

The Cognitive Face of Cerebellum; Implications for Extended Research

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Abstract

For years, the role of cerebellum was believed to be limited to motor functions. Only since almost two decades ago, a new concept about cerebellum and its contribution to non-motor functions including cognition and emotion started to emerge. During the recent years, numerous studies have focused on the cerebellar non-motor functions with their results providing supportive evidence on this view. The connections between cerebellum and cortical and subcortical areas such as frontoparietal cortices and the limbic system provide additional evidence for the involvement of cerebellum in higher cognitive functions. This review has been an effort to discuss the studies assessing different aspects of cognitive and affective disorders following cerebellar damage, as well as the cerebellar activity during cognitive tasks using novel approaches including fMRI and PET scans.

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Introduction

The cerebellum is a complex structure comprising 10 hemispheric and vermal lobules which differ in their afferent and efferent connections (1). Some of the anatomical and functional features of the cerebellum include the population of its neurons, its operation speed, its massive neural connections with the cerebral cortex, and the extensive connections of its output fibers (2). Cognitive function of the cerebellum, beyond its motor role, is now the subject of an established multidisciplinary field of investigation known as the cognitive neuroscience of the cerebellum (3). As such, in 2010, an issue of the journal 'Cortex' was dedicated to the cerebellum and cognitive functions. Many studies over the past 20 years, have prompted researchers to conclude that the cerebellum contributes to affective and higher order non-motor functions (4). The term "cerebellar cognitive affective syndrome" (CCAS) which was coined by

Schmahmann includes impairments in executive functions and disturbances in visual-spatial, and linguistic abilities, with affective disturbance ranging from emotional blunting and depression, to disinhibition and psychotic presentation. The cognitive and psychiatric components of the CCAS, together with the ataxic motor disability of the cerebellar disorders, are conceptualized within the 'dysmetria of thought' hypothesis. This concept holds the idea that cerebellum facilitates automatic modulation of the behavior around a homeostatic baseline, and the behavior being modulated is determined by the specificity of anatomic subcircuits or loops within the cerebrocerebellar system (3,5,6,7).

One way in which the cerebellum might influence different cognitive functions in brain-damaged patients is through the influence of diaschisis. A number of studies have shown that damage to the cerebellum can lead to reduced metabolic activity in

the contralateral cerebral hemisphere and elsewhere perhaps due to the loss of excitatory cerebellar input to the thalamus and forebrain structures (8).

The neuroanatomical circuits that subservise the cognitive and affective roles of cerebellum consist of the corticoponto-cerebellar and cerebello-thalamo-cortical loops which establish a close connection between the cerebellum and the supratentorial motor, paralimbic and association cortices(9). These connections suggest the contribution of cerebellum to functions such as working memory, language, emotion, etc. which are elaborated in the following sections.

Methods

Articles were identified through PubMed, Sciencedirect and Scopus databases search. Our search was performed using the following keywords without restriction of date: Cerebellum OR Cerebellar AND cognition OR working memory OR executive function, language, emotion, affective syndrome. This search yielded a large number of papers. We included 64 papers and excluded others by reviewing the abstracts. Our exclusion criteria for the retrieved papers were: 1- studies on non-human subjects, 2- Motor function of cerebellum 3- lack of direct cerebellar involvement.

Working memory and cerebellum

Working memory (WM) is the ability to actively maintain a limited amount of information in a readily-available state, even in the absence of continued sensory input. This capacity for internal representation is central to our complex cognition (10). It is achieved through the engagement of a widely-distributed network of cortical and subcortical areas. Regions within the frontal and parietal cortices as well as the cerebellum show increased activation in neuroimaging studies focusing on the WM(4).

Schlösser et al (2006) analyzed fMRI datasets in studies of working memory and proposed an extended network model including cerebellum for WM(11). Working memory impairments were present in a number of psychiatric disorders in which the cerebellum was implicated including addiction, anxiety, obsessive-compulsive disorder, depression, and schizophrenia (12).

