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Research Article

Cerebellar Tract of Cognitive Function in Autism and Neurodevelopmental Disorder

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ABSTRACT

The cerebellum is a classical subcortical center for motor control and is an important part of the circuitry that links sensory to motor areas of the brain. It represents 10% of total brain volume but contains more than 50% of its neurons. There is different cerebellar circuitry, among them the cortico cerebellar cortical circuit is very important, any disruption of this circuitry associated with ataxic hemiparesis, dysarthria and clumsy hand syndrome and dysfunctional prefrontal thalamic cerebellar circuitry leads to schizophrenia, cognitive dysmetria. The dentato-rubro-olivary circuit is a bidirectional pathway, forms a feedback loop between the cerebellum and brainstem, and it serves to control spinal cord motor activity, lesion in this triangle is associated with hypertrophic olivary degeneration. There is another circuitry between cerebellam and basal ganglia, which are densely interconnected and control, modify motor activity. Their connections play an important role in pathophysiology of various movement disorders or neurodevelopmental disorders. Parkinsonian tremor results from increased interaction between the basal ganglia and the cerebello-thalamo-cortical circuit. The cerebello-hypothalamo-cerebellar circuit is a bidirectional circuit both directly and indirectly between the cerebellum and hypothalamus, consist of both hypothalamo-cerebellar and cerebello-hypothalamic pathways. The functions of this circuit are so far unknown, but the neurophysiological and neuroimaging studies have demonstrated that this circuit may be involved in feeding, cardiovascular, osmotic, respiratory, micturition, immune, emotion and other nonsomatic regulation. The circuitry between cerebellum with limbic-related brain areas and paralimbic cortices suggests widespread cerebellar influence on behaviors including the experience and expression of emotion, sadness and grief, integrative hypothalamic visceral/sensory functions, pain perception, modulation, and intensity due to noxious stimuli, as well as other nonmotor behaviors. Lesions of this circuitry lead to the cerebellar cognitive affective syndrome both in adults and in children and dysfunction of this circuitry may lead to autism and neurodevelopmental disorder. Cerebellar dysfunction may play a crucial role in the etiology of autism spectrum disorder, schizophrenia, and other cognitive disorders. Although the main function of cerebellum is motor control, but it has some roles in olfactory function. In this paper we have reviewed different descriptive cerebellar circuitry and clinical consequences following their lesions.

Keywords

Dentatorubrothalamocorticical tract, Cortico-ponto-cerebellar, Inferior olivary nucleus, Basal ganglia, Hypertrophic olivary degeneration.

Abbreviations

ASD: Autism spectrum disorder, BG: Basal ganglia, CCAS: cerebellar cognitive affective syndrome, CCTC: cortical-thalamic-cerebellar-cortical circuit, CPC: Cortico-ponto-cerebellar, CTC: Cerebello-thalamo-cortical, DROP: Dentato-rubroolivary pathway, RV: Rabies virus, DRTT: Dentatorubrothalamocorticical tract, FRDA: Friedreich ataxia, HOD: Hypertrophic olivary degeneration, ION: Inferior olivary nucleus, OPT: Oculopalatal tremor, PT: Palatal tremor, rTMS: Repetitive transcranial magnetic stimulation.

