R E V I E W

The Cerebellum–Ventral Tegmental Area Microcircuit and Its Implications for Autism Spectrum Disorder: A Narrative Review

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Abstract: The cerebellum has long been implicated in the etiopathogenesis of autism spectrum disorder (ASD), and emerging evidence suggests a significant contribution by reciprocal neural circuits between the cerebellum and ventral tegmental area (VTA) in symptom expression. This review provides a concise overview of morphological and functional alterations in the cerebellum and VTA associated with ASD symptoms, primarily focusing on human studies while also integrating mechanistic insights from animal models. We propose that cerebello–VTA circuit dysfunctional is a major contributor to ASD symptoms and that these circuits are promising targets for drugs and therapeutic brain stimulation methods.

Keywords: autism spectrum disorder, cerebellum, ventral tegmental area, neural circuit

Introduction

Autism spectrum disorder (ASD) encompasses a cluster of neurodevelopmental disabilities characterized by challenges in social interactions, difficulties in verbal and non-verbal communication, and restricted/stereotyped patterns of behavior, activities, and interests. Multiple epidemiological studies have documented a dramatic increase in ASD prevalence over the past few decades, and current estimates suggest that ASD afflicts 1–2% of children globally.[1–3] Regrettably, existing treatments are of limited efficacy for mitigating the core symptoms of ASD. For instance, several recent reports suggest that neither pharmacotherapies nor behavioral interventions can substantially improve social skills or suppress stereotyped behaviors in most patients with ASD.[4,5] Consequently, a substantial number of ASD patients require extensive lifelong medical and social support, imposing considerable stress and financial strain on families and healthcare systems.[6–8]

The cerebellum has been the focus of ASD research for several decades due to numerous reports of morphological and histological abnormalities associated with autistic phenotypes such as communication deficits, social dysfunction, and repetitive behaviors.[9] Recent studies also suggest that dysfunctional dopaminergic signaling from the ventral tegmental area (VTA) may contribute to certain autistic traits.[10,11] Despite the strong functional connectivity between the cerebellum and VTA, the contributions of cerebello–VTA circuit dysfunction to ASD development and symptoms remain largely unexplored. This narrative review seeks to provide a better understanding of cerebello–VTA interactions related to ASD, thereby providing support for these circuits as novel targets for intervention.

Cerebellar Alterations in ASD Patients

A myriad of studies using different designs and research methods have reported abnormalities in regional cerebellar structure and function associated with autistic traits (Supplementary Table). For instance, children with ASD were reported to exhibit significantly diminished structural complexity in the right cerebellar cortex marked by flatter and less regular surface protrusions; further, these abnormalities were associated with reduced social interactions.[12] However, both the causes of these abnormalities in cerebellar development and the impacts on specific ASD symptoms remain unknown.

Volumetric Changes

Multiple studies have reported differences in regional cerebellar volumes among patients with ASD compared to typically developing (TD) controls. However, reported changes include both decreases (atrophy)[13,14] and increases,[15] while several others have found no significant changes.[16–19] One prevailing theory posits that early cerebellar development is accelerated in infants with suspected ASD, followed by deceleration in growth rate, ultimately resulting in a smaller volume by adulthood.[20] Moreover, distinct subregions of the cerebellum display varying degrees of volumetric change in ASD patients.[21,22] Of particular note, several morphometric studies have noted hypoplasia in the Crus I/II strongly associated with the severity of core ASD symptoms such as social deficits, communication difficulties, and repetitive behaviors.[23–26]

Cell Type-Specific Changes in Autistic Cerebellum

The cerebellum contains the largest number of neurons in the central nervous system, and these numbers are frequently altered in ASD. Further, multiple cell types may be differentially altered in specific regions, underscoring the complex neurobiology of the disorder.

Purkinje Cells

Purkinje cells (PCs) are the exclusive output neurons of the cerebellar cortex, projecting predominantly to three bilateral deep cerebellar nuclei (DCN), the fastigial nuclei (FN), interpositus nuclei (IN, including emboliform and globose nuclei), and dentate nuclei (DN). It is widely reported that the number of PCs is reduced in patients with ASD.[19,27–30] However, some studies have reported no significant reduction in PC density among autistic individuals.[31,32] These discrepancies may reflect regional heterogeneity, differences among developmental stages, and (or) the use of different measurement techniques. For example, no decrease was reported in lobule X, while moderate reductions were found in lobules IV–VI, pronounced reductions in the vermis, and greatest reductions in Crus I/II.[27,32,33] Further, an initial increase was found during the earlier postnatal days followed by a dramatic decrease in an ASD mouse model.[34] Finally, various histological techniques and quantitative methodologies may introduce unique biases contributing to inconsistent outcomes across studies.[35,36] Nonetheless, it appears that greatest PC loss occurs in Crus I/II among patients with ASD.[33] In summary, while there is compelling evidence for region-specific PC loss and cortical atrophy within the autistic cerebellum,[31,37] it remains uncertain how and why such ultrastructural changes manifest as ASD symptoms.

