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Review article

The 21st Century Cerebellum: An Evolution of Cognitive Functions, Connections, Disorders, and Pharmacotherapeutic Modulation

O. J. Onaolapo [1] and A. Y. Onaolapo [2,*]

[1] Behavioural Neuroscience/Neuropharmacology Unit, Department of Pharmacology, Ladoke Akintola University of Technology, Osogbo, Osun State, Nigeria;

[2] Behavioural Neuroscience/Neurobiology Unit, Department of Anatomy, Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria.

* **Correspondence:** Email: olakunleonaolapo@yahoo.co.uk; Tel: +234-806-224-0434.

Abstract: Our understanding of the cerebellum's role in health and disease has evolved considerably in the past few decades; largely due to the availability of newer and better modalities for studying the relationships between the cerebellum and other segments of the brain, and how these impact behavioural responses like motor function, emotionality, memory and more recently, cognition. In this review, we discuss the evolution of our understanding of the structure and function of the cerebellum; where we were, and how we got here. We also examine the important roles of the cerebellum in neuro-cognitive processing, cognition and cognitive disorders; and ponder on how targeting cerebellar cognition may open a new chapter in the quest for the development and identification of newer cognition-modulating agents.

Keywords: Purkinje; cerebellar cortex; Schmahmann's disease; metencephalon; cognition

1. Introduction

About thirty years ago, functional neuroimaging studies of human cognition brought to light a surprising response in the cerebellum that cannot be accounted for by motor demands; thus objectively challenging our 'traditional' concept of the roles of the cerebellum [1], which hitherto had been mainly associated with the planning and executing of functions such as the maintenance of gait, control of posture and coordination of stereotyped and non-stereotyped movement [2-4]. This observation represented the threshold of a paradigm shift in our understanding of the roles of the cerebellum, and it ushered in an era of looking at the cerebellum in a brighter light than what was initially permitted by contemporary dogma [5-7]. For a long time, there was an absence of clear anatomical evidence that the cerebellum projects to non-motor cerebral structures; however, recent scientific evidences show that the human cerebellum has extensive connections with cerebral networks involved in cognition [3, 4]. In 1997, Leiner and Leiner proposed that the cerebellar circuitry is akin to that of a computer in its structural organisation, and it has wide communication activities, as reflected by activation (as seen by functional imaging) of the cerebro-cerebellar system during the performance of complex motor, sensory, cognitive, linguistic, and affective tasks in humans[8]. Today, standing on knowledge obtained from disciplines like anatomy, physiology and functional neuroimaging among others, cerebellar cognitive neuroscience has become an established multidisciplinary field of investigation [4].

2. Cerebellum in the Beginning

The earliest references to the cerebellum were believed to have been made by the Greek philosopher Aristotle (384-322 B.C.), differentiating it from the cerebrum in the fourth century B.C. [10]. At the time, he referred to it as the *para-encephalon*, not accepting it as an integral part of the brain. Other scientists like Galen (A.D. 131-200) considered it a worm-like outgrowth and therefore named it the vermis "*Epiphysis Scolexoides*" [11, 12]. The first recognition of the cerebellum as an integral part of the brain was credited to Herophilus (335-280 B.C.) [11]; while Erasistratus (310-250 B.C.), an Alexandrian scholar, suggested the involvement of the cerebellum in the higher cognitive abilities of humans [9, 13]. He (Erasistratus) associated the extensive gyrification of the human cerebellum with intellectual abilities [9, 13]; a theory further buttressed by Malarcarne (1744-1816), an 18th century Italian anatomist and surgeon. Between the 16th and 17th centuries, Vesalius (1514-1564) described the external features of the cerebellum, noting that it was about one-tenth the size

of the cerebrum [9, 10]; while one of his contemporaries, Estienne provided one of the first accurate illustrations of the cerebellar folia [13]. Towards the end of the 17th century, renowned physician and anatomist, Thomas Willis (1621-1675) suggested that the only function of the cerebellum was in the control of involuntary movement (respiration, heart beat). These views of Willis were however disproved in the early 18th century, when two French physiologists, Lorry (1726-1783) and Legallois (1770-1840) demonstrated that the control of respiratory function was localised in the medulla and not the cerebellum [13]. It was also around this period that Michele Malacarne wrote the first monograph which was dedicated entirely to the cerebellum; in it, he described in detail the external and internal structure of the cerebellum, suggesting a specie-specific correlation between the number of cerebellar laminae and intellectual capacity [14]. Up until the beginning of the 19th century, discussions regarding the function of the cerebellum remained largely speculative; however, it was during this century that a number of the initial theories and hypotheses became backed by scientific experiments. Three researchers; Luigi Rolando (1773-1831), Flourens (1794-1867), and Luciani (1840-1919)] helped shape our understanding of the cerebellum through a number of animal studies. Luigi Ronaldo, (using the chicken cerebellum) was able to show ipsilateral motor deficiency in cerebellar injuries; Flourens demonstrated that the cerebellum was more suited for modulation and control of movement rather than for production of movement [13] and Luigi Luciani described the three classical symptoms (atonia, asthenia and astasia) of cerebellar disease from studying the postoperative behaviours of decerebellate dogs [9, 14]. A number of other scientists like David Ferrier (1846-1928) who reported alterations in eye, head and neck movements from electrical stimulation of the cerebellum in dogs, and Jan Purkyne (1787-1869) who described the neurons in the cerebellum which was later named after him (Purkinje neuron), contributed in no small measure to our knowledge of the cerebellum today.

Early in the 20th century, renowned scientists like Charles Sherrington (1857-1952), Joseph Babinski (1857-1932) and Gordon Morgan Holmes (1876-1965) revolutionised our understanding of cerebellar function. Charles Sherrington was of the opinion that the cerebellum could be described as the control centre of the proprioceptive system, also suggesting that an adequate description of cerebellar function was limited by gaps in knowledge [15]. Joseph Babinski by direct observation of patients, noted the inability of patients with cerebellar dysfunction to perform rapid successive voluntary movements, coining the term '*diadokokinesia*', a Greek terminology meaning successive movements and '*adiadokokinesia*' to connote the inability to perform this action [13]. Gordon Holmes

studying gunshot victims of World War I contributed extensively to the understanding of human cerebellar functions in health and disease, confirming Luciani's observations of atonia, asthenia, and astasia [13, 15, 16]. Holmes also described the presence of cerebellar ataxia in these patients [15, 16]. The first functional organisation of the cerebellar cortex was done in 1906 by Dutch anatomist Lodewijk Bolk who divided the cerebellum into four main regions, the anterior lobe, the posterior vermis, and the two cerebellar hemispheres. He further divided each region into lobules consisting of folia [15, 17]. In the later parts of the 20th century the efforts of researchers like John Eccles, Masao Ito and Janos Szentágothai and their collaborators provided a full description of the cerebellar cortex neural circuitry, characterising each cell type [18].