Background

The cerebellum is an important part of the circuitry that links sensory to motor areas of the brain, occupies the posterior cranial fossa, separated from the occipital lobes of the cerebral hemispheres by the tentorium cerebelli. It is the largest part of the hindbrain. The cerebellum lies dorsal to the pons and medulla, from which it is separated by the fourth ventricle. It is joined to the brain stem by the three bilaterally paired cerebellar peduncles, and these contain all the afferent and efferent fibres associated with the cerebellum [1]. It represents 10% of total brain volume but contains more than 50% of its neurons [2]. It receives afferent information concerning voluntary movement from the cerebral cortex and from the muscles, tendons, joints and also receives information concerning balance from the vestibular nerve and possibly concerning sight through the tectocerebellar tract. All these information is fed into the cerebellar cortical circuitry by the mossy fibers and the climbing fibers and converges on the Purkinje cells [3]. Inputs to the cerebellum arrive primarily through one of two pathways: climbing fibers that arise exclusively from the inferior olive and mossy fibers that arise from several brainstem nuclei. Climbing fibers and mossy fibers directly or indirectly modulate the activity and plasticity of Purkinje cells [4], the Purkinje cells constitute the only output from the cerebellar cortex [5]. It is now generally believed that the purkinje axons exert an inhibitory influence on the neurons of the cerebellar nuclei and the lateral vestibular nuclei [3]. There are four deep cerebellar nuclei embedded in the white matter of each cerebellar hemisphere. These are dentate, emboliform, globose, fastigial. The dentate nucleus is the principal way station of cerebellar output. Its activity is largely controlled by inhibitory corticonuclear connections that utilize neurohumoral transmission by γ-aminobutyric acid (GABA), and excitatory glutamatergic collaterals arising from mossy and climbing fibers [6]. Cerebellar output is directed predominantly to the thalamus and thence to the motor cortex, and also to brain stem centres such as the red nucleus, vestibular nuclei and reticular nuclei that themselves give rise to descending spinal pathways [1]. Cerebellum has no direct neuronal connections to the lower motor neurons but exerts its influence indirectly through the cerebral cortex and brainstem [3]. Cerebrovascular lesions of the cerebellum or its pathways can cause diverse movement disorders. These lesions typically result in the deterioration of coordination (ataxia, asynergia), misjudgment of distance (dysmetria), involuntary eye movement (nystagmus) and intention tremors. In addition to these typical symptoms of cerebellar dysfunction, various abnormal movements can occur in patients with cerebrovascular lesions of the cerebellum or its pathways [7].

In this article, we summarize the current knowledge about different types of cerebellar circuitry with their clinical consequences following lesions in cerebellar circuitry.

Methods

The cortico cerebellar cortical circuit

The cerebellum has been considered as a classical subcortical center for motor control,and specially neocerebellum is concerned with muscular coordination [8,9], it also plays a significant role in cognition, through connections with associative areas in the cerebral cortex. The neo-cerebellum is connected with the contralateral cerebral cortex through the dentate nucleus, superior cerebellar peduncle, red nucleus and ventrolateral anterior nucleus of the thalamus [10], which serves as a relay station for projections to the cortex. This pathway is part of the functional "cerebrocerebellum," and acts to coordinate the initiation, planning and timing of movement [11]. Cerebrocerebellar connections are composed of feed forward and feedback connections between cerebrum and cerebellum including the *cortico-ponto-cerebellar (CPC)* pathway, which starts from the frontal lobe, creates synapses on the pontine nuclei, and finally arrives at the cerebellar cortex via the middle cerebellar peduncle and the *dentate-rubro-thalamo-cortical tract (DRTT)* beingof cerebellar origin [7,12-14]. Typically, the DRTT is described as a decussating pathway, ascending to the contralateral thalamus; however, the existence of a nondecussating (i.e. ipsilateral) DRTT in humans was revealed and through which unilateral cerebellum can exert bilateral influence on movement [15]. The DRTT is the main output tract of the cerebellum [16]. The cerebellum is interconnected with the contralateral cerebrum primarily through two polysynaptic circuits. In a case of midbrain hemiatrophy syndrome, concurrent hypoperfusion of ipsilateral cerebellum and contralateral cerebral hemisphere was observed due to the bidirectional property of the DRTT [17], correspondingly therapeutic neuromodulator (e.g. repetitive transcranial magnetic stimulation (rTMS) is accomplished to modify the inhibitory or facilitatory nature of this tract that might be useful for the treatment of neurological conditions associated with dysfunctional intracortical inhibition [18].

There are no monosynaptic connections between the cerebral cortex and the cerebellum [14] Ataxic hemiparesis and dysarthria and clumsy hand syndrome caused by infarction of the cerebral peduncle or primary intracerebral hematoma in the precentral area can be associated with the disruption of the ascending DRTT or the descending CPC pathway [19]. Cerebellar infarct also can cause movement disorders, including tremor, ataxia, and incoordination, because the main role of the cerebellum is movement control by communicating between the cerebrum and cerebellum via the DRTT and CPC tract [20]. Atrophy of the dentate nucleus is one of the major neuropathological changes in Friedreich ataxia (FRDA). Neuroimaging studies demonstrated white matter degeneration in FRDA [21].