Granule Cells

While one study reported no detectable loss of granule cells among patients with ASD,[19] several others have found significant reductions in granule cell numbers.[27,29,30,35] Moreover, a mouse model carrying a mutation in the ASD-linked gene Engrailed2 specifically within granule cells exhibited cerebellar pathology associated with multiple ASD-related behaviors.[38]

Golgi Cells

One study reported heightened immunoreactivity of antibodies targeting a cerebellar-specific protein of approximately 52 kDa in Golgi cells of the autistic cerebellum compared to the healthy individuals.[39]

Basket Cells and Stellate Cells

The outputs of PCs are modulated by GABAergic basket cells and stellate cells within the cerebellar molecular layer. According to Whitney et al, the densities of basket and stellate cells per PC did not differ between autistic patients and TD controls.[40] However, despite no change in total interneuron number, Yip et al reported significant upregulation of GAD67 mRNA specifically within basket cells and a slight increase in stellate cells among ASD patients,[36] suggesting reorganization of GABAergic input to PCs and ensuing alterations in PC output patterns.

Glial cells

Greater reactivity of Bergmann glia, microglia, and astrocytes has been reported in the cerebellum of ASD patients,[19,30] suggesting potential influences on synaptic transmission, neuronal metabolism, and the immune milieu. Further, investigation of changes in other glial cells, such as oligodendrocytes, are warranted to examine the impacts on neurotransmission within cerebellar circuits.

Neurons in Deep Cerebellar Nuclei

Significant neuronal loss has also been observed in the FN and IN but not the DN of ASD patients.[29] However, dysmorphic DN neurons have been found in ASD patients.[29] Yip et al reported a marked decrease in GAD65 mRNA expression within GABAergic neurons of the DN among patients with autism, suggesting significant effects on the temporal pattern and magnitude of cerebellar outputs.[41]

Collectively, these structural and functional alterations in cerebellar neurons, particularly of PCs, suggest marked changes in cerebellar circuit transmission, integration, plasticity, and output patterns in response to cerebellar inputs. Further study is required to describe these changes in input–output functions and associated influences on ASD-relevant behaviors.

Changes in Cerebello–VTA Microcircuits
Cerebellar Projections to the VTA

Early studies utilizing classical anterograde and retrograde tracing techniques revealed that all three DCN project to the VTA in both humans and animals (Figure 1), although with distinct patterns. According to these studies, the largest number of projections originates from the contralateral DN, followed by the IN, while relatively few
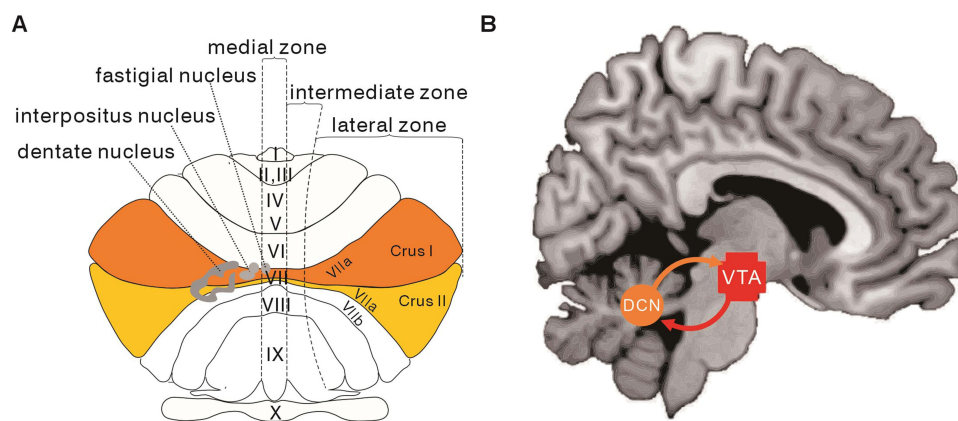

Figure 1 Depiction of cerebellar anatomy and connections with the ventral tegmental area (VTA). **(A)** Dorsal view of the cerebellum showing the numerically labeled lobules within the vermis. Crus I and II are major sites of VTA inputs (highlighted with colored overlays). **(B)** Anatomical representation of the bidirectional connections between the deep cerebellar nuclei (DCN) and the VTA based on brain magnetic resonance imaging. Adapted from Esslinger C, Braun U, Schirmbeck F et al. Activation of midbrain and ventral striatal regions implicates salience processing during a modified beads task. *PLoS ONE*. 2013; 8(3):e58536. Creative Commons.[42]

originate from the FN.[43] However, others have also identified DCN projections to the ipsilateral VTA.[44,45] Findings on the reciprocal connections between the cerebellum and VTA are summarized in Table 1.