3. Evolution of the Cerebellum

Over the last decades, tremendous success has been recorded with regards to research into cerebellar function. Historically, the cerebellum was linked to the control of posture, gait, skilled voluntary movement, control of motor learning, and coordination of movements [2-4, 19-22]. More recently, there have been new insights into to the more robust roles of the cerebellum, in both health and disease. Evidence from functional imaging studies suggests that the cerebellum is involved in cognitive processes/cognition [23-29], language and executive functioning [30].

A dramatic shift in the understanding of cerebellar function has occurred in the last 25 years or more, there are reports suggesting that large portions of the cerebellum are associated with neocortical networks that are involved with cognitive function [1]. The cerebellum's cognitive functions are mediated through reciprocal connections with regions (prefrontal, frontal, temporal, parietal and occipital cortices) of the cerebrum [2, 31-33]. This paradigm shift began in the early 1980s when Henrietta Leiner and her colleagues [26] in a review, suggested that the human cerebellum contained regions that were linked to cerebral association areas, based on studies that revealed that the lateral output nucleus of the cerebellum in apes and humans were larger compared to other species. Neuroimaging studies in the mid 1980s and 1990s went on to confirm these reports [34, 35]. Anatomical confirmation of the initially unpopular or controversial suggestions of a growing number of scientists came with development of anterograde tracing techniques, which allowed the injections of specific regions of the cerebral cortex and the study of their neural projections with relation to the pons; with the discovery that that specific regions of prefrontal cortex

associated with cognition projected to the cerebellum [36]. However, these controversies were finally resolved when studies using transneuronal tracing observed input and output projections between the cerebellum and cerebral association cortex [37, 38]. Evidence for cerebellar input in cognition have not been limited to its anatomy alone, there are neuropsychological [39] data that demonstrated cerebellar influence with respect to executive control, emotion, language, learning, pain, working memory [2], and addiction [40, 41]. Generally, the cerebellar oversight is modulated *via* its ability to enhance and sharpen precise timing of neural events, as well as promote the smooth control of rapid, stereotyped neural responses [32]. These mechanisms are believed to come to play irrespective of signal type [42, 43].

4. Neurobiology of the Cerebellum

The cerebellum (Figure 1) is a compact brain structure which is about one-ninth the volume of the cerebral cortex; however, it contains more than 80% of the neurons in the brain [44]. The primordium of the human cerebellum develops from cells of the rhombencephalon *via* the actions of the isthmus organizer [45]. The rhombencephalon is one of the three primary brain vesicles in the developing embryo; which divides in the seventh week into the metencephalon and myelencephalon. The metencephalon forms the cerebellum and pons, while the myelencephalon the medulla.

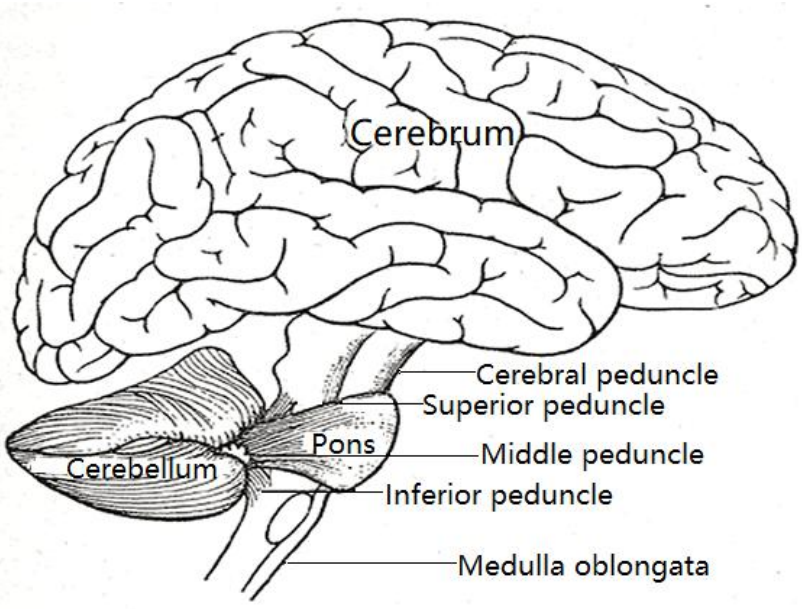

Figure 1 The schematic representation of the cerebellum, Henry Gray (1861).

The main events in the development of the cerebellum involve the establishment of two proliferative zones [45, 46], the dorsomedial ventricular zone giving rise to the interneurons of the deep nuclei and the Purkinje cells; these neurons are γ amino butyric acid (GABA) ergic [47]. This zone also gives rise to the Golgi cells, basket and stellate cells which are also GABAergic. The dorsolateral, subventricular zone of the rhombic lip is the second proliferative zone to develop; it gives rise to granule neurons as well as some neurons of the deep nuclei, these neurons are glutamatergic. The precursors of granule cell neurons form the external granular layer on the cerebellar surface [47]. The cells of the external granular layer migrate radially along the fibres of the Bergmann radial glial to form the internal granular layer. The rhombic lip has an upper and a lower lip; the upper limb gives rise to granule neurons while the lower lip, the olivary nucleus, which provide *via* climbing fibres, a crucial excitatory afferent input to the cerebellum.

The adult human cerebellum weighs about 150 g [48], which is about 10% of the weight of the cerebrum [49]. The cerebellum, like the cerebrum has a superficial layer of grey matter called the cerebellar cortex and a central core of white matter that also contains the peduncles. Anatomically, the cerebellum is divided into the flocculonodular lobe, vermis, and lateral cerebellar hemispheres. The cerebellar cortex (owing to the presence of numerous fissures) is much more extensive than is suggested from gross observation. The cerebellum is connected to other parts of the central nervous system by three paired cerebellar peduncles (superior, middle and inferior) relative to the vermis. The superior cerebellar peduncle carries efferent fibres from deep cerebellar nuclei *via* the thalamic nuclei to the upper motor neurons in the cerebral cortex. The middle cerebellar peduncle receives afferent from the pontine nuclei in the pons which are fibres relayed from the cerebral cortex. The inferior cerebellar peduncle receives afferent fibres from the vestibular nuclei, spinal cord and the tegmentum, and relay output *via* efferent fibres to the vestibular nuclei and reticular formation [50].

