SPECIAL ARTICLE

Cerebellum and psychiatric disorders

O cerebelo e os transtornos psiquiátricos

Leonardo Baldaçara,[1,2,3] **João Guilherme Fiorani Borgio,**[1]
Acioly Luiz Tavares de Lacerda,[1,4,5] **Andrea Parolin Jackowski**[1]

Abstract

Objective: *The objective of this update article is to report structural and functional neuroimaging studies exploring the potential role of cerebellum in the pathophysiology of psychiatric disorders.* ***Method:*** *A non-systematic literature review was conducted by means of Medline using the following terms as a parameter: "cerebellum", "cerebellar vermis", "schizophrenia", "bipolar disorder", "depression", "anxiety disorders", "dementia" and "attention deficit hyperactivity disorder". The electronic search was done up to April 2008.* ***Discussion:*** *Structural and functional cerebellar abnormalities have been reported in many psychiatric disorders, namely schizophrenia, bipolar disorder, major depressive disorder, anxiety disorders, dementia and attention deficit hyperactivity disorder. Structural magnetic resonance imaging studies have reported smaller total cerebellar and vermal volumes in schizophrenia, mood disorders and attention deficit hyperactivity disorder. Functional magnetic resonance imaging studies using cognitive paradigms have shown alterations in cerebellar activity in schizophrenia, anxiety disorders and attention deficit hyperactivity disorder. In dementia, the cerebellum is affected in later stages of the disease.* ***Conclusion:*** *Contrasting with early theories, cerebellum appears to play a major role in different brain functions other than balance and motor control, including emotional regulation and cognition. Future studies are clearly needed to further elucidate the role of cerebellum in both normal and pathological behavior, mood regulation, and cognitive functioning.*

Descriptors: *Cerebellum; Schizophrenia; Mood disorders; Anxiety disorders; Dementia*

Resumo

Objetivo: *Este artigo de atualização tem como objetivo avaliar estudos em neuroimagem estrutural e funcional a fim de explorar o papel do cerebelo na patofisiologia dos transtornos psiquiátricos.* ***Método:*** *Uma revisão não sistemática foi realizada através do Medline utilizando-se como parâmetro os seguintes termos: "*cerebellum*", "*cerebellar vermis*", "*schizophrenia*", "*bipolar disorder*", "*depression*", "*anxiety disorders*", "*dementia*" e "*attention deficit hyperactivity disorder*". A busca eletrônica foi feita até abril de 2008.* ***Discussão:*** *Anormalidades cerebelares estruturais e funcionais têm sido relatadas em muitos transtornos psiquiátricos, entre eles a esquizofrenia, transtorno bipolar, transtorno depressivo, transtornos ansiosos, demências e transtorno de déficit de atenção e hiperatividade. Estudos utilizando imagem por ressonância magnética estrutural relataram a diminuição do volume total do cerebelo e do vermis cerebelar na esquizofrenia, transtornos do humor e transtorno de falta de atenção com hiperatividade. Estudos utilizando ressonância magnética funcional e paradigmas cognitivos têm demonstrado alterações na atividade cerebelar na esquizofrenia, transtornos ansiosos e transtorno de falta de atenção com hiperatividade. Nas demências, o cerebelo é afetado nos estágios mais avançados dessas doenças.* ***Conclusão:*** *Contrastando com as primeiras teorias, o cerebelo parece apresentar um papel mais importante em diferentes funções cerebrais além do controle motor e do equilíbrio, incluindo a regulação emocional e cognição. Futuros estudos são necessários para melhor elucidar o papel do cerebelo em ambos os comportamentos, normal e patológico, na regulação do humor e nas funções cognitivas.*

Descritores: *Cerebelo; Esquizofrenia; Transtornos do humor; Transtornos da ansiedade; Demência*

[1] Laboratório Interdisciplinar de Neurociências Clínicas (LINC), Departamento de Psiquiatria, Universidade Federal de São Paulo (Unifesp), São Paulo (SP), Brazil
[2] Centro de Atenção Integrada à Saúde Mental (CAISM), Irmandade da Santa Casa de São Paulo, São Paulo (SP), Brazil
[3] Universidade Federal do Tocantins (UFT), Palmas (SP), Brazil
[4] Instituto Sinapse de Neurociências Clínicas, Campinas (SP), Brazil
[5] Centro de Pesquisa e Ensaios Clínicos Sinapse-Bairral, Itapira (SP), Brazil

Correspondence
Leonardo Baldaçara
Quadra 206 Sul, Alameda 12, Lote 10, apt. 302, Bloco A
Plano Diretor Sul
77020-528 Palmas, TO, Brasil
Phone: (+55 63) 3216-1515 / (+55 63) 3215-2208
Email: leonardobaldassara@terra.com.br

Submitted: March 5, 2008
Accepted: May 29, 2008

Introduction

For many years, functions related only to movement, gait, posture, and balance were attributed to the cerebellum. However, some studies have suggested a possible involvement of the cerebellum in cognition, emotion processing and behavior.[1-8] From this perspective, the cerebellum would exert a regulatory function that would enhance and supplement other brain functions, throughout direct and indirect circuits.[1,5,8]

Moreover, different sources of evidence have suggested that the cerebellum may be altered in many psychiatric disorders, including schizophrenia, bipolar disorder, unipolar depression, anxiety, and attention deficit hyperactivity disorder.[5,9] In some reports, cerebellar deficits were described as isolated findings, without relation with clinical history. But in others there is evidence that the cerebellum is a relevant brain structure possibly related to a range of psychopathological manifestations.[9]

This update article aims to report structural and functional brain imaging studies examining the cerebellum in psychiatric disorders and a possible role of cerebellum in their pathophysiological mechanisms. Finally, the implications of these findings and future directions are discussed.

The role of cerebellum

There is increasing evidence that the cerebellum is not only connected with motor pathways but also with other cortical and association areas involved in superior mental functions, suggesting the involvement of the cerebellum in cognition[9] in the pathophysiology of psychiatric disorders.

In animal studies, axonal transport mechanisms have been used to document connectivity between the cerebral cortex and the brainstem and cerebellum. Cerebellum receives input from the spinal cord, vestibular nuclei, special relay nuclei of the brainstem (including the inferior olive and pontine nuclei), and, via these relay nuclei, from the cerebral cortex.[10] Afferents from spinal cord and brain stem enter the cerebellum via the inferior cerebellar peduncle, whereas afferents from the cerebral cortex (relayed in the pontine nuclei) enter via middle cerebellar peduncle. Those peripheral pathways are related to proprioception, motor, gait and posture processing.

