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Symposium

Cognitive-Affective Functions of the Cerebellum

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The cerebellum, traditionally associated with motor coordination and balance, also plays a crucial role in various aspects of higher-order function and dysfunction. Emerging research has shed light on the cerebellum's broader contributions to cognitive, emotional, and reward processes. The cerebellum's influence on autonomic function further highlights its significance in regulating motivational and emotional states. Perturbations in cerebellar development and function have been implicated in various neurodevelopmental disorders, including autism spectrum disorder and attention deficit hyperactivity disorder. An increasing appreciation for neuropsychiatric symptoms that arise from cerebellar dysfunction underscores the importance of elucidating the circuit mechanisms that underlie complex interactions between the cerebellum and other brain regions for a comprehensive understanding of complex behavior. By briefly discussing new advances in mapping cerebellar function in affective, cognitive, autonomic, and social processing and reviewing the role of the cerebellum in neuropathology beyond the motor domain, this Mini-Symposium review aims to provide a broad perspective of cerebellar intersections with the limbic brain in health and disease.

Introduction

Jean Marie Pierre Flourens' pioneering work in pigeons demonstrated that cerebellar damage impaired flight and led to the loss of coordination in voluntary wing movements (Flourens, 1842). This early observation, along with multiple subsequent experimental findings, prompted physiologists like Sherrington and many others to conclude that the function of the cerebellum is the control of voluntary movement, gait, balance, and motor coordination (Flint, 1875; Luciani 1891; Brown, 1892; Ferrier and Turner, 1894; Russell, 1894; Sherrington, 1906; Holmes, 1908). This historical perspective overlooked earlier work that, decades before Flourens' experiments, began exploring the structures of the cerebellum, including the vermis, tonsil, nodulus, and lingula, and correlating them with intellectual faculties (Malacarne, 1776). Malacarne's interest was driven by a

desire to understand the relationship between cerebellar size and intellectual capacity (Zanatta et al., 2018). Combettes (1831) reported cases of intellectual and emotional disability in patients with cerebellar agenesis. Despite occasional case reports over the next century, the connection between the cerebellum and intellectual and emotional processing remained obscure, often based on associations rather than experimental evidence. Additionally, Franz Joseph Gall's curious ideas about the cerebellum's involvement in sexual aptitude unintentionally led to the rejection of the view that the cerebellum had functions beyond motor coordination (Gall et al., 1838).

The emerging influence of cognitive neuroscience, clinical neuropsychology, and psychiatry in the mid-20th century led to a more comprehensive understanding of cerebellar function. Electrophysiological studies revealed nonuniformities of cerebellar somatotopy in the cerebellar vermis and posterior lobes, suggesting nonuniformity of function (Snider and Stowell, 1944; Snider and Eldred, 1948). Moreover, functional interactions were observed between cerebellar hemispheres and high-order association areas (Allen and Tsukahara, 1974), as well as between the cerebellar vermis and limbic structures (MacLean, 1949; Snider and Maiti, 1976), suggesting broader connections to both neurology and psychiatry. In the 1960s and 1970s, animal studies involving fastigial nucleus stimulation and ablation yielded valuable insights into the cerebellum's role in nonmotor control. Electrical stimulation of the cerebellum was found to produce distinct behavioral responses, including feeding, attack and grooming, hypertension, and increases in heart rate (Zanchetti

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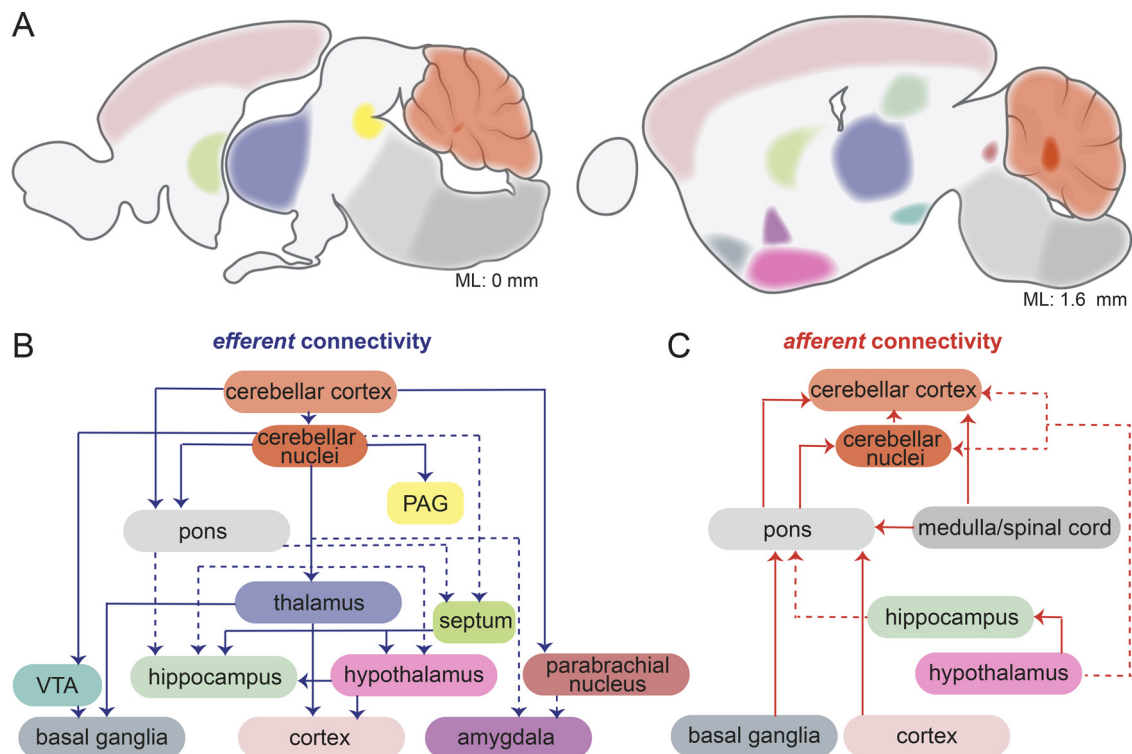


