

Review Article

Notes on the Role of the Cerebellum in ADHD

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Received: March 31, 2014; **Accepted:** April 01, 2014; **Published:** April 03, 2014

Abstract

The present article collects sources of evidence for the involvement of the cerebellum in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD) and reviews the proposed theories of the relationship between cerebellar pathology and behavioral manifestations of ADHD. We review the findings of motor symptoms in ADHD and their relationship with the cerebellum. Furthermore, we introduce the neuroimaging findings related to ADHD, its development and the cerebellum. Additionally, we briefly review the anatomical findings describing the substrate for cerebellar involvement in cognition and the findings of functional neuroimaging studies suggesting topographic organization within cerebellar regions specialized for motor, cognitive or emotional regulation. Finally, we introduce the current conceptualization of cerebellar involvement in ADHD.

Keywords: Attention-Deficit/Hyperactivity Disorder (ADHD); Cerebellum; Motor Symptoms; Internal Models

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a chronic, highly heritable, neurodevelopment disorder. The worldwide prevalence of ADHD is approximately 5.29% in the pediatric population [1] and 3.4% in adults [2]. The disorder is more common in boys than girls, although some studies suggest much lower frequency differences between sexes [3].

ADHD is characterized by developmentally excessive levels of inattention, impulsivity and hyperactivity [4]. In addition to these core features, ADHD is often accompanied by other symptoms, including executive dysfunction [5] and emotional control deficits [6]. Psychiatric comorbidity is frequent (60-70%) in ADHD, and its severity increases with age [7]. Generally, ADHD significantly impairs social, family, academic and occupational functioning [8].

Genetic studies consistently demonstrate that ADHD is familial [9]. The heritability of ADHD is approximately 76 %, which is one of the highest in psychiatry [10]. The genetics of ADHD are complex, with several interacting genes, and the most consistent candidate genes are those encoding monoamine neurotransmission-related structures and enzymes [11].

Despite the enormous number of studies and methods used, the pathophysiology of ADHD is not fully understood yet. Several plausible hypotheses have been formulated, suggesting deficits in inhibitory control [12], the regulation of motivation and reward [13], and arousal and activation [14].

Considerable progress in elucidating the pathophysiology of ADHD has been made thanks to neuroimaging studies. Initially, the research focused on prefrontal-striatal circuits because executive function deficits and reward delay problems associated with this network impairment are considered crucial for explaining the behavioral manifestation of ADHD [12]. However, an increasing number of studies found structural and functional disturbances of brain structures other than the prefrontal cortex and basal ganglia,

involving the parietal and occipital cortical areas and the cerebellum [15].

The conceptualization of ADHD is currently being remodeled. The field is moving to a dimensional view from that of a categorically defined disorder [16]. Additionally, we are moving towards research pertaining to large-scale brain networks [17] involving a number of previously omitted brain regions from the theories of single-structure impairment or single-circuit dysfunctions.

This is especially the case with the cerebellum, which was long understood to be a solely motor regulation structure. Despite many decades of cerebellar research, its acceptance to the family of “cognitive” brain regions is a matter of last twenty years. [18]. This acceptance has opened new insights but has also raised intriguing questions about the functioning of the ADHD brain.

Evidence for cerebellar involvement in ADHD

Motor symptoms in ADHD

Children with ADHD suffer a wide range of motor deficits with a frequency range between 30 to 50%. These childhood motor deficits predict a worse outcome in adolescence and adulthood [19,20-23]. Furthermore, a higher motor symptom score predicts the response to treatment with methylphenidate in ADHD children [24].

Research and clinical interest in the motor deficits associated with ADHD have waxed and waned over the past decades. However, there has been an increase in the ongoing debate about the relationship between motor regulation and the development of cognition [21,25-27] and the cerebellar role in cognition and affective regulation [28,29].

Typical motor problems of children with ADHD, categorized as neurological soft signs (NSS), include difficulties with balance, fine motor skill disability, mild dysfunction in muscle tone regulation, difficulties in coordination between the right and left arm or leg, choreiform dyskinesia and dysdiadochokinesis [30]. The scores of these NSS are useful in differentiating between children with ADHD,

typically developing (TD) children and children with pediatric bipolar disorder [31,32]. It has been documented that NSS may partially account for cerebellar dysfunction [30,33-35].

Several studies have focused specifically on the evaluation of cerebellar symptoms in ADHD subjects. They found higher scores in the ADHD group compared to typically developing children [36,31,37]. Cerebellar symptoms have also been associated with difficulties in spatial working memory in children and adolescents with ADHD [31] and variability in their reaction time, which represents one of the candidate endophenotypes in this disorder [37].