In order to appreciate the involvement of the cerebellum in cognition and psychopathological symptoms, it is important to understand its afferent and efferent connections. The cortico-ponto-cerebellar pathway is the most important of the central afferent circuits originated from motor and sensitive cortical areas. After connecting with pontine nuclei, the pontocerebellar tracts connect with contralateral cerebellar hemisphere in a somatotopic way. The other cerebellar peripheral pathways originate from brainstem: the olivocerebellar tract with fibers originating from the inferior olive that receives excitatory impulses from the red nucleus, basal ganglia, reticular formation, and spinal cord (spinal-olivar); the vestibulocerebellar tract with fibers originating from the vestibular nuclei and projects to the fastigial and flocculonodular nuclei; and the reticulocerebellar tract with fibers originating from the reticular formation and projects to the cerebellar vermis.

The main outputs of the cerebellum are to the brainstem and to the cerebral motor cortex (via the red nucleus and ventrolateral nucleus of the thalamus). There are three main cerebellar efferent pathways:

1) Fibers that originate in the cerebellar vermis projecting to the fastigial nucleus and then to the pons, medulla oblongata, and reticular formation;

2) Fibers that originate in the intermediate zone of the cerebellar hemisphere projecting to the interpositus nucleus and then to the red nucleus and thalamus (ventrolateral and ventroposterior nucleus). After connecting to the thalamus, those fibers connect to the rubrospinal pathway and basal ganglia;

3) Fibers that originate in the lateral zone of cerebellar hemisphere and project to the dentate nucleus, and then to thalamus. After the thalamic connection, those fibers are projected to the cerebral cortex (posterior parietal, superior temporal, prefrontal), reticular formation, and then to the corticospinal and reticulospinal pathways.

The cerebellar nuclei projects to the caudal ventrolateral contralateral thalamic nuclei and then to the frontal motor cortex. Cerebellar nuclei may also connect with the intralaminar and motor thalamic nuclei and then project to association and limbic cortices (cingulate and parahippocampal gyri).

Many studies have also demonstrated crossed connections between the dentate nucleus and the dorsolateral prefrontal cortex in the cerebellum-thalamic-cortical direction. The same crossed pattern was observed for specific areas of the inferior posterior parietal cortex.[9,11,12] Through these extensive interconnections, with afferent (cortico-ponto-cerebellar) and efferent (cerebello-thalamo-cortical) pathways, the cerebellum can receive information, as well as influence cortical cerebral areas related to cognition.[9]

Significant interconnections between the cerebellum and prefrontal cortex subdivisions related to executive functioning (working memory, attention, inhibition of behaviors, and decision making), verbal memory and language have been demonstrated.[13] Afferent projections from parietal, temporal, and occipital cortices, and limbic system implicated in the integration of sensitive and sensorial information, visuospatial organization, visual memory, and control of behavior and motivation have also been proposed.[14,15]

More recently, a timekeeping or "clock" function has been postulated for the cerebellar cortex and the inferior olive (the sole source of climbing fiber inputs to Purkinje cells) based on their unique microstructure and intrinsic rhythmic oscillatory properties.[16,17] Xu et al. proposed that the primary role of the inferior olive and the climbing fiber system in timing is to mediate the encoding of temporal information independent of motor behavior.[18]

Cerebellum and psychiatric disorders

1. Schizophrenia

Schizophrenia is a severe and highly heritable psychiatric disorder that has been linked to multiple genes and neurodevelopmental factors, with a lifetime prevalence of about 1% in general population. Symptoms usually begin in late adolescence or early adulthood.[19,20]

The clinical manifestations are variable, including perceptual alterations (hallucinations), form and content of thought (incoherent thought or with loosening of associations, delusion), disorganized speech, grossly disorganized or catatonic behavior, and "negative" symptoms (alogia, affective flattening, avolition, social isolation). Cognitive impairments mainly affecting intelligence, memory, language, executive functioning, and attention domains are also common.[20,21]

Over the past three decades, neurophysiological studies using different models for schizophrenia have identified several brain alterations. There are global impairments in cognition with altered executive functions (action planning, inhibition, cognitive flexibility monitoring, abstract reasoning), memory (difficulties in the semantic organization of the content of the memory and overcoat in verbal memory and visuospatial tasks), attention (difficulties intrusions

control, in the divided and sustained attention, focus changing) and language (fluency but without alterations in vocabulary).[1,9,18]

There is evidence that patients with schizophrenia have altered corticocerebellar connectivity.[18] Andreasen et al. proposed that disruption of the cortical-thalamic-cerebellar-cortical circuit (CTCC) may underlie at least part of symptomatology observed in schizophrenia.[18,22] Analogous to the cerebellar role in facilitating rapid and smooth execution of motor tasks, these authors further proposed that the CTCC performs a similar role in monitoring and coordinating the execution of mental activity resulting in normal cognitive functioning.[18,23]

Neuroanatomical, neuropathological, and brain imaging studies have consistently described enlargement of the cerebral ventricles, reduction in total cerebral volume, structural and functional alterations in frontal and temporal lobe structures, limbic system, thalamus and basal ganglia.[9] Neurostructural studies have revealed smaller total cerebellar volume, smaller vermis volume, reduction of hemispheric asymmetry, while functional neuroimaging studies using cognitive paradigms have demonstrated frontal-thalamic-cerebellar hypoactivity in schizophrenia.[23]

Magnetic resonance imaging (MRI) analyses using quantitative anthropometric techniques have yielded more consistent reports of cerebellar atrophy in schizophrenia,[22,24] with some authors attempting to delineate a subset of patients with reduced or atrophied cerebellum. Global reduction of cerebellum in patients with schizophrenia seems to be associated in some cases with perinatal brain insults,[25] in others with male gender,[26] childhood-onset,[27] very-late-onset,[28] chronic course,[29] and positive psychotic symptoms.[30] Other authors have noted atrophy limited to the vermis.[22,26]

In some diseases, cerebellar hemispheres may be reduced secondary to the contralateral atrophied cerebral hemisphere. This condition is called diaschisis. There are studies in schizophrenia suggesting that cerebellar volume reduction is not only a consequence of superior structures atrophy. Unaffected first-degree relatives of probands with schizophrenia and neuroleptic naïve patients with schizophrenia have also presented reduced cerebellar volumes. These data suggest that cerebellar atrophy may be a heritable trait rather than a treatment associated epiphenomenon.[18,22]

Studies of schizophrenia using the tools of functional imaging from our own group have found a relatively consistent pattern of abnormalities in distributed brain regions that include the cerebellum.[1,31-33] Abnormalities are seen in these studies in both the vermis and the cerebral hemispheres in patterns that are task-related. Patients with schizophrenia have decreased blood flow in the cerebellum in a broad range of tasks that tap into diverse functional systems of the brain, including memory, attention, social cognition, and emotion.[31-33] Vermal abnormalities are more frequently noted in tasks that use limbic regions (e.g., studies of emotion), whereas more lateral neocerebellar regions are abnormal in tasks that use neocortical regions (e.g., memory encoding and retrieval).[1,32]

Soft neurological signs suggestive of cerebellar dysfunction, such as subtle ataxia, difficulties in coordination, dysdiadochokinesia, intentional tremor, dysmetria of the ocular saccadic movements are frequent in patients with schizophrenia.[9] Additionally, emergence of positive symptomatology (especially delusions), as well as cognitive deficits (e.g., difficulties in synthesis and logical sequencing and verbal fluency) and negative symptomatology, including flattened affect, thought disorder, avolition, social isolation, and poor speech, have frequently been reported in individuals with cerebellar lesions.[9,34,35]

There are not studies that support the idea that cerebellum may be involved in motor disturbances in patients with schizophrenia using neuroleptics. Only one study found evidence of reduction in metabolic activity in the cerebellum of patients with akathisia using olanzapine.[36] This theory is difficult to prove mainly because in structural studies movement disorders are used as exclusion criteria and in functional studies cerebellum is used as parameter of normality in image analysis.