Figure 1. Efferent and afferent cerebellar pathways implicated in cognition and emotion. *A*, Sagittal sections of mouse brain (left, mid-sagittal, ML: 0 mm; right, parasagittal, ML: 1.6 mm), indicating anatomic location of color-matched brain areas in the connectivity maps in *B*, *C*. *B*, *C*, Efferent (*B*) and afferent (*C*) pathways for cerebello-limbic function. Solid lines indicate direct connections. Dotted lines indicate indirect or not yet fully established connections. ML: mediolateral.

and Zoccolini, 1953; Reis et al., 1973), whereas cerebellar ablations induced docile behavior or persistent pleasure reactions, suggesting possible affective and autonomic roles (Moruzzi, 1947; Berman et al., 1974). Stimulation of posterior cerebellar structures elicited electrical potentials in limbic regions, whereas stimulation of anterior cerebellum predominantly activated orbital cortex, hippocampus, and posterior hypothalamus (Martner, 1975). Patient studies provided further clinical correlations, with cerebellar vermis stimulation impacting emotion and social interaction (Cooper et al., 1974; Heath, 1977). Despite these findings, the model of nonmotor cerebellum was met with resistance from prominent influential scientists, who favored the idea of the cerebellum as a purely motor control center (Marr, 1969; Albus, 1971; Ito, 1982). The multisynaptic nature of connections between the cerebellum and many limbic areas (Kang et al., 2021; Novello et al., 2022) (Fig. 1) also hindered investigation of cerebello-limbic interactions until recently.

A shift in perspective began with the rediscovery of primary literature pointing to potential nonmotor functions for the cerebellum (Schmahmann, 1991) (i.e., functions that cannot be explained by strictly sensorimotor variables) and the development of novel tools for investigation of monosynaptic and disynaptic circuits. Novel theories (Leiner et al., 1986; Schmahmann, 1991) and hypothesis-driven anatomical investigations (Middleton and Strick, 1994; Schmahmann, 2016) further challenged the conventional view, leading to a reevaluation of cerebellar functions. This growing body of evidence prompted deeper investigations into the cerebellum's role in nonmotor functions (Schmahmann, 2010; Buckner, 2013). The paradigm shift culminated in the recognition that the cerebellar syndrome, which was traditionally defined as motor dysfunction (i.e., ataxia), including impaired balance and gait, incoordination of voluntary movements, and dysarthria, should be recontextualized as a three-part syndrome: the

cerebellar motor syndrome; the cerebellar vestibular syndrome; and the cerebellar cognitive affective syndrome. Together, they form the triad of cerebellar clinical ataxiology (Manto and Mariën, 2015).

In summary, the current historical narrative of the cerebellum has undergone a substantial shift to include both motor and nonmotor cerebellar functions. Here, we highlight various aspects of cerebellar nonmotor functions. We focus on the integrated network involving the cerebellum in cognitive, affective, and social functions, challenging the notion of separate modules for these processes. We discuss the cerebellum's role in fear conditioning and emotional learning through its connections with brain regions, such as the amygdala and prefrontal cortex (PFC) and discuss the cerebellum as a key structure for social cognition. We will also explore novel research on perineuronal nets (PNNs) in the cerebellum, their relationship to critical periods of development, and the role of the cerebellum in neurodevelopmental disorders such as autism spectrum disorder (ASD). Last, we touch on clinical strategies for diagnosing Cerebellar Cognitive Affective/Schmahmann Syndrome (CCAS) associated with cerebellar dysfunction.