Microscopic anatomy of the cerebellum (Figure 2) shows a cerebellar cortex that is composed of a well-arranged, repetitive three-layered structure composed of outermost molecular layer, the middle Purkinje layer, and the innermost granular layer [51]; the granular layer rests on white matter. There are five main types of neurons described in the cerebellar cortex; these include: (1) the Purkinje neurons: a single layer of neurons found in the Purkinje cell layer, with large flask shaped cell bodies and a single dendrite arising from the neck of the cell body. The dendrite passes upwards into the molecular layer, where it divides to form an elaborate dendritic tree; while the axon passes downwards into the granule cell layer to enter the white matter, constituting the only efferents of the cerebellar cortex; (2)

Granule neurons (also known as granule cell), which are small, numerous, spherical neurons found in the granule cell layer. The cells occupy large parts of this layer, and spaces not occupied by them are known as cerebellar islands. Each granule neuron gives off three to five short dendrites which end in claw-like endings; these dendrites are specialised synaptic structures within the cerebellar islands and synapse with the terminals of mossy fibres. The axons of the granule neurons also enter the molecular layer and therein divide into parallel fibres which synapse with the dendrites of purkinje neurons, Golgi, basket and stellate cells; (3) Outer stellate cell and inner basket cells are confined to the molecular layer. The axons of stellate cells synapse with the dendrites of Purkinje cells while their dendrites synapse with parallel fibres of granule neurons. The basket cells lie in the deepest parts of the molecular layer; their dendrites ramify within the molecular layer intersecting with parallel fibres with which they synapse. They also receive recurrent collaterals from Purkinje neurons, mossy fibres and climbing fibres [48]; (4) Golgi cells are inhibitory neurons that are found in the granule cell layer [52]; their dendrites enter the molecular layer where they branch and synapse with the parallel fibres, some of these dendrites ramifies within the granule cell layer. Embedded within the white matter are masses of grey matter which constitute the cerebellar nuclei. These include; the dentate nucleus, which lies in the central portion of each hemisphere, the emboliform nucleus which lies medial to the dentate, the globose nucleus, which lies medial to the emboliform and the fastigial nucleus which lies close to the midline in the anterior section of the vermis [48, 51].

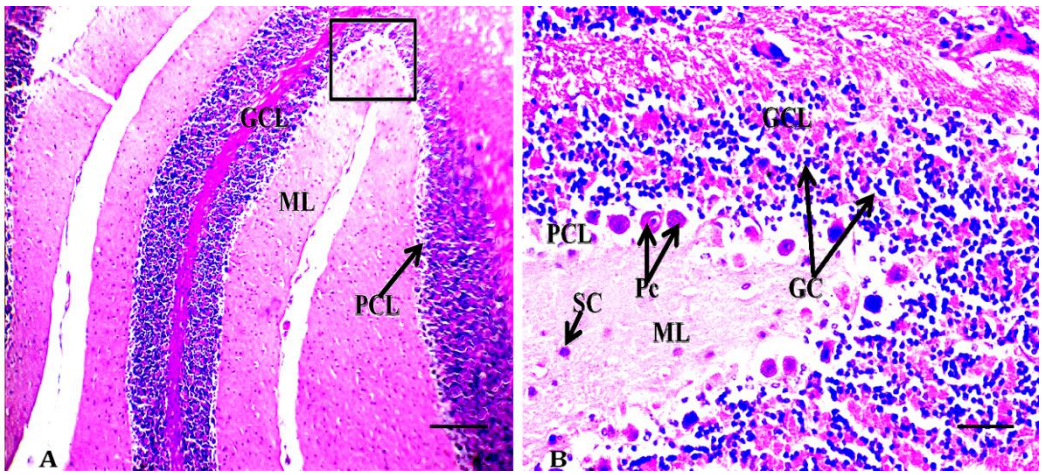

Figure 2. Microanatomy of the Swiss mouse cerebellum. A: Hematoxylin and eosin (HE) stain x 56; B: HE x 160. PC: Purkinje cell; PCL: Purkinje cell layer; GC: Granule cell; GCL: Granule cell layer; SC: Stellate cells; ML: Molecular layer.

Functionally, the cerebellum can be divided in three lobes; the flocculo-nodular lobe, anterior and posterior lobes (Figure 3). According to Larsell's classification, the cerebellum can be subdivided into 10 lobules (I to X) with the anterior lobe being composed of lobules I-V, the posterior lobe corresponding to the VI-IX and the flocculo-nodular lobe, lobule X [53, 54]. Larsell's nomenclature has impacted the understanding of symptom-lesion mapping in cerebellar disorders [55]. More recently, researchers have been able to show that the primary sensorimotor region is located in the anterior lobe and parts of lobule VI, posterior lobe (lobule VI, lobule VIIA which include crus I and crus II, lobule VIIB) correspond to the cognitive cerebellum and the flocculo-nodular lobe is vestibular [55, 56].

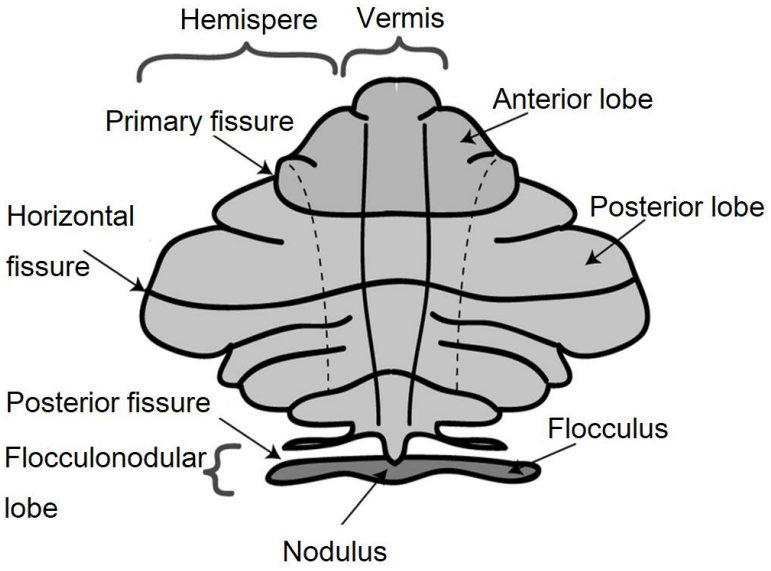

Figure 3. Schematic representation of the three anatomical subdivisions of the cerebellum.