Converging evidence from neuroimaging and cognitive studies suggests cerebellar abnormalities in schizophrenia, which could account for some of the positive, negative, and cognitive symptoms present in this disease. Up to now, there are no studies showing if treatment has an impact on cerebellar functioning or if the cerebellar abnormalities are related to course or prognosis. There are also few studies exploring changes in cerebellar functioning after neuropsychological rehabilitation.

2. Bipolar disorder

Bipolar disorder is a chronic and generally life-long condition affecting about 1.6% of the population. It is characterized by unusual shifts in mood state, energy level, and behavior. These dramatic fluctuations may alternate between depression, normal mood, and elation and/or irritability.[37,38] In spite of the progresses of the research methods in biological psychiatry and of the current knowledge on the mechanisms of action of the mood stabilizers, the pathophysiology of bipolar disorder is still poorly understood.

Several case reports have demonstrated cerebellar atrophy in patients with mood disturbances, as well as in patients with bipolar disorder.[39-41] Moreover, some studies have found abnormal cerebellar anatomy in subjects with affective disorders.[42] Two studies reported a greater rate of cerebellar atrophy in manic patients as compared to patients with schizophrenia or healthy controls.[25] Additionally, Yates et al. found a greater rate of cerebellar atrophy in patients with bipolar disorder who were over 50 years old, but not in younger bipolar patients compared with healthy volunteers.[43] Lippmann et al. found increased rates of both vermal atrophy and cerebellar hemisphere atrophy in bipolar patients with co-occurring alcohol abuse as compared with healthy volunteers, suggesting that alcohol abuse may contribute to abnormal cerebellar anatomy in bipolar patients.[44] Surprisingly, this potential confounder is rarely observed in most of the studies and may be alone responsible for cerebellar atrophy. On the other hand, one study using multiple regression analysis excluded alcohol use as a potential confounder for vermal area atrophy volume in patients with bipolar disorder.[45]

Vermal subregion V2 volume was significantly smaller in multiple-episode bipolar disorder subjects than in first-episode patients and healthy subjects, while vermal subregion V3 was significantly smaller in multiple-episode bipolar disorder subjects in comparison with healthy subjects. Taken together, these results suggest that posterior-inferior cerebellar vermal abnormalities are present in patients with multiple-episode bipolar disorder.[46] A subsequent MRI investigation of the cerebellum in patients with bipolar disorder did not reveal any gross morphological differences between patients and healthy controls. However, when patients with bipolar disorder were subdivided into first-manic-episode and multiple manic-episode groups, the V3 subregion was significantly smaller in the multiple-episode group.[46,47]

Further analysis revealed that, among multiple-episode patients, the number of previous depressive episodes, but not substance abuse or duration of lithium exposure, contributed to the reduction in V3 volume. Loeber et al. employed dynamic susceptibility contrast MRI and reported that patients with bipolar disorder had

lower cerebellar regional cerebral blood flow (rCBF) than healthy controls and patients with schizophrenia, even after controlling for volume differences.[48] The cerebellar region most frequently reported in neuroimaging studies involving bipolar patients, the vermis, showed the largest reduction in rCBF. After treatment with atypical antipsychotic drugs, however, this relative decrease in rCBF disappeared.[47]

Preliminary *in vivo* studies have shown structural and functional abnormalities in bipolar patients compared with healthy control subjects. Smaller cerebellar volume with decreased blood or increased glucose metabolism is the main finding in bipolar patients. Although controversial, the functional findings may reflect the clinical heterogeneity of the bipolar populations studied. Thus, it is possible that cerebellar hypermetabolism is a finding restricted to treatment resistant bipolar subjects.[47] Finally, there is no evidence yet whether these findings are cause or consequence of the disease.

3. Unipolar depression

Depression is a mood disorder characterized by psychic, physical, cognitive, physiological, and behavioral alterations. A variety of pathophysiological mechanisms have been proposed to explain this disorder, including genetic alterations, monoamine system dysfunction, and downregulation of neuroreceptors, among others. Structural and functional abnormalities in the prefrontal cortex, limbic system, and basal ganglia have consistently been described in patients with major depression.[9,18]

Using a PET analysis of regional blood flow, Reiman et al. investigated the neurofunctional correlates of externally generated emotions.[49] These authors scanned healthy volunteers as they watched movies designed to evoke a variety of emotional states, including happiness, sadness, and disgust. In addition to the activation of limbic and paralimbic areas, it was observed an activation of cerebellar hemispheres. Using a similar paradigm, Lane et al. extended these results by demonstrating that sadness, but not happiness, increased activity in the anterior cerebellar vermis.[50]

In another PET investigation, rCBF was compared in subjects with acute depression and healthy controls before and after a transient mood challenge. In agreement with the results obtained with fMRI, patients with depression displayed lower rCBF in cerebellum and thalamus.[51] Dolan et al. were the first to report an increase in baseline cerebellar vermal blood flow in a subset of patients with depression and cognitive impairment.[47,52] More recent data suggest that this tonic increase in cerebellar activity is characteristic of major depression, regardless of mood state or medication exposure.[47]

More recently, MRI studies have shown reduced cerebellar volume in patients with unipolar depression. There are data suggesting that cerebellar atrophy is related to severity and nonresponse to antidepressant treatment.[53] A recent MRI investigation revealed a negative correlation between total cerebellar tissue volume and baseline depression scores. In the same study, cognitive deficits in depressed patients were related to lower cerebellar cortex activity in PET analyses.[53]

There is emerging evidence suggesting that the cerebellum is involved in identification and expression of emotions.[5,9] Expression of emotions, mainly sadness, seems to be impaired in both severe and resistant depression. Some studies hypothesize that impairment in emotion expression might be, in part, due to a disruption in the functional connection between the cerebellum and frontal lobe.[5,54,55] But there are not data showing if these alterations are a risk factor for developing depression or if they are already present before the disease onset, or even a consequence of the disease. Future cohort studies as well as studies with relatives of depressed patients are warranted to address these questions.