Recently, synaptic anterograde/retrograde viral tracing in transgenic mouse lines has provided precise insights into these mutual connections. However, there is still disagreement among studies regarding the origins of DCN projections and the cell types involved. For instance, Baek et al reported abundant projections from the DN, fewer from the IN, and none from the FN to the VTA, whereas another study identified direct projections from the FN to the VTA using trans-synaptic anterograde tracing in mice.[60] A recent human study further reported that all DCN project to the VTA, with the IN contributing the largest number.[47] Moreover, multiple animal studies have found that cerebellar outputs from the three DCN target both dopaminergic neurons and non-dopaminergic neurons in the VTA.[11,55,59,61]

Table 1 Summary of Studies Investigating Reciprocal Connectivity Between the VTA and Cerebellum

Connection	Species	Methodology	Principal Results	References
CC → VTA	Rats and cats	HRP retrograde tracing	Vermis → ipsilateral VTA?	Snider, 1976[46]
	Humans	DWI and probabilistic tractography	Paravermis → mostly ipsilateral VTA (with predominance from the right hemisphere)	Hoffman, 2024[47]
	Mice	AAV anterograde tracing, AAV-retro and Fast Blue retrograde tracing	Vermian lobule IX → ipsilateral VTA	Hashimoto, 2018[48]
VTA → CC	Rats	Fluoro-Gold retrograde tracing and Cholera toxin anterograde tracing	VTA → bilateral CC (with contralateral predominance)	Ikai, 1992[45]
	Rats	Fast Blue retrograde tracing	VTA → bilateral CC (Crus I, with contralateral predominance)	Ikai, 1994[49]
	Mice	AAV retrograde tracing	No VTA → CC	Wagner, 2017[50]
	Mice	AAV/Dextran anterograde tracing, and Retrobead retrograde tracing	No VTA → CC	Li, 2023[51]
DN → VTA	Rats and cats	HRP retrograde tracing	DN → primarily contralateral VTA	Snider, 1976[46]
	Rats	HRP retrograde tracing	DN → contralateral VTA	Phillipson, 1979[52]
	Rats	HRP retrograde tracing, WGA-HRP anterograde/retrograde tracing	DN → contralateral VTA	Perciavalle, 1989[43]
	Rats	Cholera toxin retrograde tracing	DN → bilateral VTAs (with contralateral predominance)	Ikai, 1992[45]
	Rats	PHA-L anterograde tracing	DN → contralateral VTA	Parker, 2014[53]
	Mice	AAV anterograde/retrograde tracing	DN → contralateral VTA	Baek, 2022[54]
	Humans	DWI and probabilistic tractography	DN → mostly ipsilateral VTA (with predominance from the right hemisphere)	Hoffman, 2024[47]
	Mice	Rabies virus retrograde tracing	DN → VTA	Watabe-Uchida, 2012[55]
	Mice	Herpes virus anterograde tracing	DN → VTA	Carta, 2019[11]
	Rats	Dextranamine anterograde tracing, Fluoro-Gold retrograde tracing	DN → contralateral VTA	Gil-Miravet, 2019[56]
VTA → DN	Rats	Fluoro-Gold retrograde tracing and Cholera toxin anterograde tracing	VTA → bilateral DNs (with contralateral predominance)	Ikai, 1992[45]
	Rats	Fast Blue retrograde tracing	VTA → bilateral DNs (with contralateral predominance)	Ikai, 1994[49]

(Continued)

Table 1 (Continued).