The Dentato-Rubro-Olivary Circuit (The Guillain-Mollaret Triangle)

It is composed of a few fibers that connect the dentate nucleus with the contralateral red nucleus and inferior olivary nucleus (ION). Efferent fibers from the dentate nucleus pass through the superior cerebellar peduncle and create synapses with the contralateral red nucleus. Efferent fibers from the red nucleus traverse through the central tegmental tract and create synapses with the ipsilateral ION. Thereafter, efferent fibers from the ION pass through the inferior cerebellar peduncle and create synapses

with the contralateral cerebellum to complete the triangular circuit [22]. This is a bidirectional pathway, a coupled system likely to be of a feedback function, because there are also projections from the dentate nuclei to the contralateral caudal inferior olivary nucleus. The inferior olive has an intrinsic slow, rhythmic, and spontaneous activity [23]. This triangle forms a feedback loop between the cerebellum and brainstem, and it serves to control spinal cord motor activity [22]. Pathology or lesion in this triangle disinhibits (activates) the ION. The olivary nucleus then hypertrophies, enlarges and is called hypertrophic olivary degeneration (HOD), which leads to rhythmical discharges and manifest clinically as oculopalatal tremor [23,24]. HOD is characterized by enlarged and vacuolated neurons, increased number and size of astrocytes, severe fibrillary gliosis, and demyelination [25].

The Cerebellar and Basal Ganglia Circuit

The motor system, which controls the entire range of human activity, encompasses a broad range of nervous system structures and pathways. Two parallel pathways, the cerebellar and basal ganglia circuits, control and modify motor activity [7]. The cerebellum and basal ganglia are densely interconnected [26]. The basal ganglia are mainly concerned with learned, automatic behavior and with maintaining the background support or posture needed for voluntary motor activity, whereas the cerebellum conducts the coordination and correction of errors in muscle contractions during active movements [27] Taken together, these neuroanatomical findings, along with results from behavioral and imaging studies, provide a new framework for understanding cerebellar involvement in motor, as well as non-motor function. Specifically, it is now clear that the cerebellum can influence the generation and control of movement not only at the level of primary motor cortex, but also through interactions with premotor cortical areas and sensorimotor regions of the basal ganglia. Furthermore, the cerebellum can no longer be considered an exclusively motor structure, and likely contributes to non-motor processes mediated by the prefrontal and parietal cortex, such as cognition and visuospatial reasoning, as well as non-motor operations of the basal ganglia, such as reward-related learning [28]. Basal ganglia and cerebellar loops have been assumed to be anatomically separate and to perform distinct functional operations. Investigation was done to see whether there is any direct route for basal ganglia output to influence cerebellar function that is independent of the cerebral cortex [26]. The cerebellum, basal ganglia (BG), and their connections play an important role in pathophysiology of various movement disorders (like Parkinson's disease and atypical parkinsonian syndromes) or neurodevelopmental disorders (like autism) [29].

Cerebellohypothalamo Cerebellar Circuit

The cerebellum and hypothalamus are interconnected through a multitude of direct (monosynaptic) and indirect (polysynaptic) hypothalamocerebellar connection. Cerebellar nonsomatic functions such as visceral and immunological responses are mediated by the direct bidirectional connection between hypothalamus and cerebellum. The direct hypothalamocerebellar projection (mainly uncrossed [30]) originate from widespread hypothalamic nuclei/area [8], or from posterior hypothalamus [30], or from lateral, posterior, and dorsal hypothalamic areas; the supramammillary, tuberomammillary, and lateral mammillary nuclei; the dorsomedial and ventromedial nuclei; and the periventricular zone [31] and terminates in all layers of cerebellar cortex and nuclei. These afferent fibers are not mossy fiber and climbing fiber [30]. Immunohistochemistry study provides evidence that, some of the hypothalamocerebellar fibers are histaminergic and some hypothalamocerebellarneurones may contain GABA- or glycine-like immunoreactivity [8,30,32]. While indirect hypothalamocerebellar connection is polysynaptic, so it may be relayed through brainstem nuclei. Such as, hypothalamopontocerebellar pathway is important one of them. In Cerebellohypothalamic pathway axons arise from neurons of all four cerebellar nuclei, pass through the superior cerebellar peduncle, cross in its decussation, and enter the hypothalamus. Some axons recross the midline in caudal areas of the hypothalamus. These fibers terminate primarily in lateral, posterior, and dorsal hypothalamic areas and in the dorsomedial and paraventricular nuclei [31]. The functions of hypothalamocerebellar circuits are so far unknown [30]. But the Neurophysiological and neuroimaging studies have demonstrated that this circuit may be involved in feeding, cardiovascular, osmotic, respiratory, micturition, immune, emotion, and other nonsomatic regulation [8]. The study in the animal model also revealed the neurochemical evidence that the cerebellum modulates dopamine efflux in the prefrontal cortex [33]. Thus, co-occurrences of cerebellar and frontal cortical pathologies may lead to neurodevelopmental disorder which is proposed in the Figure 1 by Rogers et.al, 2013 [34].