4. Anxiety disorders

Anxiety is a normal reaction to stress and, if not excessive, is crucial for homeostasis. Prolonged or excessive anxiety states, however, may be associated with brain damage, possibly mediated by a hyperactive hypothalamus-pituitary-adrenal (HPA) axis. Anxiety disorders represent a heterogeneous group of diseases that share pathological anxiety as a core symptom.[56] Although pathophysiology of anxiety disorders is still unclear, possible mechanisms affecting regional cerebral blood flow (reduction in frontal, parietal, temporal and cingulate areas), metabolism (frontal, temporal, parietal, cerebellum, thalamus, limbic system and basal ganglia), neurotransmission (GABA, norepinephrine, and serotonin system), and neuroendocrine system have been proposed.[56]

Cerebellum might play a role in anxiety manifestations like hyperarousal symptoms, which are present in different disorders such as posttraumatic stress disorder (PTSD) and generalized anxiety disorder (GAD).[57] Recent evidence suggests that cerebellum may be involved in PTSD pathophysiology. De Bellis and Kuchibhatla reported a smaller cerebellar volume (both hemispheres) in children with PTSD secondary to maltreatment.[58] Moreover, in a case report, increased cerebellum, precuneus and supplementary motor cortex activation was observed in response to traumatic reminders.[59] This hyperactivity disappeared upon successful treatment with fluoxetine. A bilateral increase in resting cerebellum perfusion ratio on hexamethylpropyleneamineoxime single photon emission computed tomography (SPECT) was found in adult subjects with recent-onset PTSD compared with both trauma exposed subjects without PTSD and non-exposed subjects.[60] In the subgroup of subjects with comorbid borderline personality disorder and PTSD examined with functional magnetic resonance (fMRI), there was a hyperactivity in anterior temporal lobes, mesiotemporal areas, amygdala, posterior cingulate, occipital areas, and cerebellum in response to traumatic reminders.[61]

Results from studies involving combat-related PTSD subjects suggest an increased sensitivity of the sympathetic nervous system that is more evident under experimental conditions of stress or challenge.[58] In addition, cerebellar vermis activity is increased during biofeedback relaxation.[62] Moreover, left cerebellar hemisphere is activated during discrete sympathetic skin conductance responses.[63] In a PET study, mean arterial blood pressure and heart rate correlated with cerebellar hemisphere and vermis activity while subjects were performing isometric exercise and mental arithmetic stressor tasks,[64] suggested a role of cerebellum in sympathetic regulation.

A PET study reported that social anxiety induced by the mental arithmetic task was associated with activation of cerebellum and other areas such as prefrontal cortex, thalamus, insula, and ventral striatum.[65] In another PET study, panic disorder patients showed appreciably high anxiety before scanning and exhibited significantly higher levels of glucose metabolism in the bilateral amygdala, hippocampus, thalamus, midbrain, caudal pons, medulla, and cerebellum as compared to controls.[66]

The cerebellum seems to be reduced in its volume but more activated in some tasks in patients with anxiety disorders. Studies exploring the clinical implications of the cerebellum hyperactivity in anxiety disorders are still lacking.

5. Neurodegenerative dementias

Dementias constitute a heterogeneous group that share cognitive impairment of organic etiology. Although several causes and pathophysiological mechanisms underlie clinical presentation of different types of dementia, neuroimaging studies have confirmed some common findings such as atrophy of certain brain structures or even global brain atrophy and progressive impairment of different cognitive domains.[67]

Cerebellar volume seems to be reduced in patients with dementia. The most frequent hypothesis is related to diaschisis. Other hypothesis is that the cerebellar atrophy is due to vascular factors, molecular factors (dementia pathophysiological mechanisms directly affecting cerebellum) or by toxins (e.g., alcoholic dementia).[36] However, these alterations are only observed in the late stages of disease in the majority of studies.[68,69]

In Alzheimer's disease (AD), cerebral structures interconnected with cerebellum are affected by neurofibrillary tangles and neuronal loss in later stages of the disease. Hypothetically, atrophic changes in cerebral structures might underlie atrophic changes in the cerebellum.[68] A classical major neuropathological change in AD is represented by deposits of beta-amyloid plaques and neurofibrillary tangles in neocortical and subcortical regions, but these pathological processes are not present in the cerebellum.[68] Thus, cerebellum is a unique structure in terms of AD pathologic manifestations. There is a strong correlation between the loss of granule cells and duration of AD. Additionally, although cerebellum is virtually free of neurofibrillary pathology, the magnitude of cerebellar atrophy strongly correlates with duration and stage of illness.[68] In most of the of studies, cerebellum atrophy is evident only in late stages of disease.[68-72]

The climbing fibers originating from the inferior olivary nucleus act as a powerful excitatory pathway on the Purkinje cells of the cerebellar cortex that may play a substantial role in motor performances and learning of new motor skills. In vascular dementia, the existent vascular alterations may induce many hypoxic or ischemic phenomena, among others, in the olivocerebellar system affecting the climbing fibers in their way to the molecular layer of cerebellar cortex.[73] Consequently, these alterations may be related at least partly to some symptoms in these patients.

In autopsy cases of vascular dementia, the application of silver impregnation technique and electron microscopy revealed a substantial decrease in the number of climbing fibers in the cortex of vermis, flocculus, and cerebellar hemispheres.[73] The presynaptic varicosities and the synaptic terminals of climbing fibers on the Purkinje cell dendrites were decreased in number and were characterized by a marked poverty of synaptic vesicles.[73] The synaptic cleft was mostly abnormal and wider than 20 nm. Mitochondrial abnormalities such as elongated mitochondria with disruption of the crystal were seen in terminal branches of climbing fibers arborization as well as in presynaptic components. The blood capillaries demonstrated a considerable thickness of the basal membrane and perivascular astrocytic proliferation, whereas the tight junctions between the endothelial cells were ultrastructurally intact.[73]

In summary, cerebellum appears to be affected in later stages of dementia, probably due to the atrophy of superior structures and spreading of disease. To our knowledge, there are no studies examining the relationship between cerebellum volume and prognosis in different types of dementia. Since dementia prognosis is strongly associated with performance on daily activities, which, in turn, are related to motor functions, one might speculate that cerebellum insult may negatively correlate with prognosis.

