Cognitive disorders in pediatric medulloblastoma: what neuroimaging has to offer

A review

DUC HA HOANG, M.D.,1–3 ANNE PAGNIER, M.D.,4 KARINE GUICHARDET, M.PsY.,4 FANNY DUBOIS-TEKLALI, M.D.,4 ISABELLE SCHIFF, Ph.D.,4 GENEVIÈVE LYARD, M.PsY.,5 ÉMILIE COUSIN, Ph.D.,6,7 AND ALEXANDRE KRAINIK, M.D., Ph.D.2,3,6,8

1Department of Radiology, University Hospital Viettiep, Haiphong, Vietnam; 2Grenoble Institute of Neurosciences, INSERM U836, Grenoble; 3University Joseph Fourier, Grenoble; 4Department of Pediatrics, University Hospital Grenoble; 5Department of Pediatrics, University Hospital Bordeaux; 6UMS IRMaGe, Grenoble; 7Laboratory of Psychology and Neurocognition, UMR CNRS 5105, University Pierre Mendès, Grenoble; and 8Department of Neuroradiology and MRI, University Hospital Grenoble, France

Medulloblastomas are the most common malignant childhood brain tumors arising in the posterior fossa. Treatment improvements for these tumors have meant that there are a greater number of survivors, but this long-term patient survival has increased the awareness of resulting neurocognitive deficits. Impairments in attention, memory, executive functions, and intelligence quotient demonstrate that the cerebellum likely plays a significant role in numerous higher cognitive functions such as language, cognitive, and emotional functions. In addition, children with medulloblastoma not only have cerebellar lesions but also brain white matter damages due to radiation and chemotherapy. Functional neuroimaging, a noninvasive method with many advantages, has become the standard tool in clinical and cognitive neuroscience research. By reviewing functional neuroimaging studies, this review aims to clarify the role of the cerebellum in cognitive function and explain more clearly cognitive sequelae due to polytherapy in children with medulloblastoma. This review suggests that the posterior cerebellar lobes are crucial to maintaining cognitive performance. Clinical investigations could help to better assess the involvement of these lobes in cognitive functions.

(http://thejns.org/doi/abs/10.3171/2014.5.PEDS13571)

KEY WORDS • medulloblastoma • cerebellum • children • oncology • cognitive disorder • function neuroimaging

MEDULLOBLASTOMAS are the most common primitive neuroepithelial malignant tumors in children.21 These tumors are treated by a combination of surgery, radiation therapy, and/or chemotherapy.27 The good coordination and continuous improvement in these treatment methods have significantly increased the 5-year survival rate. However, the lengthened survival of these patients has resulted in the recognition of neurocognitive deficits that affect the acquisition of a range of skills, such as reading, mathematics, language, verbal and nonverbal memory, attention, and intelligence quotient (IQ).53 These cognitive deficits may result from many factors, such as mass effect to the fourth ventricle and brainstem, resection, radiotherapy, and chemotherapy, as well as the age of children at the time of treatment.20 Dennis et al.17 introduced the idea that vigilance was the principal attentional component to be affected by radiation therapy in patients with posterior fossa brain tumors following cranial radiation therapy. In addition, Brière et al.6 reported that auditory attention composite was also a significant weakness in these children, although such deficits tend to appear later in the posttreatment period. Patients with posterior fossa tumors are considered to be at an especially higher risk for neuropsychological sequelae; medulloblastomas have been the subject of this study for neuropsychological effects more so than those in any other brain location group, because of their high frequency, and because the worst outcome appears to fol-
Neuroimaging Appearances of Pediatric Medulloblastoma