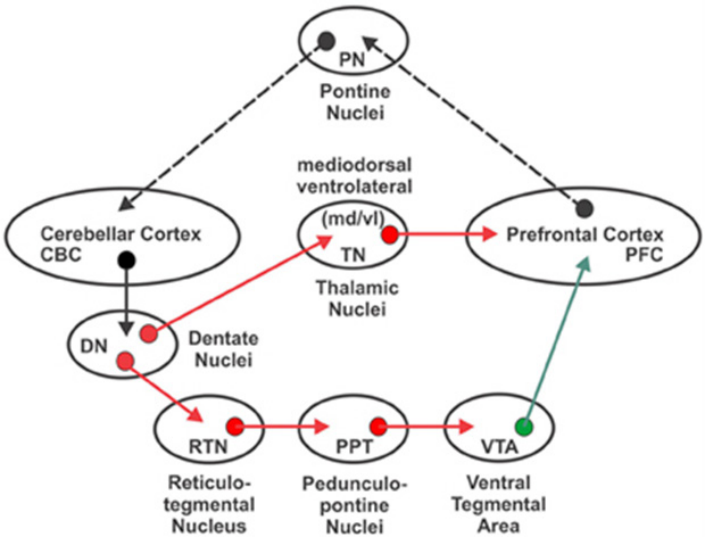

Figure 1: Proposed neural circuit involved in the cerebellar modulation. PFC dopamine efflux can be affected by a developmental disconnection in autism [34].

Circuitry between Cerebellum and Limbic System

The cerebellum is particularly well-suited to regulate emotion, as connections with limbic regions, including the amygdala, the

hippocampus, and the septal nuclei have been posited [35].The connectivity of the cerebellar cortex and nuclei (fastigeal nucleus) with limbic-related brain areas and associative and paralimbic cortices suggests widespread cerebellar influence on behaviors including the experience and expression of emotion, sadness and grief, integrative hypothalamic visceral/sensory functions, pain perception, modulation, and intensity due to noxious stimuli, as well as other nonmotor behaviors. Additionally, the cerebellum is interconnected with cingulate cortices that play a role in motivation and emotional drive, and with associative and paralimbic regions of prefrontal, posterior parietal, superior temporal polymodal, and parahippocampal regions heavily implicated in high order processing important for the integration of cognition and emotion [36]. Lesions of the connection between limbic system & cerebellum lead to the cerebellar cognitive affective syndrome (CCAS), both in adults and in children, characterized by impairments in executive function, visual–spatial processing, linguistic deficits, and affective dysregulation [37]. The connections between cerebellum (fastigeal nucleus) and limbic system (cingulum and parahippocampal region) are implicated in neurodevelopmental disorders such as autism which demonstrate neuropathology and aberrant neurochemistry in the cerebellar cortex and nuclei [36]. The amygdala facilitates acquisition of eyeblink conditioning in adult animals by enhancing conditioned stimulus inputs to the cerebellum and the unconditioned response circuitry. Amygdala inactivation impaired acquisition of eyeblink conditioning in all of the age groups and impaired freezing [36].