6. Attention deficit hyperactivity disorder

Attention deficit hyperactivity disorder (ADHD) is present in about of 5% of population in school period and about 30 a 50% of these cases can still be symptomatic in adult age.[9] In ADHD, three groups of main symptoms are: attention deficit (distractibility, difficulty with concentration and focus), impulsiveness (impatience, difficulty in postponing answers and rewards, negligence, impetuosity) and hyperactivity (excessive locomotor activity, restlessness, inadequate motive agitation).[74]

Dysfunction of noradrenergic and/or dopaminergic neurotransmission has been widely implicated in the manifestation of ADHD.[75] On the other hand, some theories about ADHD focus on frontal-subcortical functional disturbance, while structural and functional neuroimaging studies show alterations in prefrontal cortex, cingulum, basal ganglia, corpus callosum and cerebral total volume.[9]

Valera et al. conducted the first meta-analysis of structural neuroimaging findings in children and adolescents with ADHD. This meta-analysis found global reductions in brain volume, with most prominent reductions affecting total and right cerebral volumes, cerebellar regions, the splenium of the corpus callosum, and the right caudate nucleus.[76]

Relatively little is known about how brain abnormalities in ADHD change over the life span. In a study by Castellanos et al., children and adolescents with ADHD were followed over time using MRI. Volumetric abnormalities in the cerebrum and cerebellum persisted with increasing age, whereas caudate differences versus control subjects disappeared. These findings appeared to be unrelated to stimulant treatment. Few structural neuroimaging studies have been conducted in adults with ADHD, which hampers our understanding of developmental trajectories.[77] Seidman et al. previously reported volumetric reductions in frontal and anterior cingulate cortices in adults with ADHD.[78]

The association of ADHD with cerebellum alterations has been explored in the last 10 years. Some studies have shown smaller cerebellar volume in ADHD patients in comparison with normal controls.[79,80] These findings are more specific in post-inferior cerebellar hemispheres and vermis.[81,82] A negative correlation between the cerebellar volume and attention tests has also been reported.[9,83] A functional study have demonstrated reduction in the activity of cerebellum and vermis.[83]

On the other hand, there are studies showing cognitive and behavior alterations similar of ADHD in patients with posterior cerebellar lesions, e.g., difficulties in the administration of the time, difficulties in sustaining attention, difficulties in dealing with abstract concepts, impulsivity, difficulties in production and organization.[9,83]

In summary, advances in neuroimaging research have helped to elucidate the neurobiology of ADHD. There is evidence of a noradrenergic and/or dopaminergic dysregulation, as well as structural brain and cerebellar abnormalities as likely contributing to the pathophysiology of ADHD.

Conclusion and perspectives

Cerebellum makes an important contribution to the control of voluntary movement and movement coordination, as well as control of balance, gait, and posture. There is also strong evidence for a cerebellar role in cognition (memory, attention, language and executive functions), emotions, and anxiety. Cerebellum seems to work as an "internal clock", which comes into play during the control of movement, as well as during perceptual processing.

The exact nature of the cerebellar involvement in cognitive processes is so far less well understood. Functional and structural neuroimaging techniques also provide a valuable tool to study cerebellar contribution to different cognitive abilities and its role in psychiatric disorders. Abnormalities in cerebellar structure and function have been reported in some psychiatric disorders. Moreover, pharmacological and psychosocial therapeutic interventions for patients with those disorders have been associated with changes in cerebellar function, suggesting an important role of cerebellum in different mental processes, which are disturbed in some psychiatric disorders. Future studies examining cerebellum functions in patients with psychiatric disorders may extend the current knowledge on this issue. Another perspective is identifying different groups in the same disorder based on differences in cerebellum activation during the same task, as it has been described in bipolar disorder. Analyses of convergent data from genetic, neuropsychological, and structural and functional brain imaging studies could provide a unique opportunity to explore the role of cerebellum in pathophysiology of psychiatric disorders.

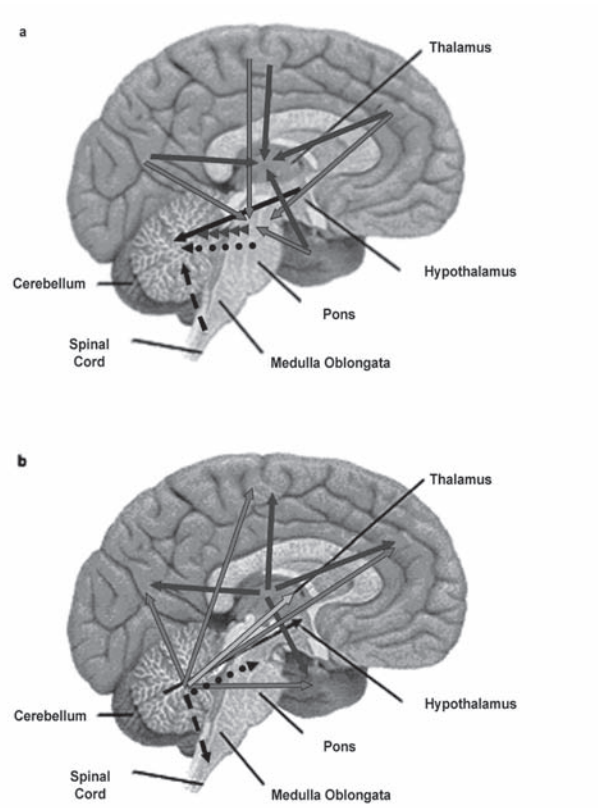
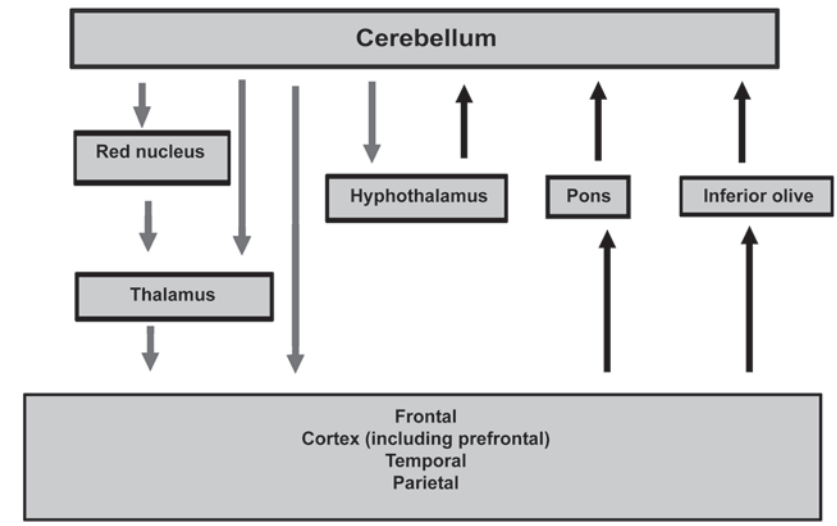


Figure 2 - Afferent (a) and efferent (b) cerebellar connections
Direct connections with cerebral cortex. Connection with the thalamus. Indirect connections with the cerebral cortex through thalamus. Connections with the hypothalamus. Connections with the brainstem (pons and inferior olive). Connections with the spinal cord. Connections with the red nucleus.



Grey arrows: efferent connections. Black arrows: efferent connections.