4.1. Topographic organisation of the cerebellum

In 1940, Jan Jansen and Brodal described a longitudinal organisational structuring of the cerebellum into three zones hemispheral, paravermal and vermal, based on the topographic projections of Purkinje cells to the deep cerebellar nuclei [57, 58]. The arrangements of the Purkinje fibres were such that the projections of individual fibres projected to distinct cerebellar nuclei and different descending pathways, enabling the control of different aspects of movement [57]. The idea of a somatomotor topographic representation of the cerebellum, which stemmed from the results of electrophysiological studies [59] that demonstrated an inverted somatomotor map in the anterior lobe, and an upright map in the posterior lobe [6, 60] has continued to gain momentum. The advent of transneuronal tracing techniques also

provided direct evidence of anatomical connectivity between cerebral motor areas and specific regions of the cerebellum [38]. Human neuroimaging studies like the task-based functional magnetic resonance imaging (fMRI), and high-resolution fMRI also confirmed somatomotor representations within the cerebellum [61].

Evidences from studies using monkeys have identified gaps in the somatomotor maps of the cerebellum, which has raised the question of what is mapped to these intervening regions. Theories that have been considered include the existence of multiple repeated somatomotor maps, which could create regions within the cerebellum with different representations; Schlerf *et al.* [62] also demonstrated evidence for a second somatomotor map posterior to the primary fissure, with suggestions that this second map was for complex skilled movements. A second theory was the possibility of cerebellar mapping to non-motor regions of the cerebral cortex, including areas involved in cognition. Buckner *et al.* [6], in a study using dataset from 1000 healthy subjects, evaluated the functional organisation of the human cerebellum using resting-state functional connectivity MRI, and demonstrated that a very large part of the human cerebellum (*e.g.*, cerebellar areas Crus I, Lobule VI, and VIIb) was mapped to association areas in the cerebral cortex. These cerebellar regions possessed separate anterior and posterior representations oriented as mirror images of one another. Crus I, Lobule VI, and VIIb correlated with regions of the cerebral cortex like the dorsolateral and dorsomedial prefrontal cortex, which are related to cognitive control. They concluded that this orderly topographic representation suggested the presence of at least two large, homotopic maps of the full cerebrum in the cerebellum, with the possibility of a smaller third map [6].

4.2. Cerebellar circuitry

The cerebellar cortex circuitry is one of the best-defined in the central nervous system; playing an integral role in the sensory control of motor function [63, 64]. The cerebellum, though made up of cells distributed within lobules [65, 66], has a well characterised cellular architecture, with an array of zones forming a topographic map. This arrangement is based on observations that climbing fibres (CF) which are afferents arising from the inferior olive are organised in parasagittal bands within the cerebellar cortex, such that neurons in the inferior olives project to Purkinje neurons (PN) localised in narrow, rostrocaudal bands [67]. Mossy fibre (MF) and the mossy fibre to parallel fibre (PF) pathway also compliment this arrangement, by the contribution of afferents, arranged in longitudinal bands to the PN. This tripartite arrangement is thought to subdivide the otherwise homogeneous cerebellar cortex

into numerous bands called ‘zones’ or ‘patches’ [63, 68]. These zones are dedicated to processing signals that originate from individual body regions or sensory modalities [67]. In the last few decades, more insights into cerebellar circuitry have enabled the further division of these zones into smaller anatomical and/or functional units called modules [57, 63, 68] or microzones [58, 69-71]. Cerebellar modules have been regarded as a key feature of cerebellar functions [57, 72]. However, in spite of a detailed knowledge of the cerebellar circuitry, understanding of the functional significance of these connections is still evolving [57, 63, 73].

The cerebellar micro-circuitry (Figure 4) begins with afferent MF conveying to the cerebellar cortex a large number of input signals representative of almost all kinds of information processed by the central nervous system; with each MF distributing signals to over 500 granule cells (GC) [28]. GCs are arguably the most abundant cell type in the central nervous system, with about 69×10^9 neurons in the human cerebellum [74]. Axons arising from GCs ascend toward the pial surface bifurcating in a T-shape, giving rise to PF which run in the transverse plane along the major axis of a folium. Evidence from the rat cerebellum demonstrates that these PFs excite PC dendrites along a distance of about 3 mm, forming about 300 synapses with PCs [28]. The extensive dendritic tree of PCs could have been likened to a bi-dimensional matrix with greater than 100,000 elements [75]. The PC also receives inputs from a single CF, which generates a powerful postsynaptic depolarisation, resulting in a train of action potentials, called the complex spike which results in a rise in intradendritic calcium (Ca^{2+}) concentration [76]. The PCs process incoming signals and generate output that leaves the cerebellar cortex *via* their axons; PC axons are the sole efferent fibres from the cortex to the deep cerebellar nuclei (DCN).

4.2.1. Purkinje neuron: The core of cerebellar circuitry

Purkinje neurons are GABAergic (inhibitory neurons) that modulate the activity of other neurons in the cerebellum [77]. Purkinje cells express a number of molecules in either a zebrin II-positive or zebrin II negative parasagittal banding pattern [73]. The relationship between Purkinje neuron, other cerebellar neurons and the deep cerebellar nuclei have been studied extensively [78-80]. Purkinje cells are a focal point for the convergence of two pathways; the climbing fibres from the inferior olive, and the mossy fibres which arise mainly from the pontine nuclei *via* parallel fibres of the granule cell layer. The Purkinje cells are the only output neurons of the cerebellar cortex, projecting axons to the deep cerebellar nuclei [81], where they form GABAergic synapses. They receive inputs from climbing and