Affective and cognitive functions of the cerebellum

Cognition encompasses various mental processes, such as attention, perception, memory, problem-solving, and decision-making (Forgas, 2008; Pessoa, 2008; Tyng et al., 2017). In patients with cerebellar disease, a large number of studies has shown impairments in various cognitive domains and subdomains, such as verbal fluency, working memory, abstract reasoning, visuospatial cognitive processes, social cognition, and problem-solving (Ahmadian et al., 2019; Argyropoulos et al., 2020; Van Overwalle et al., 2020; Jacobi et al., 2021). Key brain regions involved in these functions include the prefrontal and

parietal cortices. On the other hand, affect refers to the intricate interplay of psychological and physiological states triggered by internal or external stimuli, ranging from intense and transient emotions to subtle and enduring moods (Forgas, 2008; Pessoa, 2008; Tyng et al., 2017). Although these states exhibit variability, the terms “affect,” “emotion,” and “moods” are often used interchangeably for simplicity. The limbic system, which encompasses subcortical structures (e.g., the hypothalamus, amygdala, and basal ganglia) and cortical regions [e.g., the medial prefrontal cortex (mPFC), anterior cingulate cortex (ACC), and orbitofrontal cortex], plays a central role in affective regulation. In the past, cognitive and affective brain regions were perceived as separate modules. However, a modern perspective recognizes that cognition and affect are mediated by an integrated brain network that facilitates their dynamic interactions (Pessoa, 2008; Tyng et al., 2017). The cerebellum, traditionally associated with motor coordination, is now recognized as a hub in this integrated network that links diverse sensory, motor, cognitive, affective, and social functions (Cacciola et al., 2017; Bostan and Strick, 2018; Stoodley and Tsai, 2021). Patients with cerebellar disease exhibit flattening or blunting of affect, irritability, agitation, and emotional lability (Schmahmann, 2004). Both human and animal studies have demonstrated the cerebellum’s involvement in modulating emotional signals and behavior through extensive cerebello-cortical and -subcortical circuits (Stoodley and Schmahmann, 2009; Strick et al., 2009; Buckner et al., 2011; Adamaszek et al., 2017; Ciapponi et al., 2023) (Fig. 1). For example, the cerebellum has been implicated in what is perhaps the best studied type of emotional learning, fear conditioning. The cerebellar vermis and cerebellar nuclei (CN) contribute to the formation, consolidation, and extinction of fear memories, likely by conveying prediction and/or prediction error signals through connections with cortical and subcortical structures, including the mPFC, amygdala, parabrachial nucleus, and periaqueductal gray (PAG) (Snider and Maiti, 1976; Sacchetti et al., 2002; Bostan et al., 2013; Strata, 2015; Utz et al., 2015; Otsuka et al., 2016; Ernst et al., 2019; Frontera et al., 2020; Jung et al., 2022; Doubliez et al., 2023; Frontera et al., 2023; Hwang et al., 2023; Urrutia Desmaison et al., 2023). Although the cerebellar projections to the amygdala may be indirect (Fujita et al., 2020; Jung et al., 2022), bidirectional functional interactions between these regions have been observed. For instance, stimulating the vermis elicits responses in the basolateral amygdala (BLA), whereas inhibiting the BLA prevents learning-induced plasticity in the vermis (Snider and Maiti, 1976; Zhu et al., 2011). Similarly, stimulating the CN modulates activity in central amygdala (Magal and Mintz, 2014), whereas inhibiting central amygdala impairs acquisition and retention of cerebellar learning (Farley et al., 2018). The cerebellum has also been implicated in the regulation of innate fear via connections to the PAG (Supple et al., 1987; Koutsikou et al., 2014; Vaaga et al., 2020; Lorivel et al., 2021). Unsurprisingly then, the cerebellum is now considered a part of the limbic system, involved in processing primitive emotions and nondeclarative memory (Apps and Strata, 2015; Schmahmann et al., 2022). Ongoing research aims to elucidate the activation dynamics, cell type properties, and computations through which specific long-range cerebellar circuits convey fear- and safety-relevant information to the limbic system and modulate affective behavior.

An important unanswered question in the field of cerebellar nonmotor function is whether and how the cerebellum participates in emotion-based declarative memory, such as social recognition memory (SRM), which involves distinguishing familiar from novel individuals based on previous encounters. Unlike object recognition memory, SRM relies on processes that detect, store, and respond

to emotionally arousing sensory information, necessitating intact functioning of the mPFC, ACC, nucleus accumbens, hippocampus, and amygdala within the limbic system (Hitti and Siegelbaum, 2014; Garrido Zinn et al., 2016; Tanimizu et al., 2017; Okuyama, 2018; Phillips et al., 2019; Park et al., 2021). SRM is a crucial determinant of social behavior, in which the cerebellum plays an important role (Stoodley and Tsai, 2021). In addition to SRM, the cerebellum also influences social cognition, which encompasses the ability to imitate others’ actions (mirroring) and understand the mental states of oneself and others (mentalizing) (Adolphs, 2001; Insel and Fernald, 2004; Frith and Frith, 2012). Neuroimaging studies in humans have demonstrated that the cerebellum is a key component of the brain network involved in social cognition (Van Overwalle et al., 2020). While there is limited clinical investigation into cerebellar involvement in SRM, a recent study suggests that the cerebellar vermis is activated along with other brain regions during emotion-enhanced episodic memory (Fastenrath et al., 2022).