Figure 1 - Cerebellar connections

Disclosures

Writting group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Spekear's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Leonardo Baldaçara	UNIFESP CAISM UFT	---	FADA-UNIFESP* Lilly* Pfizer*	---	---	---	---
João Guilherme Fiorani Borgio	UNIFESP	Lilly * Janssen *	---	Novartis *	---	---	---
Acioly Luiz Tavares de Lacerda	UNIFESP Instituto Sinapse de Neurociências Clínicas Centro de Pesquisa e Ensaios Clínicos Sinapse-Bairral	Eli Lilly** Janssen-Cilag* AstraZeneca*	FADA-UNIFESP* FAPESP* CNPq*	Eli Lilly** Boehringer-Ingelheim* Janssen-Cilag Solvay Farma** Libbs* Medley* AstraZeneca* Lundbeck* Bristol Meyers-Squibb* EMS*	---	Medley* EMS*	---
Andrea Parolin Jackowski	UNIFESP	---	Prodoc-CAPES* FAPESP*	---	---	---	---

** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: UNIFESP = Universidade Federal de São Paulo; CAISM = Centro de Atenção Integrada à Saúde Mental da Irmandade da Santa Casa de São Paulo; UFT = Universidade Federal do Tocantins; FADA = Fundo de Auxílio aos Docentes e Alunos; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo; CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; CAPES = Coordenação de Aperfeiçoamento de Pessoal de Nível Superior.
For more information, see Instructions for authors.

References

1. Andreasen NC, Pierson R. The Role of the Cerebellum in Schizophrenia. *Biol Psychiatry*. 2008, in press.
2. Grill J, Viguier D, Kieffer V, Bulteau C, Sainte-Rose C, Hartmann O, Kalifa C, Dellatolas G. Critical risk factors for intellectual impairment in children with posterior fossa tumors: the role of cerebellar damage. *J Neurosurg*. 2004;101(Suppl 2):152-8.
3. Hallet M, Grafman J. Executive function and motor skill learning. In: Schmahmann JD, editor. *The cerebellum and cognition*. Academic Press; 2006. p. 297-319.
4. Hokkanen LS, Kauranen V, Roine RO, Salonen O, Kotila M. Subtle cognitive deficits after cerebellar infarcts. *Eur J Neurol*. 2006;13(2):161-70.
5. Schmahmann JD, Weilburg JB, Sherman JC. The neuropsychiatry of the cerebellum - insights from the clinic. *Cerebellum* (London, England). 2007;6(3):254-67.
6. Timmann D, Dimitrova A, Hein-Kropp C, Wilhelm H, Dorfler A. Cerebellar agenesis: clinical, neuropsychological and MR findings. *Neurocase*. 2003;9(5):402-13.
7. Schmahmann JD. Disorders of the cerebellum: ataxia, dysmetria of thought, and the cerebellar cognitive affective syndrome. *J Neuropsychiatry Clin Neurosci*. 2004;16(3):367-78.
8. Ribas GC. As bases neuroanatômicas do comportamento: histórico e contribuições recentes. *Rev Bras Psiquiatr*. 2007;29(1):63-71.
9. Bugalho P, Correa B, Viana-Baptista M. Papel do cerebelo nas funções cognitivas e comportamentais. Bases Científicas e Modelos de Estudo. *Acta Med Port*. 2006;19(3):257-68.
10. Schmahmann JD, Pandya DN. The cerebrocerebellar system. In: Schmahmann JD, editor. *The cerebellum and cognition*. San Diego (CA): Academic Press; 1997. p. 31-60.
11. Middleton FA, Strick PL. Anatomical evidence for cerebellar and basal ganglia involvement in higher cognitive function. *Science*. 1994;266(5184):458-61.
12. Clower DM, West RA, Lynch JC, Strick PL. The inferior parietal lobule is the target of output from the superior colliculus, hippocampus, and cerebellum. *J Neurosci*. 2001;21(16):6283-91.
13. Schmahmann JD, Pandya DN. Prefrontal cortex projections to the basilar pons: implications for the cerebellar contribution to higher function. *Neuroscience Lett*. 1995;199(3):175-8.
14. Schmahmann JD, Pandya DN. Course of fibers pathways to pons from parasensory association areas in the rhesus monkey. *J Comp Neurol*. 1992;326(2):159-79.
15. Vilensky JA, van Hoesen GW. Corticopontine projections from the cingulated cortex in the rhesus monkey. *Brain Res*. 1981;205(2):391-5.
16. Xu D, Liu T, Ashe J, Bushara KO. Role of the olivo-cerebellar system in timing. *J Neurosci*. 2006;26(22):5990-5.
17. Koekkoek SK, Yamaguchi K, Milojkovic BA, Dortland BR, Ruigrok TJ, Maex R, De Graaf W, Smit AE, VanderWerf F, Bakker CE, Willemsen R, Ikeda T, Kakizawa S, Onodera K, Nelson DL, Mientjes E, Joosten M, De Schutter E, Oostra BA, Ito M, De Zeeuw CI. Deletion of FMR1 in Purkinje cells enhances parallel fiber LTD, enlarges spines, and attenuates cerebellar eyelid conditioning in Fragile X syndrome. *Neuron*. 2005;47(3):339-52.
18. Konarski JZ, McIntyre RS, Grupp LA, Kennedy SH. Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? *J Psychiatry Neurosci*. 2006;30(3):178-86.
19. Razzouk D, Mari JJ, Shirakawa I, Wainer J, Sigulem D. How do experts recognize schizophrenia: the role of the disorganization symptom. *Rev Bras Psiquiatr*. 2006;28(1):5-9.
20. Razzouk D, Mari JJ, Shirakawa I, Wainer J, Sigulem D. How do experts recognize schizophrenia: the role of disorganization symptom. *Rev Bras Psiquiatr*. 2006;28(1):5-9.
21. Elkis H. A evolução do conceito de esquizofrenia neste século. *Rev Bras Psiquiatr*. 2000;22(Suppl 1):23-6.
22. Ichimiya T, Okubo Y, Suhara T, Sudo Y. Reduced volume of the cerebellar vermis in neuroleptic-naive schizophrenia. *Biol Psychiatry*. 2001;49(1):20-7.
23. Andreasen NC, O'Leary DS, Cizadlo T, Arndt S, Rezai K, Ponto LL, Watkins GL, Hichwa RD. Schizophrenia and cognitive dysmetria: a positron-emission tomography study of dysfunctional prefrontal–thalamic–cerebellar circuitry. *Proc Natl Acad Sci U S A*. 1996;93(18):9985-90.