Medulloblastomas are mainly located in the cerebellum (nearly 95%), most frequently on the midline of the inferior vermis. To evaluate the morphology, location, and correlations of these tumors and the surrounding structures, neuroimaging is crucial. On a CT scanner, medulloblastomas typically present as well-defined masses, slightly hyperdense or isodense to brain parenchyma, possibly calcified. The conventional MRI features of medulloblastoma are well-circumscribed, heterogeneously isointense to hyperintense on T2-weighted images, and hypointense to intermediate intensity on T1-weighted images with variable contrast enhancement. On advanced MRI (such as fMRI, diffusion weighted, MR spectroscopy, and others), medulloblastomas may appear hyperintense on diffusion-weighted imaging, suggesting a high cellular density. On MR spectroscopy, aggressive tumors have high levels of choline compared with N-acetyl aspartate, and a specific peak of taurine. Magnetic resonance perfusion may show hypervascular patterns.

Treatment and Sequelae Following Medulloblastoma Treatment

The most common treatment protocol incorporates surgery, radiation therapy, and/or chemotherapy, according to 3 main categories: the standard risk group (patients older than 3 years of age, with < 1.5 cm² residual tumor, and without metastasis at diagnosis), high-risk group (patients younger than 3 years of age, with ≥ 1.5 cm² residual tumor, with metastasis at diagnosis), and the infants or very young children group (less than 24 months of age). Thanks to the progress of treatment, 5-year event-free survival is currently more than 80% compared with less than 60% in the 1980s. However, the survivors commonly experience deficits in intellectual outcome and academic performance such as information processing speed, attention, and working memory, as well as motor, sensory, and endocrinological deficits, which can markedly affect their school performances and quality of life. In this paper, the role of the cerebellum and brain damage after treatments in cognitive disorders, in particular working memory deficits, is reviewed in reference to several clinical and functional neuroimaging studies.

Role of Neuroimaging in Studying Cognitive Disorders

Anatomical Connectivity

Diffusion tensor imaging has been applied to study the integrity of brain white matter because of its advantage in visualization of cerebral microstructures, white matter fibers, and the connections between brain regions in vivo without any invasive measures. With DTI tractography, cerebellar involvement in cognition can be observed in the engagement of certain dedicated cerebellar structures and in the fiber bundles that link these structures to other regions of the CNS, in particular the cortical-thalamic-cerebellar and cortico-ponto-cerebellar networks. The lateral prefrontal cortex has been confirmed as playing a critical role in working memory. Using DTI tractography, Ramnani et al. demonstrated the cortico-ponto-cerebellar tracts that connect the cerebellum and prefrontal cortex. In addition, the connections between the dentate nucleus and the cerebral cortex, striatum, hypothalamus, and thalamus could be visualized by DTI in a functional network, including working memory and other cognitive functions. Comparing a group of children treated for posterior fossa tumors to a group of healthy children in a DTI study, Law et al. confirmed the role of the cerebellar-lo-thalamo-cerebral pathway in working memory deficits in children treated for posterior fossa tumors. This working memory deficit may be due to the primary impact of cerebellar lesions associated with posterior fossa tumors in addition to the effects of radiation and chemotherapy, as well as the role of the cerebellum and the integrity of cerebro-cerebellar white matter in working memory. The role of a neural circuitry between frontal lobes and the cerebellum in neurocognitive impairment after posterior fossa tumor treatment in children was studied by Soelva et al., who showed a significantly lower volume of fronto-cerebellar fiber tracts in children with sequelae of posterior fossa tumors (cerebellar mutism syndrome) compared with healthy subjects that were well visualized by DTI. Diffusion tensor imaging tractography has therefore been considered a valuable tool to investigate the underpinnings of neurocognitive changes related to cerebellar damage.

In children with medulloblastoma, white matter is recognized as the most vulnerable element to radiation injury in the brain. Using DTI to quantify the fractional anisotropy (FA) index allows the detection of early white matter damage before the appearance of clinical disorders, which correlates to IQ reduction in medulloblastoma survivors. Similarly, Mabott et al. found that both FA and the apparent diffusion coefficient (ADC) appear to be sensitive measures of brain tissue damage due to radiation treatment. In addition, they also reported that decreased FA and increased ADC were related to lower
intellectual outcome in children with medulloblastoma. With its advantages, Khong et al. proposed using DTI with FA measure as a clinically useful biomarker for the assessment of treatment-related neurotoxicity in post-treatment childhood cancer survivors.