To examine the causal contribution of cerebellar activity to emotion-based declarative memory, researchers selectively increased the excitability of molecular layer interneurons (MLIs) using chemogenetic and optogenetic approaches to suppress Purkinje cell firing in the mouse cerebellar vermis (Chao et al., 2023). This manipulation was motivated by the dysregulated MLI inhibition on Purkinje cells, a shared phenotype observed in both ASD patients and mouse models exhibiting deficits in social behavior (Cupolillo et al., 2016; Chao et al., 2020; Yang et al., 2020). The study found that chemogenetic perturbation of MLIs impaired SRM without affecting sociability, anxiety levels, motor coordination, or object recognition memory. Optogenetic interference with MLIs at different phases of the social recognition test indicated that the cerebellum’s engagement was primarily in the retrieval, rather than encoding, of social information. Mapping c-Fos expression after the social recognition task revealed that cerebellar manipulation decreased interregional correlations across the brain and altered the network structure from mPFC and hippocampus-centered modules to amygdala-centered modules. Anatomical tracing further revealed axonal projections from the vermis to the social brain network, including connections with the amygdala, providing a structural basis for integrating sensory and emotional information into mnemonic processes. In summary, these results suggest a specific role of the cerebellum in organizing the neural matrix necessary for SRM, offering potential insights for developing novel therapeutics targeting neuropsychiatric disorders associated with social impairments (Pelphrey et al., 2004; Couture et al., 2006; Elamin et al., 2012).

Cerebellar contributions to reward-driven learning

Growing evidence implicates the cerebellum in processing reward expectation signals. Cerebellar granule cells exhibit activity that predicts upcoming reward (Wagner et al., 2017), and climbing fibers can activate both in response to reward (Heffley et al., 2018; Heffley and Hull, 2019; Kostadinov et al., 2019) and reward-predicting stimuli (Larry et al., 2019). This highlights a potential route for cerebellar contributions to cognitive behaviors. In a variety of motor and associative learning contexts, the cerebellum seems to generate predictions of the future values or trajectories of sensorimotor variables (Ivry and Keele, 1989; Doya, 2000; Sokolov et al., 2017; Raymond and Medina, 2018; Hull, 2020), and it is widely believed that similar predictive computations might extrapolate to cognitive variables as well. Timing estimation appears to be an especially important class of prediction in the cerebellum. However, in classical motor adaptation behaviors, cerebellar

time estimation was thought to be restricted to relatively brief intervals between events and the outcomes that they predict, for example, several hundred milliseconds (Medina and Mauk, 2000). By contrast, during volitional reward-driven behaviors, key cerebellar cell types, including granule cells, Purkinje cells, and CN output neurons, exhibit ramping spike rates over delays of multiple seconds that are poorly explained by body movements (Gao et al., 2018; Chabrol et al., 2019; Wagner et al., 2019; Lin et al., 2020), the function of which therefore remains unclear.

The cerebellum's reputation in short-interval sensorimotor timing stems in part from basic properties of a primary form of cerebellar plasticity: climbing fiber-dependent long-term depression (LTD) at synapses from cerebellar granule cells onto Purkinje cells. When a Purkinje cell receives a climbing fiber spike burst, any granule cell inputs onto the Purkinje cell that were active just prior (within ~150 ms) to the climbing fiber can be weakened via LTD (Marr, 1969; Albus, 1971; Ito et al., 1982; Jörntell and Ekerot, 2002; Coesmans et al., 2004; Medina and Lisberger, 2008; Suvrathan et al., 2016; Rowan et al., 2018). This brief interval for climbing fiber-driven LTD to “sense” previously active granule cells has been thought to play a defining role in the timescale of cerebellar learning and computation (Lisberger, 1998; Koekkoek et al., 2003; Yamazaki and Tanaka, 2009). Relatedly, it was postulated that the brief interval for LTD would be well served by sparse and brief granule cell signaling profiles (Medina and Mauk, 2000), which would allow learning to modify the synaptic strength of small and specific sets of neurons. Furthermore, by stipulating that climbing fibers signaled “errors,” such granule cell synaptic modifications would be transient and targeted only until correction and elimination of the causative error was achieved (Sejnowski, 1977).