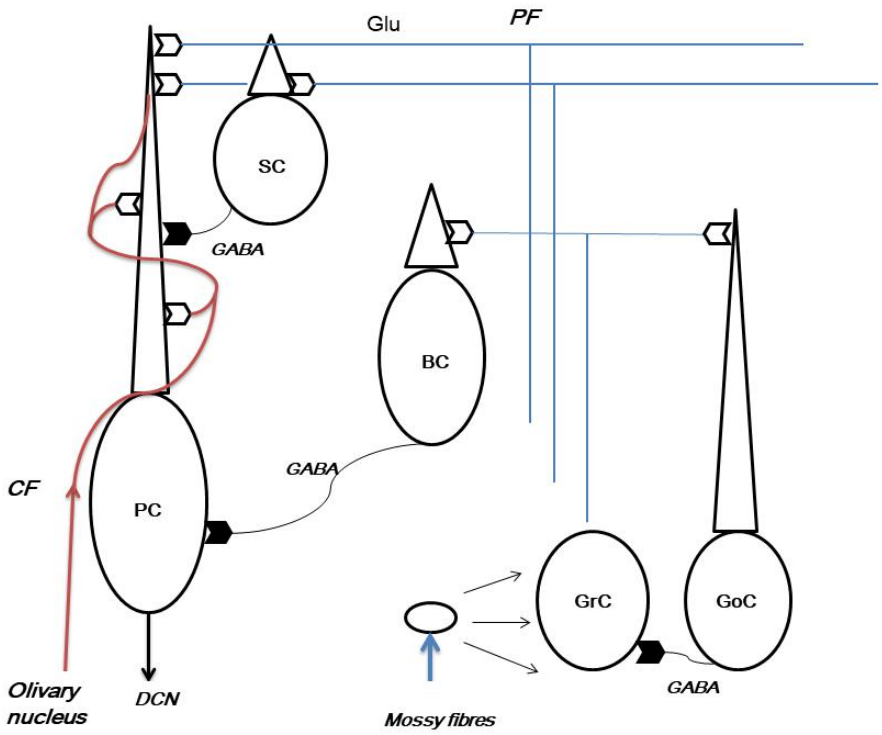

Figure 4. Neuronal circuits surrounding a Purkinje cell and neurotransmitters in the cerebellum. PC: Purkinje cell; SC: Stellate cell; BC: Basket cell; GrC: Granule cell; GoC: Golgi cell; PF: Parallel fibre; CF: Climbing fibre; DCN: Deep cerebellar nuclei; mossy fibre ⋗: Excitatory synapses; ⬬: Inhibitory synapses. Neurotransmitter candidates are shown beside each synapse. Glu: Glutamate, GABA: γ-aminobutyric acid.

mossy fibres, hence forming a cortico-nucleo-olivary loop that lies at the core of cerebellar function [82, 83]. Purkinje cells also form Purkinje-Purkinje cell axon collaterals, which extend through the granule cell layer and project back to the Purkinje cell layer, although occasionally projecting through the molecular layer [84]. There are suggestions that the Purkinje neuron plays an integral role in the normal functioning of zonal patterning [73, 85]. However, the relationship between the synaptic connections of Purkinje cells and development of zones is still contested [58]; also disputed is the role played by Purkinje cell local collaterals in zonal patterning and synaptic plasticity [86]. A number of researchers have however suggested that for normal development, the functioning of zones and the differential sensitivity to disease may depend on the molecular phenotypes of Purkinje cells [73, 85]. White *et al.* [58], in testing the hypothesis that Purkinje cells were crucial to zonal development, selectively blocked Purkinje cell transmission and found out that the inhibitory effects of the Purkinje cell was crucial in cerebellar zonal patterning and the development of

spino-cerebellar afferent topography. From their study, they also deduced that *in-vivo* synaptic neurotransmission was essential in zonal patterning [58].

The inhibitory responses of the Purkinje cells are also modulated by inputs from other cerebellar neurons (granule, stellate, basket and Golgi ells). The basket cells form powerful inhibitory complexes of synapses around the cell bodies of the Purkinje cell; and the stellate cell, upon receiving input from the parallel fibres, provide an inhibitory input to the dendrites of the Purkinje cell. The Golgi cells which have their apical dendrites in the molecular layer and cell bodies in the granule cell layer, receive input from the parallel fibres and provide inhibitory feedback to the granule cells (from which parallel fibres originate) [87]. The GC exhibits a stereotypic pattern of functional connectivity to the Purkinje cells; GCs immediately medial to a given Purkinje cell are excitatory, whereas GC located more laterally are inhibitory, a classic example of lateral inhibition in the cerebellum [88, 89].

4.2.2. Cerebellar interconnectivity

The cerebellum is connected to different regions of the cerebral cortex, and by so doing has been reported to exercise oversight over regions involved in the control of movement, reward/motivation, sensation, language [2, 90], attention [91], memory and executive function [23], and social processing [92, 93]. The cerebellum is linked to the contralateral cerebrum, *via* two polysynaptic circuits (1) an input channel to the cerebellum *via* pontine synapses; and (2) an output channel projecting to the cerebral cortex which first passes to the deep cerebellar nuclei, *via* the thalamus [36]. The projections from the cerebellar cortex to different regions of the cerebral cortex originate from distinct output channels within the deep cerebellar nuclei; the cerebral cortical area that is the target of each output channel is also a major source of input to the channel. Thus creating a closed-loop circuit, that is the backbone of cerebro-cerebellar interactions [2].

4.2.3. Cerebellar neurotransmitters, neuromediators and receptors

In addition to glutamate and GABA (neurotransmitters which are intrinsic to the cerebellum, Figure 4), the cerebellar cortex also receives projections from neuromodulatory neurons which release dopamine, acetylcholine, norepinephrine, and serotonin [94]. The cell bodies of these neurons, which are grouped in specific brainstem nuclei, are distributed all over the cerebellar circuitry *via* their widespread projections. The GABA receptor is a member of the family of ligand-gated receptor-channel complex. Activation of this receptor

results in the opening of chloride channels and the inhibition of neurons. In the cerebellar cortex, the position, origin, and role of GABAergic synapses are well characterised since the anatomical classification of their pre- and post-synaptic elements are easily identified. Numerous studies have reported the regional distribution of the $GABA_A$ receptors using ligand-binding autoradiographic or immunocytochemical studies [95-98]. GABA immunoreactive receptors were found on all classes of cerebellar neurons with the exception of Golgi cells [96]; the somatic and dendritic membranes were also immunopositive, although no immunoreactivity was observed in the axons. $GABA_B$ receptors have also been localized perisynaptically at excitatory parallel fibre synapses on Purkinje cell dendritic spines [99].