Resting-State Functional Connectivity

The human brain is a very effective, precise network that functions throughout life, even during sleep, and a great number of networks in different regions are constantly exchanging information with each other. The information is continuously being processed and transported between the regions of the brain by means of structural and functional connections. Whereas the main functional imaging methods are based on the principle of cognitive subtraction, which analyzes the difference between two or more cognitive conditions (including resting state), the default mode network can be captured by blood oxygen-level dependent (BOLD) fMRI when the subject is at rest (eyes closed or passive fixation). In a remarkable work of research on 1000 healthy subjects using resting-state functional connectivity MRI, Buckner et al. explored global topographic organization of the cerebellum and the organization of cerebro-cerebellar circuits at resting state. These investigators highlighted Crus I/II as a major cerebellar region coupled to the default network. In a more recent study of resting-state functional connectivity involving 228 young healthy adults, Sang et al. showed in a detailed manner the different patterns of resting-state functional connectivity between the hemispheric subregions and the vermis. They suggested a strong resting-state functional connectivity: between hemispheric lobules I–VI, vermal VIIb, IX, and the visual network; hemispheric lobules VI, VIIb, VIII and the auditory network; lobules I–VI, VIII, and the sensorimotor network; hemispheric Crus I/II and the frontoparietal network; or between hemispheric lobules VIIb, VIII, and the task-positive network (see the anatomy of cerebellar lobules in Fig. 2). These results clearly showed the existence of both functional integration and segregation among the cerebellar subregions and the cerebral cortex. Functional connectivity studies in addition to anatomical connectivity findings improve our understanding of functional cerebellar organization. Similarly, Bernard et al. found anatomo-functional relationships between the lobules of the anterior cerebellum and the cerebral motor networks, whereas the posterior cerebellum was related to prefrontal and parietal cortices involved in cognitive networks.

To identify the cognitive networks between brain regions and explain and predict the cognitive impairment caused by local brain lesions, a combined study of anatomical and functional connectivity would make it possible to define structural lesions and their functional consequences better and would be useful for deciding on the best neurosurgical and therapeutic strategy. Cruz-Gómez et al. suggested that resting-state fMRI may be applied to children with multiple sclerosis to evaluate their cognitive disorders due to white matter damage and cortical atrophy. Using this technique to evaluate the functional connectivity between the cerebellum and the brain in patients with schizophrenia, Collin et al. found

**Fig. 1.** Magnetic resonance images of the cerebellum before (A–E) and after (F) resection of a medulloblastoma in the fourth ventricle. The tumor appears heterogeneous on axial T2-weighted imaging (A), isointense on sagittal T1-weighted imaging (B), with enhancement on sagittal postcontrast T1-weighted imaging (C), hyperintense on axial diffusion-weighted imaging (D), and with a restriction of the ADC (E, axial). A postoperative axial T1-weighted image (F) shows the cerebellum after resection of the tumor.
Cognitive disorders in pediatric medulloblastoma

FIG. 2. Anatomical mapping of the human cerebellum with lobules labeled from the spatially unbiased infratentorial template of the cerebellum and brainstem by Diedrichsen.18 These axial (A and D), coronal (B and E), and sagittal (C and F) T1-weighted MR images are mainly focused on the posterior cerebellar lobes.