In light of these basic properties of the cerebellar circuit and its principal plasticity mechanisms, recent granule cell and climbing fiber findings pose several mysteries. Empirical observation of the activation of many granule cells at once (Giovannucci et al., 2017; Knogler et al., 2017; Wagner et al., 2017) is at least superficially incompatible with using spike coincidence-based synaptic modification via climbing fiber-directed LTD as a means to modify small and specific sets of granule cell synapses. Similarly, granule cell signals that are sustained for extended periods (Wagner et al., 2019; Lin et al., 2020) appear to challenge the temporal specificity of climbing fiber-directed LTD based on spiking coincidences. Finally, climbing fiber signals that fail to decay with learning (Heffley and Hull, 2019; Wagner et al., 2021) appear incompatible with a framework in which they transiently modify relevant synapses to correct an error. Together, it remains unclear how non-canonical granule cell and climbing fiber signals observed during volitional and especially reward-driven behaviors jointly contribute to a meaningful learning computation.

Cerebellar control of arousal and autonomic function

In the previous sections, we have highlighted the diverse roles the cerebellum can assume in regulating cognitive-affective and social behaviors. It is important to note that emotional experiences, thoughts, and the generation of internal models not only engage the cerebellum but undoubtedly influence autonomic responses and arousal; and vice versa, autonomic changes and arousal state can impact cognitive processes and emotional experiences (Packard and Goodman, 2012; Calderon et al., 2016). This reciprocal regulation extends to the initiation, maintenance, and refinement of motor programs as well. The coordination of complex behaviors therefore requires activation of many parallel neural circuits in a context-dependent manner. Dysregulation of

autonomic functions co-occurs with motor and cognitive-affective symptoms and has been linked to many disorders, including depression (Olbrich et al., 2016; Schmidt et al., 2017), attention deficit hyperactivity disorder (Strauß et al., 2018), ASD (Bast et al., 2018; Zhao et al., 2022), and sleep disorders, all conditions that emerge with cerebellar dysfunction (Becker and Stoodley, 2013; Canto et al., 2017; Bruchhage et al., 2018; Depping et al., 2018). But does the cerebellum simultaneously intersect with motor, cognitive-affective, and autonomic circuits? Although there is intriguing evidence for this hypothesis, the precise mechanisms that underlie cerebellar control of autonomic function and its role in behavior remain enigmatic.

A series of classic studies provide compelling evidence for a cerebellar involvement in arousal and autonomic function (Watson, 1978; Haines et al., 1984). Early experiments performed in decerebrate cats demonstrated that stimulation of the fastigial CN resulted in sham rage behavior and dramatic increases in arterial blood pressure, hyperpnea, and mydriasis (Zanchetti and Zoccolini, 1953). These results were reproduced in intact cats that displayed behavioral escalation from grooming to feeding and attack that correlated with increasing heart rate and blood pressure on fastigial nucleus stimulation (Reis et al., 1973) and a drop in blood pressure and heart rate after fastigial inactivation (Chen et al., 1994). Others found that fastigial lesioning led to a drowsy state in cats (Giannazzo et al., 1969). Similarly, vermal lesions in monkeys caused changes in aggressive behavior (Berman et al., 1974). Later studies implemented a more selective optogenetic manipulation of Purkinje cells and recapitulated the effects of cerebellar stimulation on aggression in mice (Jackman et al., 2020). Likewise, diminishing tonic GABA signaling and producing hyperexcitability of the granule cell layer in mice caused a hyperarousal phenotype characterized by hyperlocomotion, decreased exploratory behavior, and diminished social interest (Rudolph et al., 2020) in mice. These observations are consistent with a longstanding theory that the cerebellum fine-tunes cortical arousal by acting on a distributed network of forebrain regions (Dow et al., 1962; Fadiga et al., 1968). Several cerebellar output regions could contribute to autonomic control, including the PAG, the hypothalamus, and other brainstem regions with known projections to the hippocampus, cerebral cortex, and septum (Dietrichs, 1984; Rutherford, 1995; Fujita et al., 2020; Rudolph et al., 2020; Vaaga et al., 2020; Chen et al., 2021; Novello et al., 2022; Hwang et al., 2023). Some of these areas have been directly implicated in wakefulness and increased locomotion (Pedersen et al., 2017; Lu et al., 2020; Farrell et al., 2021). However, the precise link between arousal, autonomic regulation, cerebellar activation, and its role in cognitive-affective behaviors remains poorly understood. Future fundamental and clinical studies will aim to elucidate this long known but often neglected aspect of cerebellar function and integrate it into our existing mechanistic frameworks. Ultimately, understanding the interplay between cognitive-affective states, autonomic responses, and their regulation by the cerebellum will provide a better grasp of complex human behavior and shed light on how disruption of these processes might contribute to neurodevelopmental and psychiatric disorders.