In the cerebellum, three types of glutamate *N*-methyl-*D*-aspartate (NMDA), a-amino-3-hydroxy-5-methyl-4-isoxazole proprionate (AMPA) and metabotropic glutamate (mGluRs) receptors have been identified [100-102]. The NMDA receptors are heteromeric ligand-gated ion channels with two families of subunits (NR1 and NR2). The NR1 subunit has at least eight splicing variant isoforms while the NR2 has four (NR2A, NR2B, NR2C and NR2D), all subtypes of NMDA receptors are found in the cerebellum [100]. The AMPA receptor is a non-NMDA-type ionotropic trans membrane glutamate receptor that is composed of four receptor subunits (GluR1, GluR2, GluR3 and GluR4); it mediates fast synaptic transmission. The AMPA receptors on Purkinje cells are involved in the induction and expression of long-term depression (LTD) [103]; and cerebellar synaptic plasticity [104]. mGluRs belong to the G-protein-coupled receptor (GPCR) superfamily of seven transmembrane domains. Eight genes that encode different subtypes of mGluRs have been identified and numbered accordingly in the order of cDNAs cloning. All of these mGluR subtypes are found in the cerebellar cortex with the exception of mGluR6 which is expressed exclusively in the retina [102]. Also localised in the cerebellum are the ð glutamate receptors (d_1 and d_2), which constitute a separate family of proteins which on the basis of their amino acid sequence, have been positioned between the NMDA and AMPA receptor families [105, 106]. The d_2 glutamate receptors have been reported to be prominently expressed in Purkinje cells and are co-expressed with ionotropic receptors in the postsynaptic membrane. They are also thought to play important roles in the induction of cerebellar long-term depression [107], for details see review by Hoxha *et al.* [75].

The discovery of dopaminergic fibres in the cerebellum arose from the need to determine the source of cerebellar dopamine; following suggestions that dopamine in the cerebellum was a precursor of noradrenaline in the afferent fibres of the locus coeruleus

neurons, and also an independent transmitter in the neural system [108]. The cerebellar dopaminergic projections arise from projections from the A10 dopaminergic cell group in the ventral tegmental area [108]. These dopaminergic fibre projections terminate mainly in the granular cell layer, and Purkinje cell layer. In these regions, they are distributed mainly in the crus I ansiform lobule and paraflocculus, and to a lesser extent in the crus II ansiform lobule [108]. Studies have reported that in the cerebellar cortex, Purkinje neurons showed the most dopamine receptor protein immunoreactivity [109]. Dopamine-influenced cerebellar plasticity in Purkinje cells occur *via* a dopamine and adenosine 3V:5V-monophosphate (cAMP) regulated phosphoprotein of M(r) 32 kDa (DARPP-32,) [110] regulation of cerebellar long-term depression, and expression of rebound potentiation [111].

Serotonergic influences in the cerebellum stem from the presence of a large serotonergic fibre input (third in size after the mossy and climbing fibres) that modulates all parts of the cerebellar circuitry *via* a number of serotonergic receptors [112, 113]. The cerebellar serotonin input arises from neurons in the medullary and pontine reticular formation [114, 115], and also from the raphe nucleus [116, 117]. Within the cerebellar cortex, serotonergic fibres form a dense plexus throughout the granule cell and Purkinje cell layers [94]. A serotonergic input (with the same topographical organization as the mossy fibres) accompanies the cerebellar mossy fibre input; also within the cerebellar nuclei, there is a dense plexus of serotonergic fibres [115], which carry afferents from a number of brainstem nuclei.

Anatomical and pharmacological studies have demonstrated that the cerebellar cortex expresses multiple subtypes of serotonin receptors (5-HTR); with the PC expressing the 5-HT_1, 5-HT_2, 5-HT_5 and 5-HT_7 subtypes, and GC expressing 5-HT_3 and 5-HT_6 [113]. 5-HT has the potential to modulate both excitatory and inhibitory synaptic signals in the cerebellum; activation of 5-HT_1Rs causes a suppression of cerebellar cortex activity by reducing glutamate release from PF to PC [118], and increasing inhibitory synaptic transmission to PC [119]. Lippiello *et al.* [120], using patch-clamp recordings in cerebellar slices of adult mice, demonstrated that 5-HT_7 receptors are important in synaptic plasticity of the PF-PC synapse. They reported that activation of 5-HT_7 receptors by a selective agonist resulted in LTD of the PF-PC synapse. The cerebellar norepinephrine input, like the serotonergic input also modulates all parts of the cerebellar cortex; however the innervation pattern is patchy. Cerebellar noradrenergic fibres originate from the dorsal and ventral parts of the locus coeruleus and project to all parts of cortex [121]. These fibres are found around the PC dendrites and around glomeruli that make close contacts with GC dendrites. Norepinephrine

modulates the cerebellum *via* its activities at presynaptic adrenergic receptors on basket cells [122, 123], beta-adrenergic receptors [124] and beta-adrenergic modulation of GABAergic neurons in the deep cerebellar nuclei [125]. Studies have demonstrated that cerebellar NE levels correlate with cerebellar learning; with increase in NE content accompanying exposure to novel learning environment [125], a significant decrease in the ability to learn a novel motor task in rats following the loss of the modulatory effect of NE [126], and impaired novel locomotor task acquisition with depletion of NE levels [127].

Results from *in situ* hybridisation and immunostaining studies have revealed that the cerebellar cortex expresses mRNA for all subtypes of α_1 and α_2 adrenergic receptors [128], with immunostaining demonstrating a strong expression of α_{1A}, α_{2A} and α_{2B}-AR [129, 130] and expression of β_2-AR [131] in the PC and interneurons of the molecular cell layer. Electrophysiological studies have also demonstrated that activation of the locus coeruleus [132], or iontophoretically applied norepinephrine [133] induces a depression of spontaneous discharges in PCs. These effect have been associated with the potentiation of inhibitory GABAergic transmission at basket cell-PC synapses (actions that are mediated by presynaptic β_2-ARs) [119, 134], or inhibitory effect at the CF-PC synapse, resulting in a decreased glutamate release from CFs (mediated by presynaptic α_2-ARs) [135].

The cerebellar cholinergic input is a diffuse plexus of beaded fibres in the cerebellar cortex and nuclei. They originate largely from the pedunculo-pontine tegmental nucleus, lateral paragigantocellular nucleus, as well as in the raphe nuclei [136]. The presence of cholinergic innervation to the cerebellum was demonstrated using antibodies against choline acetyltransferase (ChAT); when this was combined with retrograde tracing, it revealed a significant amount of ChAT-positive mossy fibres in the flocculo-nodular lobe (originating mainly from the vestibular nuclei), and a moderate number of ChAT-immunoreactive fibres in the DCN [136].

The cerebellum also expresses both muscarinic and nicotinic cholinergic receptors; the muscarinic receptors which are mainly M_2-type are localised throughout the cerebellar cortex, particularly in the cerebellar nuclei and molecular layer of nodulus. It also expresses several subtypes of nicotinic acetylcholine receptors (nAChRs) [137]. Acetylcholine modulates strong and long-lasting increase in the Purkinje cell glutamate response [138] and may potentiate GC-PC synapses, *via* muscarinic acetylcholine receptors [138]. The nicotinic acetylcholine receptors have also been suggested to modulate cerebellar activity of PCs in the deep nucleus [139].