Speech—specially covert—has a critical role in WM through creating and refreshing motor memory

traces, allowing new information to be processed whereby the cerebellum generally supports working memory through engaging inner speech mechanisms (10,12). Verbal WM problems may partly underlie the compromised performance of the cerebellar lesion patients on at least some complex cognitive tasks (2). Evidence on human lesions and brain imaging data have proposed cerebellar contribution to verbal WM (2,12,13). Patients with damage to the cerebellum exhibit a selective deficit in verbal WM (4). Cerebellum has a great cognitive involvement in WM which is not confined to the phonological loop but also supporting the central executive sub-functions(14).

Neuroimaging studies have suggested a functional topography within the sub-regions of the cerebellum that subservise the verbal WM (12). The superior-lateral region(10), right inferior cerebellum hemisphere (VIIIB)(2), more lateral regions of the superior cerebellum in Lobules VI and Crus I, the inferior cerebellum (Lobule VIII), the ventral dentate(12), bilateral regions of the superior cerebellar hemispheres (left superior HVIIA and right HVI), portions of posterior vermis (VI and superior VIIA), and the right inferior cerebellar hemisphere (HVIIB) (1) are among key regions suggested to contribute to verbal WM.

Likewise, it is reported that the cerebellar volume in healthy adults (as well as the total cerebral grey and white matter volumes) is genetically associated with WM performance (15).

Cerebellum and Attention

Higher attentional functions such as divided-attention and WM are often correlated and hence difficult to isolate from each other. They appeared to be modulated in the same part of the cerebellum, namely, the right side of the postero-lateral portion (16).

In an investigation on the attentional and neuropsychological functions, patients with focal cerebellar lesions showed distinct deficits in qualitative aspects of divided-attention and WM tasks. The performance in the selective attention was however unimpaired(17).

Schweizer et al. (2007) provided evidence implicating the cerebellum as a critical player in the neuroanatomical network underlying visual-temporal attention (18).

There exist evidence that autistic patients and patients with acquired cerebellar lesions were similarly impaired in a tasks requiring rapid and

accurate shifts of attention between the auditory and visual stimuli. These findings are consistent with the notion that cerebellar maldevelopment in autism may contribute to an inability to execute rapid attention shifts, and also with the proposal that the human cerebellum is involved in the coordination of rapid attentional shifts (19).

Attention deficit hyperactivity disorder (ADHD) runs in almost 5% of population in school period (20) and more than 4% in adult age (21). In ADHD, the three clusters of main symptoms include attention deficit, impulsiveness and hyperactivity. The association of ADHD with cerebellum alterations has been explored over the past decade (20).

Perlov et al. (2010) investigated the neurochemical alterations in the cerebellar neurochemistry among adult with ADHD and found a significantly increased glutamate-glutamine (Glx) to creatine (Cr) ratios in the left cerebellar hemisphere (22).

Patients with ADHD have significantly smaller brain volumes in cerebrum and cerebellum, even after adjustment for significant covariates (23). Quantification of the cerebellar and vermal volumes from MRIs has revealed that vermal volume is significantly less among boys with ADHD. This reduction involves mainly the posterior-inferior lobe (lobules VIII to X) but not the posterior superior lobe (lobules VI to VII) (24).

On the other hand, Ravizza et al. suggested that the apparent attention-shifting deficit might be secondary to the motor demands involved in preparing, controlling, and terminating responses in high cognitive-demands. When the motor demands were reduced, the cerebellar patients showed a significant improvement upon alternating attentional tasks (25).

Language and cerebellum

A variety of linguistic disorders were found to occur following acquired cerebellar lesions. Those include impaired phonological and semantic fluency (26,27), naming and word-finding difficulties (9,13,26), cerebellar-induced aphasia (28), reading and writing difficulties, higher-level language deficits, including disturbed listening comprehension, impaired language proficiency and metalinguistic ability (26), central-auditory functions (26,29), agrammatism (2,9,26,29,30), dysprosodia (9), morphosyntactic features and the lexical access (31). The contribution of cerebellum in some higher-order linguistic processes such as

speech timing, phonological aspects of lexical access, top-down mechanisms giving rise to expectations of upcoming verbal events (9), verb generation (8,32), and rhyming judgments (33) has widely been discussed.