Sensitive periods in cerebellar development

Critical periods (which we will refer to as “sensitive periods” in the cerebellum) are an early stage in life when the brain is uniquely plastic to intrinsic and extrinsic stimuli and has the ability to create new connections (Hubel and Wiesel, 1970; Balmer et al., 2009). One factor modulating critical periods are

PNNs, which emerge around neurons at the closure of critical periods in late postnatal development. PNNs are defined as lattice-like structures that physically surround specific neurons in the brain, restricting the production of new synapses and the pruning of old synapses, which regulates neuronal plasticity (Celio et al., 1998; Pizzorusso et al., 2002; Deepa et al., 2006; Gogolla et al., 2009). The intensity of PNNs, as the brain reaches maturity, correlates with development of inhibitory interneuron circuitry (Bannon et al., 2020). PNNs are involved in various brain functions, such as learning and memory, but their role in cerebellar circuits is less clear (Shen, 2018).

Throughout the brain, PNNs preferentially surround parvalbumin-expressing interneurons (Porter et al., 2001). Parvalbumin interneurons provide inhibitory control of local excitatory circuits and sensory deprivation decreases synaptic transmission within layers of the neocortex (Lo et al., 2017). This circuit controls the excitatory/inhibitory balance and pruning of dendritic spines, important for refining neural connections (Mataga et al., 2004; Ferguson and Gao, 2018). In the cerebellar cortex, PNNs surround large excitatory Golgi neurons and Purkinje cells (Mabuchi et al., 2001; Carulli et al., 2006; Giamanco et al., 2010). Reducing Purkinje cell PNNs by chondroitinase ABC (chABC), an enzyme that degrades chondroitin sulfate glycosaminoglycan, has been found to increase GABA release, enhance synaptic plasticity, and improve conditioned response rate in eyeblink conditioning (Hirono et al., 2018).

In the CN, the main excitatory output of the cerebellum, PNNs surround large glutamatergic neurons and modulate their firing (Mabuchi et al., 2001; Carulli et al., 2006; Giamanco et al., 2010; Hirono et al., 2018). The CN has distal connections to brainstem, thalamus, and the ventral tegmental area (VTA) (Dietrichs, 1984; Rutherford, 1995; Fujita et al., 2020; Chen et al., 2021; Kang et al., 2021; Jung et al., 2022; Novello et al., 2022; Hwang et al., 2023) (Fig. 1), which suggests that PNNs in the CN could guide development and maturation of distal brain regions. While it is known how PNNs form in early-life, questions remain regarding how PNNs are maintained and if they degrade to allow for another period of plasticity. PNNs can be degraded chemically (chABC), but may also reduce during periods of learning (Hirono et al., 2018) or as a result of environmental enrichment (Foscarin et al., 2011; Stamenkovic et al., 2017). PNN intensity in the CN during eyeblink conditioning is reduced with environmental stimuli and returns to pretraining levels after memories are fully acquired. This effect is not found by chemically degrading PNNs using chABC, as while learning improves, memory cannot be retained (Carulli et al., 2020). It is thought that reducing PNNs may enhance learning, facilitate recovery from disease, and curtail cognitive decline in aging (Pang and Hannan, 2013; Hirase and Shinohara, 2014).

Moreover, PNNs have been found to be associated with critical periods in neurodegenerative and neuropsychiatric disorders (Bitanirwe and Woo, 2014; Wen et al., 2018; Scarlett et al., 2022). In neurodevelopment, a number of PNN molecules, including Reelin, semaphorins 3A and 4D, the hyaluronan surface receptor CD44, and Otx-2 (Weiss et al., 2009; Hussman et al., 2011), have been inversely correlated with ASD symptoms. This is striking as atypical cerebellar development is highly correlated with an ASD diagnosis (Wang et al., 2014; Sydnor and Aldinger, 2022). This suggests that there is a connection between PNNs and typical neurodevelopment of the cerebellum, but the purpose of PNNs both in early-life and across the lifespan still requires more investigation. Furthermore, sexually dimorphic

expression of PNNs in the cerebellum has not been strongly studied, although PNN sex differences have been found in various other brain regions, including the hippocampus and hypothalamus (Griffiths et al., 2019; Zhang et al., 2021).

Cerebellar function in autism: what can we learn from ASD mouse models?

ASD is a highly heterogeneous neurodevelopmental disorder, which is characterized by deficits in social interaction and repetitive behaviors (American Psychiatric Association, 1980). It also often results in difficulties in flexible adaptation to changes in the environment (Cheng et al., 2021) and sensorimotor deficits (Hannant et al., 2016; Coll et al., 2020). Indeed, sensory and motor dysfunctions are often regarded as one of the core ASD symptoms (Mosconi and Sweeney, 2015; Khoury et al., 2020). Although a common neural correlate underlying ASD traits has not been established, cerebellar structural abnormalities and changes in the cerebello-cortical connectivity have been seen in many clinical studies (D'Mello et al., 2016; Stoodley et al., 2017; Sathyanesan et al., 2019), and could potentially contribute to the high rate of sensorimotor deficits observed in people with ASD. The perinatal period seems to be a particular window of vulnerability for the cerebellar damage, which significantly increases the risk of ASD (Wang et al., 2014; van der Heijden et al., 2021). This can be explained by the sensitive periods of cerebellar development described above.