Discussion

From ongoing varieties of description we can know, the Cerebellum is part of the hind brain, an important part of the circuitry that links sensory to motor areas of the brain located at the back of the brain in posterior cranial fossa, considered as a classical subcortical center for motor control, muscular coordinationand coordination of initiation, planning and timing of movement [1,7-9,11]. It can influence a variety of motor control centers in the brain, including the motor cortex through its output pathway mainly through dentate-rubro-thalamo-cortical tract (DRTT), which is the main efferent fiber of the cerebellum [7]. In another study it was stated that the major output from the cerebellum projects to the motor cortex via the cerebello-thalamo-cortical (CTC) pathway [38]. According to Fisher and Bogousslavsky, any disruption of this cortico-cerebellar-cortical circuit that are ascending DRTT or descending CPC pathway are associated with ataxic hemiparesis, dysarthria and clumsy hand syndrome caused by infarction of the cerebral peduncle or primary intracerebral hematoma in the precentral area [19]. But some authors said that cerebellar infarct can cause movement disorders, including tremor, ataxia and incoordination, because the main role of the cerebellum is movement control by communicating between the cerebrum and cerebellum via the DRTT and CPC pathway [20]. Recently Mollink et al. described that, in FRDA the dentate nucleus become atrophied [16], which acts as a principal way station of cerebellar output [6]. According to some authors, pathologic laughter and crying arose from disruption of the CPC pathways, prevent the cerebellum from automatically adjusting the execution of emotional display to cognitive and situational context, and result in inadequate or chaotic behavior [39]. Some authors described about the disruption of the cortical-thalamic-cerebellar-cortical circuit (CCTC) leads to an impairment of synchrony, results in cognitive dysmetria and the impairment in this basic cognitive process defines the phenotype of schizophrenia and produces its diversity of symptoms [40]. Andreasen et al. said that dysfunctional prefrontal-thalamic-cerebellar circuitry leads to schizophrenia and may suffer from a cognitive dysmetria [41]. According to other authors, the cerebellum commonly observed in autism, schizophrenia, and other cognitive disorders could result in a loss of functionality of cerebellar-medial prefrontal cortex circuitry that is manifested as aberrant dopaminergic activity in the medial prefrontal cortex. Additionally, these results specifically implicate glutamate as a modulator of medial prefrontal cortex dopaminergic activity [42]. Recently D'Mello and Stoodley mentioned, disruptions in specific cerebro-cerebellar loops in ASD might impede the specialization of cortical regions involved in motor control, language, and social interaction, leading to impairments in these domains [43], which is proposed in the Figure 2 by D'Mello and Stoodley, 2014 [44].

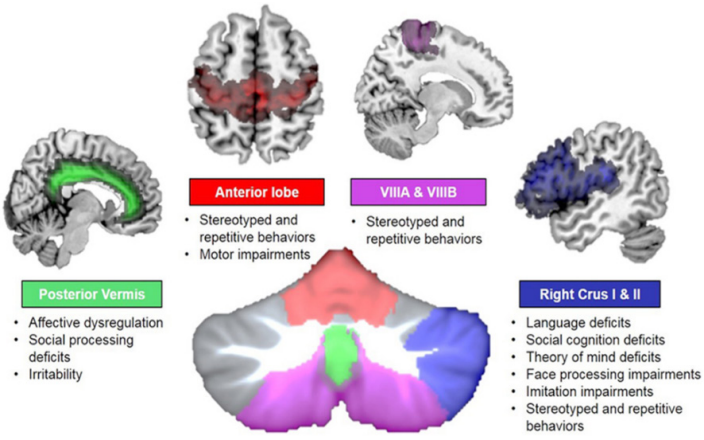

Figure 2: Cerebro-cerebellar circuits and task performance in ASD (autism spectrum disorder). Disruption of color-coded connectivity zones is related to behavioral deficits [44].

The Guillain-Mollaret triangle comprises the ipsilateral red nucleus in the midbrain, the inferior olive in the medulla and the contralateral dentate nucleus in the cerebellum: together, these form the dentato-rubro-olivary pathway [24]. Khoyratty and Wilson mentioned that, lesion in the triangle of Guillain-Mollaret is associated with hypertrophic olivary degeneration (HOD) [23]. This is mainly observed in patients developing palatal tremor (PT) or oculopalatal tremor (OPT). Oculopalatal tremor refers to the synchronous combination of PT (characterized by involuntary movements of the soft palate and pharynx) and pendularnystagmus [25]. Sanverdistated that, HOD is almost always unilateral; however, rare bilateral cases have been reported. Midline lesions or lesions in the brachium conjunctivum (superior cerebellar peduncle), finally interrupting decussation of the

dentato-rubroolivary pathway (DROP), can result in bilateral HOD [45].