A marked loss of functional-connectivity between the right cerebellar region and the supratentorial regulatory language areas may underlie the abnormal language function in children with ASD-LI (34).

The majority of neuroimaging studies employing non-motor language tasks typically show a lateralized involvement of ventral part of the dentate nucleus and lateral, posterior cerebellar regions (involving lobules VI–VIII) that are reciprocally linked to the supratentorial language networks of the dominant hemisphere (2,9,35). They form a phylogenetically new cerebro-cerebellar system in humans which facilitate linguistic function (2).

Learning the second language can lead to increased gray matter volume in the cerebellum, a structure that has been related to processing of the grammatical rules. Additionally, GM density in the bilingual brain is correlated to the bilinguals' performance in behavioral tasks (36).

The role of cerebellum in Emotion

Recent evidence from the clinical, experimental, and neuroimaging studies suggest that cerebellum is critically involved in cognitive and emotional processes. The anatomical studies also provide supportive evidence on the connections between cerebellum and other cortical and subcortical areas associated with emotional processing including limbic system and prefrontal cortex. The emotional changes observed in patients with cerebellar syndrome and the activation of cerebellum following the emotional stimuli also support this prospect (37-39). Furthermore, the anatomo-clinical analyses of cerebellum have indicated that the posterior vermis, or limbic cerebellum, is mainly involved in the regulation of emotion and affect (40). Many studies have investigated the relationship between cerebellum and emotions. In an study using functional MRI, Baumann and Mattingly found that all five primary emotions evoked activity in the cerebellum, including vermis and the intermediate parts of the cerebellar hemispheres (38). The reduced ability to experience pleasant feelings, but normal unpleasant emotions experience was found in patients with cerebellar lesions (41). Different studies on children with

damage to the vermis showed impaired regulation of affect including irritability, impulsivity, disinhibition, and liability of affect (7). Levisohn et al. noted dramatic mood swings and uncharacteristic giddiness in patients with damage to the vermis (42). In addition, weaker emotional response to happiness-evoking stimuli has been seen in patients with cerebellar stroke relative to healthy control group (39). In the same vein, the pathological laughter and crying phenomena as an emotional disorder was found to be connected with lesions in cerebellum (43). The dysfunctional syndrome described in a 38-year-old woman who had a tumor removed from the fourth ventricle via a surgical incision in the cerebellum provide additional evidence for the contribution cerebellar damage to emotional impairment (44). Evidence for the contribution of cerebellum to some emotional deficits which occurred in chronic alcoholics found in another study (45). Evidence for reduced emotion regulation following application of slow frequency rTMS to inhibit the cerebellar activity, has also been provided (46). Moreover, the altered cerebellar function during emotion processing and theory of mind, was suggested in a review of neuroimaging studies among patients with schizophrenia (47). According to the aforementioned studies, cerebellum, and particularly its vermis, plays an important role in emotion processing and emotional regulation.

Cerebellum and executive functions

'Executive function' is a term explaining the processes needed for the conscious control of thought and emotion. The prefrontal cortex and subcortical structures are known to regulate the executive functions (48).