24. Nopoulos PC, Ceilley JW, Gailis EA, Andreasen NC. An MRI study of cerebellar vermis morphology in patients with schizophrenia: evidence in support of the cognitive dysmetria concept. *Biol Psychiatry*. 1999;46(5):703-11.
25. Nasrallah HA, Jacoby CG, McCalley-Whitters M. Cerebellar atrophy in schizophrenia and mania. *Lancet*. 1981;1(8229):1102.
26. Okugawa G, Sedvall G, Nordstrom M, Andreasen N, Pierson R, Magnotta V, Agartz I. Selective reduction of the posterior superior vermis in men with chronic schizophrenia. *Schizophr Res*. 2002;55(1-2):61-7.
27. Keller A, Castellanos FX, Vaituzis AC, Jeffries NO, Giedd JN, Rapoport JL. Progressive loss of cerebellar volume in childhood onset schizophrenia. *Am J Psychiatry*. 2003;160(1):128-33.
28. Barak Y, Aizenberg D, Mirecki I, Mazeh D, Achiron A. Very late onset schizophrenia-like psychosis: clinical and imaging characteristics in comparison with elderly patients with schizophrenia. *J Nerv Ment Dis*. 2002;190(11):733-6.
29. DeLisi LE, Sakuma M, Tew W, Kushner M, Hoff AL, Grimson R. Schizophrenia as a chronic active brain process: a study of progressive brain structural change subsequent to the onset of schizophrenia. *Psychiatry Res*. 1997;74(3):129-40.
30. Nopoulos PC, Ceilley JW, Gailis EA, Andreasen NC. An MRI study of midbrain morphology in patients with schizophrenia: relationship to psychosis, neuroleptics, and cerebellar neural circuitry. *Biol Psychiatry*. 2001;49(1):13-9.
31. Katsetos CD, Hyde TM, Herman MM. Neuropathology of the cerebellum in schizophrenia--an update: 1996 and future directions. *Biol Psychiatry*. 1997;42(3):213-24.
32. Crespo-Facorro B, Wiser AK, Andreasen NC, O'Leary DS, Watkins GL, Boles Ponto LL, Hichwa RD. Neural basis of novel and well-learned recognition memory in schizophrenia: a positron emission tomography study. *Hum Brain Mapp*. 2001;12(4):219-31.
33. Crespo-Facorro B, Barbadillo L, Pelayo-Terán JM, Rodriguez-Sánchez JM. Neuropsychological functioning and brain structure in schizophrenia. *Int Rev Psychiatry*. 2007;19(4):325-36.
34. Leroy I, O'hearn E, Margolis R. Psychiatric syndromes in cerebellar degeneration. *Int Rev Psychiatry* (Abingdon, England). 2001;13:323-9.
35. Pollak L, Klein C, Rabey J, Schiffer J. Posterior fossa lesions associated with neuropsychiatric symptomatology. *Int J Neurosci*. 1996;87(3-4):119-26.
36. Landgrebe M, Marienhagen J, Langguth B, Sand P, Eichhammer P, Hajak G. Cerebellar and thalamic metabolic changes visualized by [18]-FDG-PET in olanzapine-induced acute akathisia. *Neuro Endocrinol Lett*. 2006;27(6):737-9.
37. Rocca CC, Lafer B. Alterações neuropsicológicas no transtorno bipolar. *Rev Bras Psiquiatr*. 2006;28(3):226-7.
38. Rocca CC, Lafer B. Neuropsychological disturbances in bipolar disorder. *Rev Bras Psiquiatr.* 2006;28(3):226-37.
39. Hamilton NG, Frick RB, Takahashi T, Hopping MW. Psychiatric symptoms and cerebellar pathology. *Am J Psychiatry*. 1983;140(10):1322-6.
40. Yadalam KG, Jain AK, Simpson GM. Mania in two sisters with similar cerebellar disturbance. *Am J Psychiatry*. 1985;142(9):1067-9.
41. Jurjus GJ, Weiss KM, Jaskiw GE. Schizophrenia-like psychosis and cerebellar degeneration. *Schizophr Res*. 1994;12(2):183-4.
42. Soares JC, Mann JJ. The anatomy of mood disorders--review of structural neuroimaging studies. *Biol Psychiatry*. 1997;41(1):86-106.
43. Yates WR, Jacoby CG, Andreasen NC. Cerebellar atrophy in schizophrenia and affective disorder. *Am J Psychiatry*. 1987;144(4):465-7.
44. Lippmann S, Manshadi M, Baldwin H, Drasin G, Rice J, Alrajeh S. Cerebellar vermis dimensions on computerized tomographic scans of schizophrenic and bipolar patients. *Am J Psychiatry*. 1982;139(5):667-8.
45. DelBello MP, Strakowski SM, Zimmerman ME, Hawkins JM, Sax KW. MRI analysis of the cerebellum in bipolar disorder: a pilot study. *Neuropsychopharmacology*. 1999;21(1):63-8.
46. Mills NP, Delbello MP, Adler CM, Strakowski SM. MRI analysis of cerebellar vermal abnormalities in bipolar disorder. *Am J Psychiatry*. 2005;162(8):1530-2.
47. Konarski JZ, McIntyre RS, Grupp LA, Kennedy SH. Is the cerebellum relevant in the circuitry of neuropsychiatric disorders? *J Psychiatry Neurosci*. 2005;30(3):178-86.
48. Loeber RT, Sherwood AR, Renshaw PF, Cohen BM, Yurgelun-Todd DA. Differences in cerebellar blood volume in schizophrenia and bipolar disorder. *Schizophr Res*. 1999;37(1):81-9.
49. Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ, Friston KJ. Neuroanatomical correlates of externally and internally generated human emotion. *Am J Psychiatry*. 1997;154(7):918-25.
50. Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ. Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiatry*. 1997;154(7):926-33.
51. Liotti M, Mayberg HS, McGinnis S, Brannan SL, Jerabek P. Unmasking disease-specific cerebral blood flow abnormalities: mood challenge in patients with remitted unipolar depression. *Am J Psychiatry*. 2002;159(11):1830-40.
52. Dolan RJ. A cognitive affective role for the cerebellum. *Brain*. 1998;121(Pt 4):545-6.
53. Sassi RB, Soares JC. Ressonância magnética estrutural nos transtornos afetivos. *Rev Bras Psiquiatr*. 2001;23(Suppl 1):11-4.
54. Agid R, Levin T, Gomori JM, Lerer B, Bonne O. T2-weighted image hyperintensities in major depression: focus on the basal ganglia. *Int J Neuropsychopharmacol*. 2003;6(3):215-24.
55. Beyer JL, Krishnan KR. Volumetric brain imaging findings in mood disorders. *Bipolar Disord*. 2002;4(2):89-104.
56. Graeff FG. Anxiety, panic and the hypothalamic-pituitary-adrenal axis. *Rev Bras Psiquiatr*. 2007;29(Suppl I):S3-6.
57. Abadie P, Boulenger JP, Benali K, Barré L, Zarifian E, Baron JC. Relationships between trait and state anxiety and the central benzodiazepine receptor: a PET study. *Eur J Neurosci*. 1999;11(4):1470-8.
58. De Bellis MD, Kuchibhatla M. Cerebellar volumes in pediatric maltreatment-related posttraumatic stress disorder. *Biol Psychiatry*. 2006;60(7):697-703.
59. Fernandez M, Pissiota A, Frans O, von Knorring L, Fischer H, Fredrikson M. Brain function in a patient with torture related post-traumatic stress disorder before and after fluoxetine treatment: a positron emission tomography provocation study. *Neurosci Lett*. 2001;297(2):101-4.
60. Bonne O, Gilboa A, Louzoun Y, Brandes D, Yona I, Lester H, Barkai G, Freedman N, Chisin R, Shalev AY. Resting regional cerebral perfusion in recent posttraumatic stress disorder. *Biol Psychiatry*. 2003;54(10):1077-86.
61. Driessen M, Beblo T, Mertens M, Piefke M, Rullkoetter N, Silva-Saavedra A, Reddemann L, Rau H, Markowitsch HJ, Wulff H, Lange W, Woermann FG. Posttraumatic stress disorder and fMRI activation patterns of traumatic memory in patients with borderline personality disorder. *Biol Psychiatry*. 2004;55(6):603-11.
62. Critchley HD, Melmed RN, Mathias CJ, Dolan RJ. Brain activity during biofeedback relaxation: a functional neuroimaging investigation. *Brain*. 2001;124(Pt 5):1003-12.
63. Critchley HD, Elliott R, Mathias CJ, Dolan RJ. Neural activity relating to generation and representation of galvanic skin conductance responses: a functional magnetic resonance imaging study. *J Neurosci*. 2000;20(8):3033-40.
64. Critchley HD, Corfield DR, Chandler MP, Mathias CJ, Dolan RJ. Cerebral correlates of autonomic cardiovascular arousal: a functional neuroimaging investigation in humans. *J Physiol*. 2000;523(Pt 1):259-70.
65. Kilts CD, Kelsey JE, Knight B, Ely TD, Bowman FD, Gross RE, Selvig A, Gordon A, Newport DJ, Nemeroff CB. The neural correlates of social anxiety disorder and response to pharmacotherapy. *Neuropsychopharmacology*. 2006;31(10):2243-53.
66. Sakai Y, Kumano H, Nishikawa M, Sakano Y, Kaiya H, Imabayashi E, Ohnishi T, Matsuda H, Yasuda A, Sato A, Diksic M, Kuboki T. Cerebral glucose metabolism associated with a fear network in panic disorder. *Neuroreport*. 2005;16(9):927-31.
67. Tamai S. Tratamento dos transtornos do comportamento de pacientes com demência. *Rev Bras Psiquiatr*. 2002;24(Supl I):15-21.
68. Wegiel J, Wisniewski HM, Dziewiatkowski J, Badmajew E, Tarnawski M, Reisberg B, Mlodzik B, De Leon MJ, Miller DC. Cerebellar atrophy in Alzheimer's disease-clinicopathological correlations. *Brain Res*. 1999;818(1):41-50.
69. Ackermann H, Daum I. [The cerebellum and cognition--psychopathological, neuropsychological and neuroradiological findings]. *Fortschr Neurol Psychiatr*. 1995;63(1):30-7.