5. Cerebellum and Cognition

The first insight into the cerebellum's role in cognition was gained when human functional neuroimaging studies (evaluating brain areas that are involved in cognition) observed cerebellar response to cognitive stimuli which could not be explained by motor demands. This observation challenged the well-entrenched view that cerebellar function was solely limited to motor-processing [2]. For decades after this, the role of the cerebellum in cognition continued to be debated; and a few prominent researchers were of the opinion that available evidence did not support a non-motor role for the cerebellum [140]. Therefore, the overwhelming emphasis of literature remained unwavered from the focus on motor control. The emphasis on motor control stemmed partly from the peculiar features of the cerebro-cerebellar circuitry, which prevented the use of traditional anatomical techniques in describing the full organisational property of the cerebellum [1]. Recurring evidence from neuroimaging studies (which allow the surveillance of brain activity in living subjects performing cognitive tasks), insights from anatomical studies, and clinical presentation of patients with cerebellar cognitive affective disorder were major factors in driving the reconsideration of the cerebellum's non-motor functions [27, 30, 36, 38]. In the last decade, the idea of the cerebellum's involvement in other roles like cognition is becoming more popular, moving gradually from the sphere of fringe to contemporary science; there is also an increasing interest in the cerebellum's role in emotion [141].

5.1. Cerebellum and cognition: Evidence from computational studies

The description of a detailed micro-circuitry of the cerebellum, and the discovery that the cerebellar cortical microcircuits seem to be structurally-similar, gave rise to the idea of a 'cerebellar algorithm'. A number of hypotheses were proposed, leading to microcircuit models by Marr [21] and Albus [22]; these models differed in a number of areas, although their commonalities gave rise to the 'Marr-Albus framework' of cerebellar function, which has been influential in experimental and theoretical investigations. The Marr–Albus based models have been applied in the understanding of a wide range of behaviours, including the vestibulo-ocular reflex [142, 143] classical eyeblink conditioning [144], limb control [143] and high-level interpretations of cerebellar function; with respect to its ability to act as: an internal model [145, 146] a state estimator [147] or a Smith predictor [148]. The cerebellum has been described as a collection of elementary processing units (ePU) which share processed input data and influence one another, with only a limited number of collaterals

arising from the output fibre [149]. A large part of research in computational-modelling of the cerebellum had focused on motor control, possibly due to the prevailing dogma (at the time) on the role of the cerebellum in motor coordination. Computational models of the cerebellum have demonstrated that although major areas of the cerebellum are linked with motor systems, the D2 zone is linked with the cerebral association cortex, an area important to cognition [2, 33, 70]. The major computational models of the cerebellum include the network models like the adaptive filters [150, 151] and Simple Perceptron [152]; and control system models such as the model-based control [153] and adaptive control [154], which have been generally applied to movement and motor control. Presently, the roles of these models (or other models) in the improvement of our understanding of the cognitive functions of the cerebellum is evolving.

5.2. Cerebellum and cognitive processing

Cognitive functioning in the central nervous system generally depends on the plasticity mediated by NMDA and GABA receptors. These receptors and their neurotransmitters are found in the cerebellum. Hypofunction of the NMD-R modulation of the inhibitory GABAergic interneurons results in reduced GABAergic inhibitory tone. This in the long-term results in an initial injury to target neurons from glutamate excitotoxicity, which result from increased neurotransmission at ionotropic glutamatergic AMPA, kainite, and cholinergic receptors; the subsequent cell damage causes a final hypoglutamatergic state [155]. The neuroanatomical basis of the cerebellum's role in cognition and affective processing is the presence of a dense network of crossed cerebro-cerebellar pathways which consists of cortico-ponto-cerebellar and cerebello-thalamo-cortical loops establishing close connections between the cerebellum and the supratentorial motor, paralimbic and association cortices that modulate cognitive processes [156]; neuroimaging and lesion-behaviour studies have been used to demonstrate somatotopic organisation of the human cerebellum for higher-order cognitive and affective functions [156].

The involvement of the cerebellum in cognition in humans was demonstrated using the verbal working memory tests (VWM); which involves a subject's ability to store verbalizable (alphabets, words, numbers, or nameable objects) information temporarily. Baddeley [157] described it as a phonological loop *via* which speech-based information is stored and rehearsed. Using the VWM, researchers determined that motor and non-motor cerebellar contributions to working memory in the two-stages of the phonological loop differed from

one another. Superior cerebellar lobule (VI) and Crus (I) initiate internal motor sequences during information encoding while the Inferior cerebellar lobules (VIIb/VIII) support storage during the maintenance of verbal information. Evidence of cerebellar involvement in VWM also followed reports of mild to moderate VWM deficits in patients with cerebellar infarctions [158, 159] tumours [160, 161] and spinocerebellar ataxia [162, 163] compared to healthy, age-matched controls. The cerebellar cognitive affective syndrome is a clinical representation of the cerebellum's role in cognition.

5.3. Cerebellar long-term depression and potentiation

In neurobiology, it is generally accepted that storage of information in the brain is dependent on long-term, use-dependent alterations in synaptic strengths; which in the cerebellum involves long-term depression (LTD) and long-term potentiation (LTP). LTD is a form of synaptic plasticity that occurs at excitatory synapses and involves the co-activation of climbing and parallel fibre (PF) inputs to PC, inducing a persistent input-specific depression of the parallel fibre-Purkinje neuron (PF-PC) synapse that is expressed as reduced responsiveness to transmitter glutamate, and promotes adaptation of the vestibulo-ocular reflex and eye-blink conditioning [164].

LTP occurs when the PF-PC synapse is strengthened by repetitive parallel fibre stimulation, thus endowing the synapse with the capacity for use-dependent bidirectional modification which may result in the extinction of learned associations in previously trained animals [165]. The reversibility of synaptic plasticity that occurs following both LTP and LTD has been linked to motor learning [165]. However, recent studies have demonstrated that (1) LTD may not be essential for cerebellar motor learning [166]; (2) LTP may be more important in motor learning than previously considered [167]. There have also been suggestions of the involvement of other synapses in synaptic plasticity; for example, postsynaptic LTDs that occur at climbing fibre-purkinje neuron synapses [168] or rebound potentiation (RP) that follows activation of an inhibitory climbing fibre synapse on a Purkinje neuron, resulting in the enhancement of GABAergic transmission [169]. PF-PC synapses have been reported to undergo two forms of LTP, expressed either presynaptically (repetitive stimulation of PF at higher frequency) or postsynaptically, which involves repetitive stimulation of PF at lower frequency [170, 171]. The expression of postsynaptic LTP is believed to extinguish LTD, while the expression of presynaptic LTP leaves LTD still saturated [172].