Numerous neuroanatomical and neuroimaging studies have proposed the relationship between the cerebellum and executive functions (16,48,49). Cerebellum is now identified as a non-motor center playing a significant role in controlling of executive function such as language, visuo-spatial organization, emotional response, personality, reasoning, planning and sequencing (48). Some neuroanatomical studies show the connection between dorsolateral prefrontal cortex and neocerebellum (50). In addition, neuroimaging studies confirm that when a number of varied tasks are performed, the cerebellum and dorsolateral prefrontal cortex are activated at the same time(48). A study by Berman et al. using PET scans showed that when young adult were performing the Wisconsin card sorting test (WCST), the cerebellum

and dorsolateral prefrontal cortex were activated (51). Likewise, Nagahama et al. observed a similar pattern in their study (52). Tasks demanding working memory activate both prefrontal cortex and cerebellum(48). Clinical reports have explained the executive dysfunction followed cerebellar damage (49). The classic executive dysfunctions are common and include impairments in set-shifting, planning, abstract-reasoning, verbal-fluency and working memory (16, 42,53,54). Executive function disorders are complicated and their management is challenging (48). Schweizer et al. described the use of a cognitive rehabilitation technique, Goal Management Training (a rehabilitation approach which relies on the verbally-mediated, metacognitive strategies to systematically target disorganized behavior resulting from executive and attentional impairment), in a patient with persisting executive dysfunction after right cerebellar hemorrhage (49,55).

The cerebellar cognitive affective syndrome

The cerebellum has been affiliated with motor function and also necessary for the coordination of movement and balance (56). However anatomical, physiological and functional neuroimaging studies have revealed the role of cerebellum in non-motor or higher-order function (42,57). Cerebellum has connection with non-motor cortical area related to cognitive and emotional processing (58). Therefore, patients with cerebellar lesions, degeneration or stroke tend to have problem in cognitive functions associated with the cerebellar disorder itself (59). Schmahmann's syndrome represents a novel clinical condition consisting of a constellation of cognitive and affective deficits following cerebellar disease (60-62). The portrait was first described in 1998 as cerebellar cognitive affective syndrome (CCAS) on the basis of a careful neurological examination, detailed bedside mental state tests, neuropsychological investigations and anatomical neuroimaging in a group of 20 patients with focal cerebellar disorders (60).

The cerebellar cognitive affective syndrome is characterized by: 1- disturbance in executive functions including deficient planning, working memory, abstract-reasoning and decreased verbal fluency; 2- difficulties in spatial cognition such as visuo-spatial disorganization and impaired visual-spatial memory; 3- personality changes including blunting of affect and 4- a language disorder featuring with agrammatism , dysprosodia and anomia(42).

Schmahmann and Janet reported that changes in executive and visuo-spatial function with the existence of lesions of the anterior lobe of the cerebellum are minor(42).

Bonne and colleague described the cerebellar cognitive affective syndrome (CCAS) in pediatric cases of acute post-infectious ataxia (APCA). They observed patients with APCA and showed signs of disturbance in cognitive function (corresponding to CCAS) beside motor symptoms. They conclude that CCAS may be a neglected complication to APCA (60,63).

In general, one may observe that the symptoms of CCAS among patient are different related to the location of the focal lesion. Tedesco reported that patients with defects in the posterior inferior cerebellar artery perform the worst in terms of cognitive functions (60).

Some case studies indicate that cognitive functions become normal and the performance may improve in a 9- and 17-month follow-up (64).

Conclusion

The importance of cerebellum involvement in motor coordination, gait and speech has been clear for years while its role in higher cognitive functions has remained less considered until recently. The emotional and cognitive impairments following cerebellar damages opened a new window to research on the cognitive implications of the cerebellum. The contribution of cerebellum in higher mental abilities such as emotion, attention, working memory and language was at first as strong as a hypothesis based on disorders observed in patients with cerebellar dysfunctions. However, the development of new technologies like fMRI and PET scans in brain research provided evidence to confirm such hypotheses. Based on the studies included in this review, the cerebellar activity is important in different cognitive functions. The topographic organization of the cerebellum reveals that any part of cerebellum is predominantly linked to a specific task. For instance, in the case of emotional regulation, the vermis has the most importance role whereas during the executive function the co-activation of neocerebellum and dorsolateral prefrontal cortex is deemed essential. Different regions of the cerebellum including superior, inferior and ventral dentate parts are proposed to be related to working memory. Language deficits in patients suffering from cerebellar malfunctions also have been anticipated in some studies.

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