an impaired functional connectivity between the cerebellum and several left-sided cerebral regions, including the hippocampus, thalamus, middle cingulate gyrus, triangular part of the inferior frontal gyrus, supplementary motor area, and lingual gyrus. Resting-state fMRI has also been applied to study the role of the cerebellum in children with developmental disorders such as autism. Paakki et al.58 showed an abnormal neural connectivity (neural function less synchronized or regional homogeneity reduction) in bilateral cerebellar Crus I and several brain subregions on resting-state fMRI in patients with autism compared with healthy children. Thus, the authors also suggested a role of the cerebellum in nonmotor functional deficits. The cerebellum has a functional connection with the brain cortex,67 which can be interrupted due to cerebellar lesions after surgery in children with medulloblastoma. In addition, these patients have white matter damage34–42 and cortical atrophy43 due to radiotherapy and chemotherapy. Although there have been no studies using resting-state fMRI to assess cognitive function in patients with medulloblastoma, we believe that this method is feasible to diagnose and further study cognitive disorder in these patients and it can be applied in the future to children with posterior fossa tumors, similar to patients with multiple sclerosis.

Functional MRI

Functional MRI is based on the BOLD effect and uses deoxyhemoglobin concentration as an endogenous paramagnetic contrast agent. Functional MRI using a sequence (echo-planar imaging/T2*-weighted imaging) that is sensitive to the paramagnetic effects of deoxyhemoglobin allows the measurement of the local variations in deoxyhemoglobin concentration induced by neuronal oxygen consumption and neurovascular coupling.37 This technique indirectly reflects the neuronal activity that accompanies a sensory stimulus or the performance of a motor or cognitive task. Functional MRI has several advantages over the other neuroimaging methods.72 Because this technique is widely accessible, noninvasive, and nonirradiating, with high spatial and temporal resolution, it allows functional and anatomical images to be obtained simultaneously, with individual results.39 For all these reasons, fMRI has become the most widely used functional neuroimaging technique for mapping the brain, be it in clinical practice or the cognitive neurosciences.

Indeed, fMRI illustrates cerebellar activation during a variety of cognitive tasks including language, visuospatial, executive, and working memory processes (see example in Fig. 3). Hautzel et al.29 found that both verbal and nonverbal working memory tasks activate the cerebellum with robust BOLD signal increase predominantly in the posterior lobes (Crus I/II, lobule VI, VIIb, VIII, and IX; the location of these cerebellar lobules are illustrated in Fig. 2). This study demonstrated the crucial role of the posterior cerebellar lobes in the phonological loop and visuospatial sketchpad. Marvel and Desmond46 have conducted several studies investigating the role of the cerebellum in verbal working memory, in which activation was related to encoding, maintenance, and retrieval. Consistent with this finding, Thürling et al.77 highlighted the contribution of the cerebellum to the phonological loop, particularly lobule VI and Crus I, but did not find evidence for a contribution of the cerebellum to the visuospatial sketchpad. Reviewing several fMRI studies, Stoodley74 highlighted the cerebellar topography in cognitive function: bilateral lobule VI and Crus I/II are engaged in language processing; left lobules VI and VII are engaged in spatial processing; bilateral lobules VI, VII, and VIIa are engaged in working memory; bilateral lobules VI and VII and Crus I/II are engaged in executive function; and bilateral lobules VI and VIIa, and Crus
Neuronal activations during cognitive tasks in the cerebellum and cerebral cortex demonstrated using fMRI suggest the relationship between these active regions and an existence of a cerebro-cerebellar network. For example, Kirschen et al.36 showed that with auditory verbal information, activations were in the medial region (in particular the left inferior cerebellum [lobules VIII/IX]) of the cerebellar hemisphere, bilateral temporal gyrus, left supramarginal gyrus, and inferior parietal lobule, whereas with visual verbal information, activations were in the superior lateral region of the cerebellar hemisphere (superior cerebellum [lobule VI and Crus I]) and bilaterally in the fusiform gyrus and inferior occipital gyrus, as well as the superior parietal gyrus.