The cerebellum and the basal ganglia are major subcortical nuclei with long-established roles in motor control [46]. Basal ganglia and cerebellar loops have been assumed to be anatomically separate and to perform distinct functional operations [26]. Different studies and experiment were done to see any direct route for basal ganglia output to influence cerebellar function that is independent of the cerebral cortex, among them viral tracings are ideally suitable [46]. So, rabies virus (RV) was injected into selected regions of the cerebellar cortex in cebus monkeys and used retrograde transneuronal transport of the virus to determine the origin of multisynaptic inputs to the injection sites. The finding was that the subthalamic nucleus of the basal ganglia has a substantial disynaptic projection to the cerebellar cortex. This pathway provides a means for both normal and abnormal signals from the basal ganglia to influence cerebellar function [26]. Recently Kaji et al. have done animal studies, showed physiologically tight disynaptic connections between the cerebellum and the striatum. They also reviewed clinical evidence in light of this new functional interaction between the cerebellum and basal ganglia, and put forward a hypothesis that dystonia is a basal ganglia disorder that can be induced by aberrant afferent inputs from the cerebellum [47]. The cerebellum, basal ganglia (BG), and their connections play an important role in pathophysiology of various movement disorders (like Parkinson's disease and atypical parkinsonian syndromes) or neurodevelopmental disorders (like autism) [29]. Recently Helmich stated that, perkinsonian tremor results from increased interaction between the basal ganglia and the cerebello-thalamo-cortical circuit, driven by altered dopaminergic projections to nodes within both circuits, and modulated by context-dependent-factors, such as psychological stress [48]. Another author said that damage to the basal ganglia or cerebellar components of circuits with motor areas of cortex leads to motor symptoms, whereas damage of the subcortical components of circuits with non-motor areas of cortex causes higher-order deficits [49].

The cerebello-hypothalamo-cerebellar circuit is a bidirectional circuit both directly and indirectly between the cerebellum and hypothalamus [30]. This circuit consists of both hypothalamocerebellar and cerebellohypothalamic pathway. There are different hypothesis and conception about the origin of the hypothalmocerebellar pathway. According to some authors it is originated from posterior hypothalamus [30]. Haines et al. said that, its origin is from lateral, posterior and dorsal hypothalamic areas; the supramammilary, tuberomammilary, and lateral mammillary nuclei; the dorsomedial and ventromedialnuclei; and the periventricular zone [31]. Another study mentioned, it originates from widespread hypothalamic nuclei [8]. Others have said, its origin is mainly from lateral hypothalamic area, and also from posterior and dorsal hypothalamic areas and the lateral mammillary, tuberomammillary, and periventricular nuclei [50]. There is different opinion about the functions of this circuit. As stated in publication, the functions of hypothalamocerebellar circuits are so far unknown [30]. But the Neurophysiological and neuroimaging studies have demonstrated that this circuit may be involved in feeding, cardiovascular, osmotic, respiratory, micturition, immune, emotion, and other nonsomatic regulation [8]. Some authors have discussed about the role of cerebellohypothalamic GABAergic projection in cerebellar immunomodulation [51,52]. These observations provide support for the hypothesis that the cerebellum is an essential modulator and coordinator for integrating motor, visceral and behavioral responses, and that such somatic-visceral integration through the cerebellar circuitry may be fulfilled by means of the cerebellar-hypothalamic circuits.

There is an emerging body of evidence suggesting that the cerebellum participates in limbic-related functions including emotion and affect [36]. Any disruption of this pathway or neuronal circuit may leads to different symptoms. According to some authors, lesions of the limbic cerebellum led to the cerebellar cognitive affective syndrome (CCAS), both in adults and in children, characterized by impairments in executive function, visual–spatial processing, linguistic deficits, and affective dysregulation [37]. Other authors said dysfunction of the cerebellolimbic circuitry may lead to autism, a neurodevelopmental disorder [36,53]. Some authors said inactivation of amygdala results in impaired acquisition of eyeblink conditioning in all of the age groups and impaired freezing [54].