Neuroimaging of the cerebellum in ADHD

Structural neuroimaging studies suggest that ADHD is characterized by a mixture of fixed and progressive neuroanatomic deficits, and abnormalities in the cerebellum are very common [38]. In their large case-controlled study of 152 children with ADHD, Castellanos et al. found an overall reduction in cerebellar volume in the ADHD group compared to typically developing controls. Furthermore, their analyses revealed that the left cerebellar volume, together with the right globus pallidus volume and caudate symmetry, is a significant, independent predictors of ADHD patients versus controls [39]. Given the general research focus on the prefrontal cortex and basal ganglia and as a result of the leading fronto-striatal hypotheses of ADHD, the finding of decreased cerebellar volume was unexpected. However, the authors suggested a potential relationship of this result with the debate on the cerebellar role in executive functions [39]. Berquin et al. focused specifically on the cerebellum, and in a sample of 46 right handed boys (mean age 11.7 years) with ADHD, found significantly less vermal volume in the proband group, mainly in the posterior-inferior lobes (lobules VIII-X) but no reduction in lobules I-V or VI-VII (after adjustment for total brain volume and IQ) [40]. When only girls with ADHD were analyzed, Castellanos et al. (2001) found, in a reasonable sample (N=50), a significantly smaller posterior-inferior cerebellar vermis volume (lobules VIII-X) compared with typically developing girls [41]. Several smaller studies also found comparable results. Mostofsky et al. found a smaller posterior vermis (lobules VIII-X) size in a sample of 12 boys with ADHD (mean age 11.3 years, also after correction for overall brain size) with no significant differences for lobules I-V or VI-VII between the two groups [42]. In a group of 12 children with ADHD or ADHD and conduct disorder (8-12 years old), Bussing et al. reported a difference in the volume of the posterior-superior and inferior lobes of the vermis in pure ADHD patients, as well as in a comorbid group, compared to controls [43]. Finally, in a sample of 23 children (mean age 9.35 years) diagnosed with ADHD, significantly smaller cerebellar lobules I-V and VIII-X were found, but no group differences were observed for the total cerebellar volume or for the area of cerebellar lobules VI-VII [44]. Cerebellar structural abnormalities may also explain a significant amount of the variance in the parent-reported levels of ADHD symptoms in a recent study of children with the combined subtype of ADHD [45].

Developmental trajectories of the cerebellum in ADHD

When looking at developmental trajectories of structural abnormalities measured in their cross-sectional study [39], the authors found a fixed, non-progressive reduction in the total cerebellar volume, and this reduction was among the most persistent

anatomical deviations in both boys and girls [15]. Mackie et al., using an advanced method of scan analysis, reexamined longitudinal data from the brain scans of 36 children with ADHD from the study mentioned above [46] and found that the ADHD group had a non-progressive loss of volume in the superior cerebellar vermis, and the volume loss persisted regardless of their clinical outcome [46]. Similar to what Castellanos et al. suggested in their cross-sectional measures, where cerebellar volumes (together with the frontal and temporal gray matter and the caudate) correlated significantly with parent and clinician ratings of the ADHD severity [15], a longitudinal analysis also found a relationship between structural development and clinical measures [46]. Patients with ADHD who exhibited decreasing volumes in the right and left inferior-posterior cerebellar lobes had worse clinical outcomes [46].

Recently, Ivanov et al. found smaller regional volumes in the lateral surface of the left anterior and the right posterior cerebellar hemispheres in a sample of 46 children and adolescents with ADHD compared to controls. Furthermore, stimulant medication was associated with larger regional volumes in the left cerebellar surface. Similar to the findings of Mackie et al. (2007), this study found that more severe ADHD symptoms were associated with smaller regional volumes in the vermis [47].

Cerebellar involvement in dopaminergic neurotransmission.

Although the dopamine receptors are minimally present in the cerebellum, cerebellum is involved in regulation of dopaminergic neurotransmission by indirect mechanisms. Dopamine transporter (DAT) have been localized in the posterior-inferior vermis in the non-human primate [48], however DAT serves here to regulation of noradrenergic rather than dopaminergic neurotransmission [49]. Nevertheless, it has been found that the vermis and paravermal regions of the cerebellum have a modulatory effect on the turn-over rate of dopamine and noradrenaline in the caudate and nucleus accumbens [50]. Thus abnormalities of the cerebellar vermis in ADHD patients may impair dopaminergic neurotransmission in basal ganglia and be related to their motivation and effort problems, which underlie some of the typical behavioral manifestations of ADHD [51,52]. Furthermore, It is suggested, that cerebellum might be specifically related to dopaminergic neurotransmission within prefrontal cortex. While stimulation of nucleus dentatus and cerebellar cortex increased dopamine efflux in prefrontal cortex, no effects of this stimulation were found for noradrenaline and serotonin [53]. This study also shown, that the effect of the stimulation was dependent on an intact Purkinje cells [53]. It is reasonable therefore to study cues that may negatively involve Purkinje cells development and functioning with regard to suggested dopaminergic dysfunction in several neurodevelopment disorders including ADHD, autism, schizophrenia etc.

