with their associated neurocircuits and neurotransmitters, are central to dystonia's pathogenesis [53]. Rather than one region exclusively dominating, the involvement of BG vs. CRB appears to vary dynamically. Depending on the dystonic disorder's type, timing, and the specific genetic, developmental, and environmental conditions present, either BG or CRB dysfunction may predominate, a phenomenon that could be termed "*dynamic BG-CRB shifting*."

Direct synaptic connections between cerebellum and basal ganglia: a game-changer

One of the most transformative breakthroughs in the cerebellum (CRB) and basal ganglia (BG) debate has been the recent discovery of direct disynaptic connections between the CRB and BG in non-human primates - a finding that is likely applicable to humans as well [62]. For decades, it was widely believed that the CRB and BG operated in isolation, with no direct connectivity. This assumption led researchers to attribute many "cerebellar" phenomena, such as the resting tremor seen in Parkinson's disease (PD), exclusively to BG dysfunction. The recent neuroanatomical discovery of these connections has prompted a reevaluation of the pathophysiological mechanisms underlying various movement disorders, including PD and dystonia.

The disynaptic connection between the CRB and BG - mediated through the thalamus - holds significant physiological and pathophysiological implications. Through this pathway, the CRB sends signals to the BG, which influence both motor planning and execution. This connection may help to synchronize the CRB's role in movement coordination with the BG's role in movement initiation and control. Furthermore, the CRB influences the subthalamic nucleus, a central structure within the BG. This connection enables the CRB to indirectly modulate BG circuits involved in movement control, including those that are altered in dystonia.

Adding to this complexity, the CRB appears to have a notable role in dopaminergic modulation, which is increasingly recognized as a key factor in movement disorders. Research suggests that the dopaminergic system within the cerebellum may also regulate vestibular circuits, adding another layer of influence on balance and motor stability [63]. Although further research is needed to determine how these dopaminergic pathways specifically relate to dystonic symptoms, this new understanding of the CRB's neuroanatomy and neurochemical connections is already reshaping our understanding of motor abnormalities. These findings underscore the need for a paradigm shift in the study and treatment of primary dystonia. No longer can we view dystonia solely through a BG-centered lens; rather, we must adopt a dynamic BG-CRB model that recognizes the interplay between these two regions [64]. This broader perspective opens new avenues for understanding and addressing dystonia's complex symptomatology.

Does white matter matter?

Recent advancements in neuroimaging have spurred interest in white matter (WM) alterations as a critical factor in dystonia research. Subtle but pathophysiologically significant WM changes have been documented across various forms of dystonia, underscoring the potential role of WM integrity in motor dysfunction [65–69]. Intriguingly, MRI scans of astronauts returning from extended space missions also reveal unique WM changes, likely due to the effects of prolonged weightlessness on motor control [39, 58, 70]. These findings highlight the adaptability of the cerebellum-basal ganglia (CRB-BG) circuit and suggest that neuroplasticity - especially involving WM changes - may play a significant role in dystonia's development and manifestations. Indeed, WM changes have been observed in dystonia patients and even in response to targeted peripheral treatments, such as botulinum toxin injections for cervical dystonia [71].

Emerging research increasingly implicates cerebellar WM in dystonia, suggesting a larger-than-expected role for the cerebellum in this disorder. WM in the cerebellum comprises myelinated axons that connect it to the basal ganglia, motor cortex, and brainstem, facilitating complex motor coordination and communication. Alterations within these WM pathways - whether structural or metabolic - could be critical to the abnormal muscle contractions and motor control issues typical of dystonia. Diffusion tensor imaging (DTI), which assesses WM microstructure, has identified altered WM integrity in dystonia patients, particularly affecting pathways like the cerebello-thalamo-cortical circuit, which links the cerebellum to the thalamus and cortex. Disruptions in this pathway impair the cerebellum's ability to relay precise timing and coordination signals, contributing to the disordered motor output characteristic of dystonia.

Further, WM disruptions within the CRB-BG circuit affect connectivity between the cerebellum and basal ganglia, skewing the balance between motor initiation (a BG function) and motor coordination (a CRB function). This imbalance may contribute to dystonia's hallmark symptoms: disorganized movement timing, abnormal muscle contractions, and postural irregularities. Additionally, the cerebellum's involvement extends beyond mere coordination to encompass sensorimotor integration, which is essential for refining movement through sensory feedback. WM alterations interfere with this sensory processing, leading to proprioceptive challenges and decreased movement accuracy - effects that closely resemble those reported by astronauts and likely mirror the sensory experiences of neonates during the first days of life outside the womb. In fact, imaging studies in neonates, including preterm infants, reveal that WM integrity is closely linked to motor development and could predict dystonia-like motor abnormalities [72, 73].

These findings underscore the importance of WM integrity within the BG-CRB framework, validating WM as a key factor in both typical and pathological motor processes. By focusing on WM changes within this framework, we may open new avenues for personalized treatments in dystonia and improve our understanding of motor adaptation under unique physiological conditions.

Discussion and future perspectives

This opinion article explores dystonia and dystonia-like disorders through the lens of recent pathophysiological findings in both dystonia patients and individuals in unique environments - such as the womb and space. We advocate for a new Cerebellum-Basal Ganglia (CRB-BG) paradigm to advance our understanding of dystonic phenomena. This approach is poised to benefit from emerging technologies and methodologies, including advanced neuroimaging, omics, telemedicine, neuroanatomy, and neuropathology, in both human and animal models.

We propose examining this CRB-BG paradigm across three distinct environments: the womb, Earth, and space. This "environmental triad" offers a comprehensive framework for studying dystonic phenomena within physiological states (e.g., the floating fetus), pathological states (e.g., generalized dystonia), and paraphysiological states (e.g., human beings in microgravity). By exploring these varied environments, we aim to improve personalized treatment strategies for dystonia patients and address the motor control challenges that long-term space travel may pose.

Author contributions

DI contributed to the ideation, writing and content of this manuscript.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

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