Although the main function of cerebellum is motor control but it has some roles in olfactory function. According to some authors, cerebellum is involved in olfaction in human. Odorant induced activation primarily in the posterior lateral regions and sniffing induced activation primarily in the anterior central regions [55]. Another authors mentioned that, the cerebellum plays a role in olfactory processing stems from four sources: (a) early reports of olfactory deficits in patients with tumours in or near the cerebellum (b) indications of cerebellar anomalies in some disorders, such as schizophrenia, known to be associated with smell loss (c) evidence that the staggered mutant mouse, a mouse with functional deficits in the olivocerebellar pathway, is hyposmic and (d) recent functional magnetic resonance imaging studies that show marked odour-induced cerebellar activity that is independent of sniffing [56]. Other authors said that olfactory dysfunction has been reported to occur in patients with cerebellar disorders, including degenerative ataxia and essential tremor. Olfactory dysfunction in essential tremor patients occurs independently of mild cognitive deficits and supports recent works that the cerebellum may play a role in central olfactory processing [57]. But in another publication some authors have mentioned that, the pathways through which olfactory information reaches the cerebellum and the functional role of the cerebellum in olfaction remain unknown [58].

Cerebellar neuropathology commonly occurs in autism spectrum disorder individuals. Cerebellar hypoplasia and reduced cerebellar Purkinje cell numbers are the most consistent neuropathologies linked to autism [59]. According to some authors, it is one of