Connection	Species	Methodology	Principal Results	References
IN → VTA	Rats and cats	HRP retrograde tracing	IN → primarily contralateral VTA	Snider, 1976[46]
	Rats	Cholera toxin retrograde tracing	IN → bilateral VTAs (with contralateral predominance)	Ikai, 1992[45]
	Mice	AAV anterograde tracing	IN → contralateral VTA	Judd, 2021[57]
	Rats	Fluoro-Gold retrograde tracing	IN → contralateral VTA	Gil-Miravet, 2019[56]
	Humans	DWI and probabilistic tractography	IN → mostly ipsilateral VTA (with predominance from the right hemisphere)	Hoffman, 2024[47]
	Rats	HRP retrograde tracing, WGA-HRP anterograde/retrograde tracing	IN → contralateral VTA	Perciavalle, 1989[43]
	Mice	Herpes virus anterograde tracing	IN → VTA	Carta, 2019[11]
	Mice	AAV anterograde/retrograde tracing	IN → contralateral VTA	Baek, 2022[54]
VTA → IN	Rats	Fluoro-Gold retrograde tracing and Cholera toxin anterograde tracing	VTA → bilateral INs (with contralateral predominance)	Ikai, 1992[45]
FN → VTA	Rats and cats	HRP retrograde tracing	FN → primarily ipsilateral VTA	Snider, 1976[46]
	Mice	AAV anterograde tracing	FN → contralateral VTA	Chao, 2023[58]
	Rats	HRP retrograde tracing, WGA-HRP anterograde/retrograde tracing	None FN → VTA	Perciavalle, 1989[43]
	Rats	Cholera toxin retrograde tracing	None FN → VTA	Ikai, 1992[45]
	Mice	AAV anterograde/retrograde tracing	None FN → VTA	Baek, 2022[54]
	Rats	Fluoro-Gold retrograde tracing	None FN → VTA	Gil-Miravet, 2019[56]
	Rats	PHA-L anterograde tracing	FN → contralateral VTA	Parker, 2014[53]
	Humans	DWI and probabilistic tractography	FN → mostly ipsilateral VTA (with predominance from the right hemisphere)	Hoffman, 2024[47]
	Mice	Herpes virus anterograde tracing	FN → VTA	Carta, 2019[11]
VTA → FN	Rats	Fluoro-Gold retrograde tracing and Cholera toxin anterograde tracing	None VTA → FN	Ikai, 1992[45]

Notes: The table lists only those studies that specified the individual cerebellar nuclei [eg, fastigial nucleus (FN), interposed nucleus (IN), and dentate nucleus (DN)]. Studies not distinguishing individual cerebellar nuclei, such as one employing rabies virus retrograde tracing to map projections to the VTA,[59] have been omitted.

VTA Projections to Cerebellum

Several studies have documented direct dopaminergic projections from the VTA to the cerebellum (as shown in Figure 1), with a particularly large projection terminating in bilateral Crus I with contralateral predominance in rats.[45,49] Alternatively, a combined anterograde and retrograde tracing study by Li et al challenged this notion, suggesting instead that in mice, dopaminergic afferents to the cerebellum may originate from PCs in the cerebellar cortex constituting an intrinsic dopaminergic system.[51] However, numerous subsequent studies have confirmed reciprocal cerebellar connections with the VTA, particularly in the Crus I/II region (Table 1), and further reported associations with ASD pathogenesis.[62]

VTA Alterations in ASD

The VTA consists primarily of dopaminergic neurons interspersed with smaller numbers of GABAergic and glutamatergic neurons.[63,64] These dopaminergic projection neurons are crucial for the reward-dependent reinforcement of

behaviors, including social activities.[65] Notably, intranasal administration of oxytocin, a neurotransmitter strongly implicated in social bonding, improved social communication in patients with ASD,[66] possibly through actions within the VTA.[67]

Alterations in the VTA dopaminergic system have been observed in various animal models of ASD, including a reduction in dopaminergic output.[68] These alterations likely contribute to ASD-relevant social deficits in animals as they can be mitigated by specific activation of VTA dopaminergic neurons.[10,68–70] The neural mechanisms underlying these alterations warrant further investigation.

Cerebello–VTA Circuit Dysfunction and Autistic Traits

The cerebellum and VTA are crucially involved in reinforcement, social actions, and motor behaviors. However, the influence of cerebello–VTA circuit activities on autistic behaviors remains largely unexplored. Nonetheless, there is emerging evidence to suggest that modulating this circuit can influence autistic phenotypes. For instance, chemogenetic inhibition of PC activity in the right Crus I of wild-type mice induced ASD-like social deficits as well as repetitive and restricted behaviors, whereas activation of these cells mitigated social impairments in ASD model mice.[71]

Stereotyped Behavior

The cerebellum serves as a crucial neural substrate for predictive processing by encoding adaptive internal models that facilitate automatic, rapid, and finely-tuned behaviors.[72] Mice with diminished numbers of cerebellar PCs displayed more frequent repetitive behaviors[73] and these behaviors were negatively correlated with PC numbers.[73,74]

Circuits reciprocally connecting the cerebellum and VTA likely transmit limbic signals to cortico-ponto-cerebellar loops essential for the execution and coordination of voluntary movements.[45] Consequently, the cerebellar abnormalities and reorganization of VTA pathways detected in ASD patients (Supplementary Table) may lead to diminished dopaminergic modulation of motor outputs and ensuing behavioral stereotypy.[75] Additionally, stronger connectivity between the VTA and bilateral thalamus has been reported in ASD patients, and was associated with repetitive and restrictive behaviors.[76] Thus, VTA outputs triggered by cerebellar projections may also activate thalamo-basal ganglia-cortical circuits, resulting in stereotyped behaviors.