70. Aylward EH, Reiss A. Area and volume measurement of posterior fossa structures in MRI. *J Psychiatr Res*. 1991;25(4):159-68.
71. Azzarelli B, Muller J, Ghetti B, Dyken M, Conneally PM. Cerebellar plaques in familial Alzheimer's disease (Gerstmann-Straussler-Scheinker variant?). *Acta Neuropathol*. 1985;65(3-4):235-46.
72. Rowe CC, Ackerman U, Browne W, Mulligan R, Pike KL, O'Keefe G, Tochon-Danguy H, Chan G, Berlangieri SU, Jones G, Dickinson-Rowe KL, Kung HP, Zhang W, Kung MP, Skovronsky D, Dyrks T, Holl G, Krause S, Friebe M, Lehman L, Lindemann S, Dinkelborg LM, Masters CL, Villemagne VL. Imaging of amyloid beta in Alzheimer's disease with 18F-BAY94-9172, a novel PET tracer: proof of mechanism. *Lancet Neurol*. 2008;7(2):129-35.
73. Baloyannis S. Pathological alterations of the climbing fibres of the cerebellum in vascular dementia: a Golgi and electron microscope study. *J Neurol Sci*. 2007;257(1-2):56-61.
74. Poeta LS, Rosa Neto F. Estudo epidemiológico dos sintomas do transtorno de déficit de atenção/hiperatividade e transtornos de comportamento em escolares da rede pública de Florianópolis usando a EDAH. *Rev Bras Psiquiatr*. 2004;26(3):150-5.
75. Arnsten AF. Fundamentals of attention-deficit/hyperactivity disorder: circuits and pathways. *J Clin Psychiatry*. 2006;67 Suppl 8:7-12.
76. Valera EM, Faraone SV, Murray KE, Seidman LJ. Meta-analysis of structural imaging findings in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2007;61(12):1361-9.
77. Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS, Blumenthal JD, James RS, Ebens CL, Walter JM, Zijdenbos A, Evans AC, Giedd JN, Rapoport JL. Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *JAMA*. 2002;288(14):1740-8.
78. Seidman LJ, Valera EM, Makris N, Monuteaux MC, Boriel DL, Kelkar K, Kennedy DN, Caviness VS, Bush G, Aleardi M, Faraone SV, Biederman J. Dorsolateral prefrontal and anterior cingulate cortex volumetric abnormalities in adults with attention-deficit/hyperactivity disorder identified by magnetic resonance imaging. *Biol Psychiatry*. 2006;60(10):1071-80.
79. Berquin PC, Giedd JN, Jacobsen LK, Hamburger SD, Krain AL, Rapoport JL, Castellanos FX. Cerebellum in attention-deficit hyperactivity disorder: a morphometric MRI study. *Neurology*. 1998;50(4):1087-93.
80. Giedd JN, Blumenthal J, Molloy E, Castellanos FX. Brain imaging of attention deficit/hyperactivity disorder. *Ann N Y Acad Sci*. 2001;931:33-49.
81. Casey BJ, Nigg JT, Durston S. New potential leads in the biology and treatment of attention deficit-hyperactivity disorder. *Curr Opin Neurol*. 2007;20(2):119-24.
82. Steinlin M. The cerebellum in cognitive processes: supporting studies in children. *Cerebellum* (London, England). 2007;6(3):237-41.
83. Mackie S, Shaw P, Lenroot R, Pierson R, Greenstein DK, Nugent TF 3rd, Sharp WS, Giedd JN, Rapoport JL. Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. *Am J Psychiatry*. 2007;164(4):647-55.