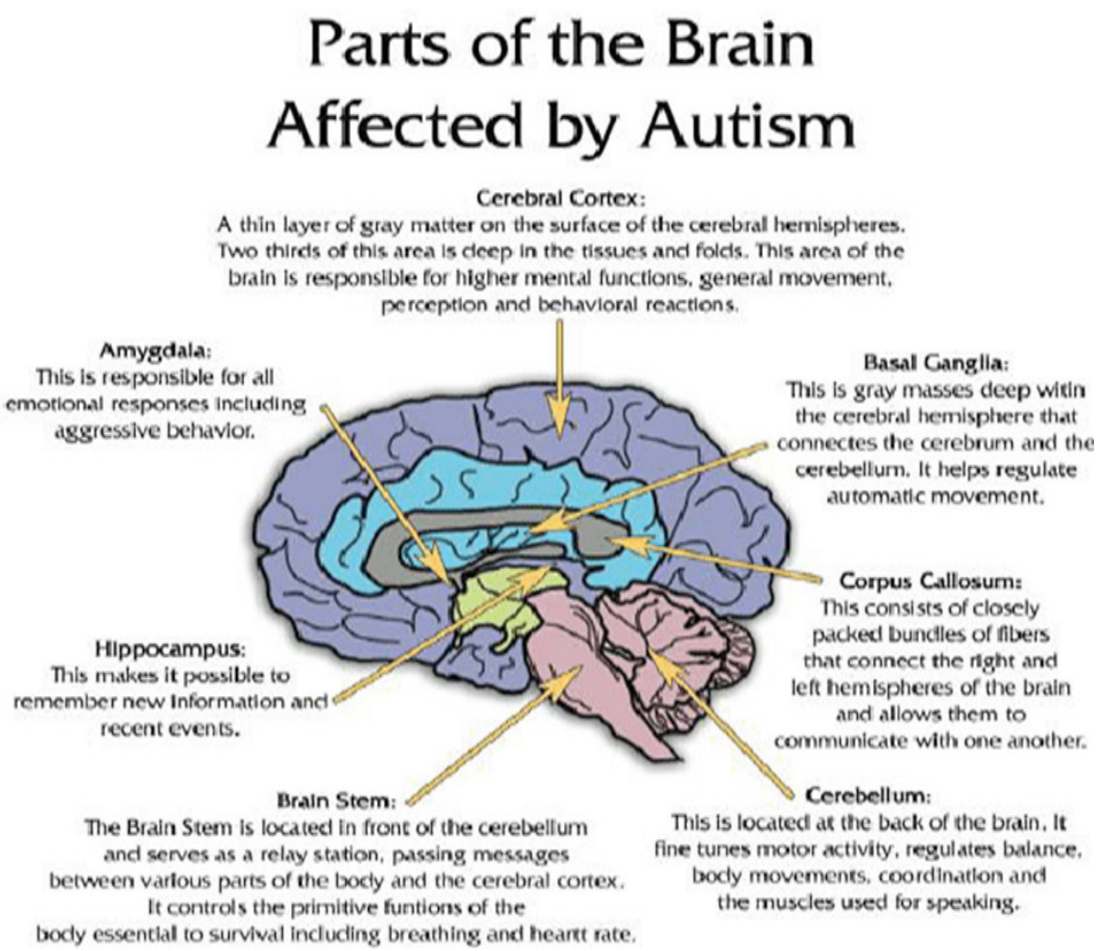

Figure 3: Parts of the brain affected by Autism [63].

the most consistent sites of abnormality in autism spectrum disorder and cerebellar damage is associated with an increased risk of autism spectrum disorder symptoms, suggesting that cerebellar dysfunction may play a crucial role in the etiology of autism spectrum disorder. They also said, integrity of cerebro-cerebellar loops might be important for early cortical development; disruptions in specific cerebro-cerebellar loops in autism spectrum disorder might impede the specialization of cortical regions involved in motor control, language, and social interaction, leading to impairments in these domains [43]. Other authors have mentioned, the cerebellum commonly observed in autism, schizophrenia, and other cognitive disorders could result in a loss of functionality of cerebellar-medial prefrontal cortex circuitry that is manifested as aberrant dopaminergic activity in the medial prefrontal cortex. Additionally, these results specifically implicate glutamate as a modulator of medial prefrontal cortex dopaminergic activity [42]. Some authors said, the striatum and the cerebellum, two structures known not only to control movement but also to be involved in cognitive functions such as memory and language and dysfunction within the motor system may be associated with abnormal movements in autism spectrum disorder (ASD) that are translated into ataxia, abnormal pattern of righting, gait sequencing, development of walking, and hand positioning [60]. Recently other authors said that, in autism, both the basal ganglia and the cerebellum are impacted both in their motor and non-motor domains and recently, found to be connected via the pons through a short disynaptic pathway. These authors also stated, there is emerging evidence that parts of the basal ganglia are structurally and functionally altered disrupting normal information flow. The basal ganglia through its interconnected circuits with the cerebral cortex and the cerebellum can potentially impact various motor and cognitive functions in the autism brain [61]. Other authors have mentioned, the cerebellum, basal ganglia (BG), and their connections play an important role in pathophysiology of various movement disorders (like Parkinson's disease and atypical parkinsonian syndromes) or neurodevelopmental disorders (like autism) [29]. According to other authors, dysfunction of the cerebellolimbic circuitry may lead to autism, a neurodevelopmental disorder [36,53]. Together, several parts of the brain affected by autism illustrated in Figure 3. For proper neurodevelopment, nervous system requires sensory, motor and cognitive experiences in some certain widows of time which is known as critical periods. The disruption of the specific cerebellar zone during this sensitive-period may leads to autism [62]. Parts of the brain affected by Autism is shown in Figure 3 [63].

Conclusion

This review highlights the role of cerebellum and its descriptive circuitry in their different spectrum of functions and their clinical consequences following lesions in these circuitries. It is an essential modulator and coordinator for integrating motor, visceral and behavioral responses. Lesion in different cerebellar circuitry results in ataxic hemiparesis, dysarthria, clumsy hand syndrome, HOD, various movement disorder like Parkinson disease and atypical parkinsonian syndrome, neurodevelopmental disorder like autism, and cerebellar cognitive affective syndrome. We have also summarized in this article about the current knowledge regarding autism spectrum disorder and the role of cerebellum in olfaction. These observations provide support for the hypothesis that the cerebellar circuitry and clinical dimension of their anatomical pathway. The clinical consequences of disruptions in the cerebellar circuit can be the result of various underlying causes, including traumatic brain injury, stroke, tumors, infections, degenerative diseases, and genetic disorders. These disorders can have a significant impact on an individual's quality of life and can be challenging to diagnose and manage. Early identification and proper management of these conditions related to cerebellar circuitry and its anatomical pathway can help prevent further complications and improve quality of life. Treatment for cerebellar circuit-related disorders may include medications, physical therapy, and other supportive interventions, depending on the specific condition and the severity of symptoms.

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