A recent pilot study showed a significant positive response to the anti-Yo antibody (marker of paraneoplastic cerebellar degeneration) immunoreactivity in the Purkinje cells of the cerebellum of combined subtype of ADHD children, in compare with typically developing children and the group with psychiatric disorder other than ADHD [54]. The hypotheses of immune reaction against cerebellum as an etiological factor in the ADHD is also supported by finding of presence of autoantibodies against the glutamic acid decarboxylase isoform 65 (GAD65) in the serum of patients diagnosed ADHD and

reactivity of these patient's serum with Purkinje cells, but as well with other cells of the mouse cerebellum [55]. Furthermore this study suggests, that ADHD and autism may share risk factors, as similar results were established in the group of children with autism [55].

Yun et al. found the increased expressions of apoptotic factors and the increased astrocytic factor in Purkinje cells of the cerebellar vermis in spontaneously hypertensive rats (SHR), widely used animal model of ADHD [56]. These rats performed worse in balance tests than the control group of Wistar-Kyoto mice [56]. It has been found, that the treadmill exercise was associated with the reduction of Purkinje cell loss and astrocytic reaction in the cerebellar vermis, which was reflected in recovered balance ability. This effect was comparable with the effect of methylphenidate [56].

The interaction between cerebellum and prefrontal cortex, however, differs inter-individually. It is suggested that it might be a function of dopamine D4 receptor genotype [57]. In subhuman level it has been found that D4 -/- mice had lower metabolism in the prefrontal cortex and greater metabolism in the cerebellar vermis than D4 +/+ and D4 +/- mice [57]. Also the effect of methylphenidate on the metabolic activity within these regions differed with regard to D4 expression. Methylphenidate increased metabolism in the prefrontal cortex and decreased it in the vermis in D4-/- mice, whereas in D4+ /+ and D4+ /- mice methylphenidate decreased metabolism in the prefrontal cortex and increased it in the vermis [57]. As D4 receptors are minimally expressed in cerebellar vermis, the effect of MPH may reflect an indirect modulation via fronto-striato-cerebello-frontal loops and/or cerebello-striatal loops and/or blockade of norepinephrine and dopamine transporter expressed in the cerebellar vermis [57]. Cerebellar metabolism has been found related to the level of D2 receptors expression in the striatum. Higher level of striatal D2 receptors predicted methylphenidate induced increases in cerebellar metabolism [58].

Cerebellum and non-motor regulation

For a long time the cerebellum has been linked with the control of a variety of motor processes, including the coordination of complex sequences of movements, balance control, etc. The first hints of cerebellar function beyond motor control emerged after finding a cerebellar interconnection with the cerebral association cortex [59]. Based on clinical research, Cerebellar Cognitive Affective Syndrome (CCAS) has been described as a range of executive, visuospatial, linguistic and affective deficits in patients with cerebellar lesions [60]. Since that time, several research groups have described multiple cognitive and emotional deficits in adult and pediatric patients with acquired or congenital cerebellar lesions [61-65]. The neuropsychological profile of these patients greatly resembles patients with ADHD [36].

Anatomical substrate for cerebellar involvement in cognition

Neuroanatomical transneuronal tracing studies using neurotropic viruses found surprisingly rich interconnections between the cerebellar dentate nucleus and multiple non-motor areas in the brain cortex, such as the prefrontal and posterior parietal cortex [66]. These pathways are organized into cortico- ponto-cerebellar and cerebello-thalamo-cortical loops. Each of the areas of the cerebral cortex that is a target of cerebellar output also projects to the cerebellum [66].

The portions of the nucleus dentatus with projections to non-motor cortical areas are larger in great apes and humans, not only relative to other cerebellar nuclei but also relative to motor portions of the dentate nucleus [67]. Furthermore, the nucleus dentatus is much larger in humans than in primates [67].

For a long time, it was believed that there was no direct interconnection between the basal ganglia and the cerebellum. However, it has been found that the nucleus dentatus projects to the striatum, and these projections originate from both motor and non-motor domains [68]. This projection allows the cerebellum to influence the processing of not only motor but also non-motor information within the basal ganglia [69]. In parallel, the nucleus subthalamic projects to the cerebellum, and these projections terminate in both motor and non-motor regions of the cerebellar cortex [70]. Thus, the basal ganglia may influence behavioral functions via the cerebellum [71].