Social Interaction

Supekar et al proposed that deficits in mesolimbic reward pathways contribute to impaired social skills among children with autism,[65] and that the cerebello–VTA pathway may contribute to socio-affective disorders by disrupting normal reward-seeking behavior, resulting in reduced social motivation. In accord with this notion, optogenetic modulation of the cerebellum–VTA pathway was reported to bidirectionally influence social behavior and reward in ASD model animals.[62] Moreover, the integrity of the DN–VTA pathway in mice was found to be necessary for normal social preference behaviors.[11]

Reinforcement

The cerebello–VTA pathway also appears to strongly influence reinforcement. Carta et al reported that transient optogenetic silencing of the DN–VTA in mice reduced the influence of rewarding stimuli on behavior.[11] Similarly, the modulation of the DCN–VTA pathway in mice altered food intake irrespective of baseline satiety levels.[77] These findings suggest that specific regions of the cerebellum regulate reward signals (a core feature of VTA dopaminergic functions), thereby either promoting or inhibiting reinforced (reward-dependent) behaviors. Moreover, individuals with ASD were reported to exhibit abnormal structural and functional connections between the VTA and the nucleus accumbens, the primary integration site for reward-related signals and motor commands, potentially leading to reduced motivation for social interaction.[65,78,79]

Hyphedonia

Lesioning of the rat DN resulted in decreased hedonic motivation, a hallmark of emotional disorders.[80] A recent study also reported that PCs in Crus I influenced VTA activity in mice through connections with the DN.[54] Additionally, the

deactivation of DN neurons projecting to the VTA attenuated depressive symptoms in animals,[54] while conversely, dysfunction of the cerebello–VTA circuit was associated with hyphedonia-like symptoms.

Conclusions

Developmental abnormalities in the cerebellum and VTA may contribute to ASD pathogenesis and autistic phenotypes. Indeed, the cerebellum and VTA are strongly and reciprocally connected, and this review summarizes emerging evidence that cerebello–VTA circuit dysfunction is an important contributor to ASD pathology. However, several outstanding issues warrant further exploration.

(1) Elucidating the precise neural pathways between the cerebellum and VTA: Precise mapping of VTA projections to cerebellar cortex and deep nuclei and of feedback fibers from the cerebellum to the VTA is critical for delineating the contributions of regional cerebello–VTA circuit abnormalities to ASD pathogenesis and symptoms.

(2) Exploring the potential of cerebello-VTA circuit modulation in clinical ASD research: Findings of cerebello-VTA circuit abnormalities in ASD present new research opportunities, although clinical applications remain highly speculative at this stage. While bilateral cerebellar repetitive transcranial magnetic stimulation has shown benefits for Parkinson's disease patients,[81] its efficacy for ASD requires much additional investigation. Future research could employ non-invasive neuroimaging to better characterize cerebello-VTA connectivity in the different stages of ASD and among patients with variations in symptom profile. Moreover, integrating knowledge of cerebello-VTA circuits into existing behavioral therapies may facilitate more targeted interventions.

(3) Understanding the pathophysiological mechanisms linking cerebello–VTA circuit abnormalities to ASD: Preclinical and clinical studies are crucial for a deeper understanding of how cerebello–VTA circuit activity changes during development and how these changes relate to the emergence of autistic symptoms. Animal models of ASD and genetic tools offer promising avenues for elucidating the contributions of these circuits to ASD pathogenesis.

In conclusion, this review suggests that impaired cerebello–VTA circuitry may contribute to autistic symptoms and further suggests that cerebello–VTA circuits are promising targets for the clinical treatment of ASD. Future systematic reviews are warranted to offer a more structured analysis of this important field.

Abbreviations

AAV, adeno-associated virus; ASD, autism spectrum disorder; CC, cerebellar cortex; DCN, deep cerebellar nuclei; DN, dentate nucleus; DWI, Diffusion weighted imaging; FN, fastigial nucleus; HRP, Horseradish peroxidase; IN, interpositus nucleus; PC, Purkinje cell; PHA-L, Phaseolus vulgaris leucoagglutinin; TD, typically developing; VTA, ventral tegmental area; WGA, wheat germ agglutinin.

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