The importance of the cerebellum for ASD research is further supported by the fact that the vast majority of the 232 high-confidence ASD risk genes, defined as “Category 1” by the Simons Foundation Autism Research Initiative database, show high levels of expression in the cerebellum (Aldinger et al., 2021; Sydnor and Aldinger, 2022), with some presenting a notable enrichment in this area (Li et al., 2018). Moreover, patients with mutations in these genes frequently report sensorimotor performance and learning deficits (Frazier et al., 2015; Piven et al., 2017; Kosillo and Bateup, 2021).

Studies using mouse models with global mutations of ASD high-risk genes invariably show cerebellar morphologic and physiological abnormalities and altered motor behavior (Kloth et al., 2015; Peter et al., 2016; Kawamura et al., 2021; Matas et al., 2021; Kaiser et al., 2022; Liu et al., 2022; Serra et al., 2022). Intriguingly, cell-specific deletions of the same genes restricted to the cerebellar Purkinje cells have successfully reproduced many phenotypes resembling human ASD characteristics, including motor coordination deficits, affected social interactions, and cognitive impairment (Levin et al., 2006; Tsai et al., 2012; Reith et al., 2013; Kloth et al., 2015; Cupolillo et al., 2016; Yamashiro et al., 2020), strengthening the hypothesis that altered cerebellar development is one of the key components of ASD (Wang et al., 2014). These findings are in line with studies that show that region-specific perturbations that alter (lower or increase) cerebellar activity during sensitive periods lead to decreased cognitive flexibility and social dysfunctions (Badura et al., 2018; Gibson et al., 2022; Verpeut et al., 2023).

However, although targeted deletions and perturbations offer many valuable insights into cerebellar mechanisms that potentially drive ASD deficits, the global mouse models can better recapitulate multisystem symptoms and comorbid conditions that often accompany ASD diagnosis (Casanova et al., 2020). This is of particular importance when testing potential behavioral and pharmacological interventions aimed at ameliorating some of the deficits.

Of note, the pervasiveness of cerebellar structural abnormalities in ASD has recently been contested (Laidi et al., 2022). Although this particular study focused only on cerebellar structural changes without analyzing cerebello-cortical connectivity, it is a topic that should be further investigated. We need large, longitudinal studies, reporting structural and functional data from the same participants to better estimate cerebellar involvement in ASD. Similarly, collaborative studies using several ASD mouse models, investigated throughout the whole developmental trajectory, are essential to understand the role of cerebellum in this highly heterogeneous condition.

Diagnosing CCAS

In 1998, CCAS was introduced to encompass the nonmotor deficits observed in patients with cerebellar disease. CCAS includes impairments in executive, language, and visual-spatial functions, as well as neuropsychiatric abnormalities (Schmahmann and Sherman, 1998). These deficits are often mild and can be easily overlooked during routine examinations (Ahmadian et al., 2019). However, it is important to recognize cognitive and affective symptoms as they can significantly impact patients' daily lives (Schmahmann et al., 2021).

Since its initial description, many studies have confirmed the presence of CCAS in cerebellar patients (Mariën et al., 2014; Adamaszek et al., 2017; Argyropoulos et al., 2020). MRI studies have mapped nonmotor functions to specific cerebellar areas. Three nonmotor representations have been identified in the cortex of the posterolateral cerebellar hemispheres: (1) lobules VI-Crus I, (2) lobules Crus II-VIIB, and (3) lobules IX-X (Buckner et al., 2011; Guell et al., 2018; King et al., 2019; Guell and Schmahmann, 2020). Functional compartmentalization has also been observed at the level of the CN, with one nonmotor area in the ventro-caudal parts and one motor area in the rostro-dorsal parts of the dentate nucleus (Steele et al., 2017; Guell et al., 2020; Palesi et al., 2021).