Cerebellar topographic organization

Studies on patients with cerebellar lesions have suggested that separate regions of the cerebellum are responsible for different cognitive and emotional operations. Thus, the cerebellar anterior lobe was proposed to be engaged in motor control; the posterior lobe contributes to cognitive operations; and the impairment of the cerebellar vermis leads to deficient emotional regulation [61,65]. The results of a meta-analysis of functional neuroimaging studies are consistent with these clinical studies [72]. The authors found agreement within studies that sensorimotor tasks activates the anterior lobe (lobules V, VI and VIII), and the posterior lobe is involved in cognitive tasks. Language and verbal tasks activated VI and Crus I, and executive functions were associated with Crus I and VIIB activation and lobule VI. Emotional processing was associated with vermal lobule VII and Crus I [72].

As mentioned above, in ADHD individuals most structural abnormalities of the cerebellum were found in the posterior vermis [42,15,73]. This finding might also point to the emotional symptoms usually present in ADHD [74]. Patients with lesion of the vermis suffer by range of emotional deficits [60,72].

Theoretical models of cerebellar regulation and ADHD

In motor regulation, the cerebellum is crucial for developing the smooth performance of very complex movements. Given the almost uniform internal organization of the cerebellum, it seems reasonable to assume that what the cerebellum does for movement, it also does for cognition [75].

Using mathematical methods, two models of cerebellar regulation have been developed: network models and control system models [28]. The control system model offers an explanation of not only motor but also non-motor regulation within the cerebellum [76]. According to this concept, in motor regulation, the cerebellum creates internal models that simulate the controlled object (for example moving limb). The forward model represents the anticipation of consequences or outcomes of cerebral cortex commands and can be thought of as a table of input-output relationships, where both input and output signals carry spatiotemporal information about the represented object [27]. This function allows the cerebral cortex to act as a controller in the manipulation of a controlled object without

being delayed by relatively slow sensory feedback [75].

The universal evolutionary principle of the organization of behavior is to search for reward and avoid harm. Greater flexibility in the ability to apply this principle in a changing environment (what we call adaptation) corresponds to a better chance of survival. Preparation is everything. Thus, proactive control of behavior brings a huge advantage compared to reactive control and is a result of evolutionary pressure [27]. In parallel with the prefrontal cortex, the cerebellum expanded through evolution in great apes and humans in what may reflect an increase in demands for the control of fine motor skills but also for a cerebellar role in cognitive, anticipatory operations necessary for adaptation through proactive goal-directed behavior [77].

The theory of forward internal models might also be useful for understanding the mechanism of cerebellar involvement in behavioral regulation [76]. While the internal model simulates a body part as a controlled object in motor regulation, the internal model might simulate mental structures containing abstract features of the situation in cognitive processes [75]. This hypothesis is supported by neuroimaging studies showing co-activation of the cerebellar hemisphere with the prefrontal and temporo-parietal cortices during a variety of cognitive paradigms [78]. In this view, a controlled object is encoded by neurons in the temporo-parietal cortex, and the prefrontal cortex is assumed to have the role of the controller [75].

Cerebellar-based impairments decrease the capability to create predictive models and are hypothesized to be a major cause of disability in attention disorders [79]. Deficiency in the temporal generation and/or maintenance of a predictive brain state may represent one of the sources of performance variability [79], which is a prominent characteristic of ADHD and one of the candidate endophenotypes of this disorder [80]. The relationship of cerebellar impairment and variability in response times in the Go/No-Go task has been found in a sample of children with ADHD [37].

Individuals with ADHD typically complain that what others do routinely and effortlessly, they must keep under conscious control. Furthermore, the initiation of tasks that do not emerge in the mind as spontaneous needs or pleasures is a frequent problem in ADHD patients of all ages. Usually, this limitation is interpreted as a manifestation of executive function deficits and is related to an impairment of goal representation within the prefrontal cortex [12]. However, this may also point to an impairment of the development of automatic regulation within the brain, rooted in structures other than the cortical [81]. Typical features of the cerebellum include learning and creating automatic regulatory schemes of motor actions that are triggered unconsciously. The process of creating and refining these regulatory schemes or models is performed through error learning, where errors are signals of the differences between the produced state and a current model [82]. Through repetition, these models are improved and stored and might be triggered and switched upon the registration of a change in the environmental context [75]. This cerebellar mechanism of automatic regulation development is also suggested for behavioral functions, and its impairment may underlie some symptoms of ADHD [81].

Conclusion

ADHD is a very complex disorder, and even a single symptom might be caused by impairment of several brain regions interconnected within functional network. Thus, it is not easy to interpret the role of a particular structure in the pathophysiology of the disorder. However, several lines of research confirm the involvement of the cerebellum in ADHD and open many questions pertaining to the definitions of bottom-up and top-down in the hierarchy of behavior regulation.

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