5.4. Cerebellum and social cognition

Social cognition is the ability to infer the social implications of behaviours (self, or those of another person, "body" reading) and/or the state of mind [173]. Emotion attribution from faces has been reported to be crucial to social cognition, and deficits in perception of facial emotions underlie a number of cerebellar pathologies [174]. A large part of research in this area had been directed to the cerebrum and core areas of the cortex that support social-reasoning and cognition [175]; however, recent evidences supporting the involvement of the cerebellum in cognition has attracted increased interest in studying the possible role of the cerebellum in social cognition. A number of studies examining the role of the cerebellum in social cognition in humans have reported evidence of robust clusters in the cerebellum, with demonstrable activity in one third of the social-cognitive studies, and in all studies involving more complex and abstract social inferences [176-178]. It has also been argued that the cerebellar clusters involved in social cognition during mind and body-reading, overlap with the default and somatomotor networks [1, 6]. Van Overwalle *et al.* [179] found large overlaps between the clusters such as (1) social mentalising and the mentalising/default network of Buckner *et al.* [6]; and (2) social behaviour understanding and the somatomotor networks of Buckner *et al.* [6]. Although there is no consensus yet on the roles of the cerebellum in social cognition, results of connectivity analysis and clinical studies support a critical role for the cerebellum in social mentalising and emotional attribution from faces. A domain-specific mentalising connectivity between the cerebrum and the cerebellum has also been demonstrated; however, the basic processes underlying the propagation of information between the cerebrum and the cerebellum are evolving.

5.5. Therapeutic options for Cerebellar cognitive affective disorder

In adults and children, cerebellar lesions can manifest as complex behavioural patterns which has been termed 'Cerebellar Cognitive Affective Syndrome' [180]. Initially defined as arising from acquired causes, cerebellar cognitive affective syndrome (CCAS) is now known to stem from an array of causes such as developmental cerebellar disorders [181, 182] and hereditary ataxias [180, 183]; or follow acute cerebellar lesions like haemorrhage, stroke or cerebellitis [180]. In children, underlying lesions could be prenatal, early postnatal, or developmental in origin [184].

The syndrome is characterised by impaired cognitive efficiency, associated with specific neuropsychological deficits (executive and visuospatial disorders), disorders of language

expression (mild agrammatism, dysprosodia and anomia), affective disorders (with blunting of affect) and personality changes (disinhibited and inappropriate behaviours) [4, 180, 185]. The deficits seen in CCAS are ascribed to impairment of the modulatory effects from reciprocal pathways that link the cerebellum to the limbic circuitry and the prefrontal, temporal and parietal association cortices [56]. Topographical deficits affecting the cerebellar vermis induce affective and social disorders; while those of the cerebellar hemispheres are more frequently associated with selective neuropsychological deficits involving mainly executive functions, visuospatial and linguistic abilities [182]. The description of CCAS openly challenges the long-held view that the cerebellum is only important in the regulation of motor functions, and brings to the fore, the importance of the cerebellum in cognitive processing.

Therapies for CCAS include cognitive behavioural therapy and pharmacological agents; alternative therapies such as deep brain stimulation have also been considered. However, since it is a syndrome that could arise from a variety of causes, therapy often needs to be tailored to individual cause/need; also, it is possible that some of the symptoms may spontaneously improve over time. Pharmacological treatment for traumatic and post-surgical brain injuries has shed light on the application of drugs to CCAS management; and literature has shown that pharmacological agents are applicable to the treatment of cognitive and behavioural deficits resulting from traumatic brain injuries in adults [183]. Damage to cerebellar dopaminergic neuron groups, leading to impaired dopaminergic transmission has been implicated in akinetic mutism; and this may explain the potential use of dopamine agonists like bromocriptine in this subset of CCAS. Aripiprazole, a partial dopamine agonist has also been reported to be successful in treating CCAS-associated impairment of executive cognitive and emotional functions following resection of posterior fossa tumour in a patient [184].

Attentional problems and disinhibited behaviours are some of the symptoms of CCAS; methylphenidate, an inhibitor of reuptake of dopamine and norepinephrine (which permits increased availability of norepinephrine and dopamine at the synaptic space) has been used successfully in children with attention and behavioural disorders, prompting its use in related pathologies that occur following brain injury. Methylphenidate was successfully used to manage symptoms in a female adolescent with cerebellar atrophy presenting with an episode of CCAS/attention deficit hyperactivity disorder (ADHD); control of symptoms was achieved by giving low doses of methylphenidate for a week [185]. Atomoxetine a selective norepinephrine uptake inhibitor used in the treatment of ADHD has also been evaluated in the management of CCAS. Studies have demonstrated its ability to decrease fatigue, improve

executive functioning and enhance short-term plasticity [186, 187]. Atomoxetine has been shown to restore prefrontal networks related to executive functions [188]; prompting suggestions that it may be useful in the management of attention and executive function deficits related to the cerebellum, such as those that follow posterior fossa surgery. Donepezil is a reversible, non-competitive acetylcholinesterase inhibitor which was developed as a symptomatic treatment for cognitive decline in Alzheimer disease [189]. As shown by earlier studies on the cerebellum, acetylcholine modulates strong and long-lasting increase in the Purkinje cell glutamate response [138]; and may also potentiate granule cell to Purkinje cell synapses, *via* muscarinic acetylcholine receptors [138]. The presence of a strong cholinergic connection within the cerebellum, suggest that enhanced cholinergic transmission through delayed degradation of acetylcholine might prove beneficial in the management of cerebellar cognitive deficits.

6. Conclusion

In the light of recent advances in the knowledge of the involvement of the cerebellum in a broad variety of non-motor functions; our understanding of the role of the cerebellum in cognitive, linguistic and affective processes has also increased significantly. However, specific targeting of cerebellar cognitive pathways for therapeutic benefits is not yet possible, due to the fact that we are yet to be able to identify, characterise and manipulate neurotransmitters or receptors that are unique to the cerebellum. Therefore, a lot of research is still needed to deepen our understanding of the non-motor roles of the cerebellum, especially, the cognitive functions; as this may open a new chapter in the management of cognitive disorders.

Conflict of Interest

Authors of this manuscript declare no conflict of interest related to the content of this manuscript.

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