Despite the well-established concept of CCAS in cerebellar disease, a definitive diagnostic standard for detecting CCAS is still lacking. In the past, most studies have used different and often extensive cognitive test batteries to assess CCAS. In 2018, a brief bedside test called the CCAS-Scale was developed in American English. Subsequently, it has been validated in adults with various cerebellar disorders. The CCAS-Scale can be easily administered within 10–15 min and is designed to screen for CCAS (Hoche et al., 2018). Currently, the CCAS-Scale has been translated into different languages, including German (Thieme et al., 2020), Spanish (Rodríguez-Labrada et al., 2022), Portuguese (de Oliveira Scott et al., 2023), Dutch, and French (Van Overwalle et al., 2019). The scale is already widely used (Naeije et al., 2020; Stephen et al., 2020; Benussi et al., 2021; Maas et al., 2021; Abderrakib et al., 2022; Chirino-Pérez et al., 2022; Thieme et al., 2022), and it is recommended for upcoming clinical trials (Klockgether et al., 2023). The CCAS-Scale consists of 10 test components that can be either passed or failed. According to the authors of the original CCAS-Scale, the number of failed test items determines the probability of CCAS: “CCAS possible” if one item is failed, “CCAS probable” if two items are failed, and “CCAS definite” if three or more items are failed (Hoche et al., 2018). However, based on these diagnostic criteria, several studies have reported a high number of false-positive test results in healthy subjects (Chirino-Pérez et al., 2022; Rodríguez-Labrada et al., 2022; Thieme et al., 2022; de Oliveira Scott et al., 2023). Age and education effects, which

were not described in the initial validation trial (Hoche et al., 2018), explain these findings at least in part (Thieme et al., 2021; Chirino-Pérez et al., 2022; Rodríguez-Labrada et al., 2022; de Oliveira Scott et al., 2023). Furthermore, the CCAS-Scale may be more sensitive in degenerative ataxias with known cerebral involvement (e.g., SCA2 and SCA3) than in those with primarily “pure cerebellar” involvement (e.g., SCA6) (Maas et al., 2021; Rodríguez-Labrada et al., 2022; Thieme et al., 2022). In most studies that have applied the CCAS-Scale to cerebellar patients and a control group, the word fluency tests of the scale have shown the best differentiation between patients and healthy controls (Maas et al., 2021; Chirino-Pérez et al., 2022; Thieme et al., 2022). This finding is consistent with a meta-analysis that included 10 studies examining CCAS in a total of 212 patients with isolated cerebellar lesions. The meta-analysis showed that patients performed significantly worse on word fluency tests, the Stroop test, the block design test of the revised Wechsler Adult Intelligence Scale, and the visual memory test of the revised Wechsler Memory Scale. Some tests, which are also part of the CCAS-Scale (e.g., go/no-go and digit span backward test), did not reach statistical significance but showed a trend toward poorer performance in patients. The digit span forward test, which is also part of the CCAS-Scale, did not show any difference between patients and controls (Ahmadian et al., 2019).

Considering these findings, it may be necessary to reevaluate the weighting, introduce a correction formula, exclude certain items, or add additional items to improve the diagnostic properties of the CCAS-Scale. Moreover, language- and culture-specific adaptations are needed. The Spanish and Portuguese versions have already adjusted the cutoff values in their respective scale versions (Rodríguez-Labrada et al., 2022; de Oliveira Scott et al., 2023).

There is also a growing need to introduce more objective measures, such as machine learning-based approaches, for behavioral evaluation in clinical settings related to CCAS. Currently, clinical assessments heavily rely on subjective judgments and cognitive test batteries, which may be prone to biases and variability. By incorporating these approaches, it will become possible to analyze large datasets across diverse ethnic, racial, and socioeconomic backgrounds and identify objective behavioral markers that accurately reflect the cognitive and affective deficits associated with CCAS. This objective approach holds the potential to enhance diagnostic accuracy, monitor disease progression, and evaluate treatment effectiveness in a more standardized and reliable manner.

In conclusion, here we have discussed recent evidence that corroborates the role of the cerebellum in cognitive and affective processing throughout the lifespan. The evidence supports and extends earlier observations in animal studies, begins to offer mechanistic explanations to findings from human studies, and establishes the cerebellum as part of the limbic system. Despite this progress, several key questions remain unanswered. The nature of the computations used by local and long-range cerebellar circuits that serve cognition, affect, and reward learning, and the relationship of these computations to cerebellar motor signals, remain unclear. In addition, little is known about the neuromodulatory mechanisms that enable the cerebellum to dynamically adapt its computations to internal state. These are fundamental questions, the resolution of which would improve our understanding of cerebellar function and of how cognition and affect are implemented in the mammalian brain. The properties of the cell types that form local and long-range cerebellar circuits for

nonmotor function need to be elucidated, as do the activation dynamics that produce and propagate cerebellar computations to the limbic system. Along the same lines, a deeper understanding of how PNNs and disease-relevant genetic mutations modulate cerebellar output is needed to shed light onto cerebellar sensitive periods of development and how their disruption contributes to neurodevelopmental and neuropsychiatric disorders. Defining the precise link between arousal, autonomic regulation and cerebellar activation would also contribute toward this goal. Animal models are crucial for understanding the underlying mechanisms and exploring potential treatments for CCAS. Developing reliable behavioral assays in animal models will provide valuable insights into the disease's pathophysiology and may lead to innovative diagnostic and therapeutic approaches, ultimately improving patient care.

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