Several studies in patients with cerebellar lesions have reinforced the role of the cerebellum in cognitive function and working memory. Kirschen et al.37 performed an fMRI study on 12 children treated for cerebellar tumors and found that damage to lobule VIII in the left inferior hemisphere may be associated with impaired auditory digit span performance (phonological storage). This finding in particular confirmed the role of the cerebellum in cognition and verbal working memory. Using fMRI to investigate cognitive deficits in survivors of childhood cancer, in which the majority of these patients had a tumor located in the posterior fossa, Zou et al.80 found that the BOLD activation volume was significantly smaller in brain tumor survivors than in other groups, reflecting the influence of the cerebellar tumor lesions and the treatment methods on cognitive function; additional disorders of neurovascular coupling, probably due to radiotherapy, were also suggested.80 This was confirmed in a recent study by these authors,79 allowing them to suggest that fMRI is useful in evaluating neural responses to cognitive remediation. Thus, the fMRI outcomes in healthy subjects and patients with sequelae of cerebellar tumors have confirmed the role of the cerebellum in cognition and working memory and these studies demonstrate the feasibility of using BOLD fMRI to investigate cognitive function in survivors of childhood cancer.

**Cerebellum and Cognitive Impairment Through Clinical Studies**

That the cerebellum plays a role in motor coordination and control has been extensively documented since the early 1900s.34 Several case reports based on descriptions of patients with cerebellar lesions (such as strokes or tumors) moved progressively toward the hypothesis that the cerebellum could play a critical role in higher cognitive functioning.20 With advanced neuroimaging, the role of the cerebellum in these functions becomes gradually more evident.

Some clinical observations showed the cerebellar influence on nonmotor function. Schmahmann and Sherman69 reported a clinical study in 20 patients with various cerebellar pathologies and described these patients presenting with several cognitive impairments called...
Cognitive disorders in pediatric medulloblastoma
cerebellar cognitive affective syndrome. These included impairments in executive, visual-spatial, and linguistic abilities, with affective disturbance ranging from emotional blunting and depression to disinhibition and psychotic features. Steinlin et al.73 studied 24 patients who underwent operations during childhood for benign cerebellar tumors and revealed that these patients had resulting significant problems in attention, memory, processing speed, and communication. Clinical studies on the role of the cerebellum have mainly focused on two basic cognitive processes: language and memory.

Language Disorders

Speech ataxia in patients with cerebellar disease shares some characteristics with articulatory disorders caused by lesions to the anterior perisylvian regions, such as those observed in speech apraxia and Broca’s aphasia. This suggests that there is significant cooperation between the anterior perisylvian regions and the cerebellum with regard to speech timing. Silveri and Mischei70 also reported that patients with cerebellar lesions may develop a speech disorder called “agrammatism” that is an impairment of speech production characterized by the simplification of syntactic structures, shorter sentences, and by the omission and substitution of grammatical morphemes. In the short term, children who have undergone an operation for a cerebellar tumor may present with akinetic mutism, which is characterized by a difficulty in initiating complex behaviors such as verbal and nonverbal tasks. This may be followed by dysarthria and may have a later influence on learning and on reading ability. Dysarthria following resection of a childhood posterior fossa tumor was also reported by Morgan et al.,31 who concluded that speech deficits may persist even as long as 10 years after surgery, more significantly in children treated for left cerebellar hemisphere displayed visuospatial impairments in executive processing. On the other hand, working memory and verbal fluency deficits can result from a local cerebellar lesion.62 Similarly, in a study of patients presenting with cerebellar lesions, Bailleul et al.3 have shown that memory, attention, and cognitive function deficits were the most common signs in these patients. Patients who have undergone resection of a tumor involving the left cerebellar hemisphere displayed visuospatial impairment. A general impairment of working memory accompanied by visual memory and/or auditory memory impairment with no functional predominance has been observed in children undergoing operations for cerebellar tumors.12 Cognitive deficits following treatment for pediatric cerebellar tumors have been shown to affect visual working memory in particular.38 In children treated for a malignant posterior fossa tumor, Puget et al.64 showed that damage to the dentate nuclei and the inferior vermis could predict the degree of impairment of neurological and neuropsychological functions in these children. The IQ scores in these children were inversely correlated with the severity of the damage to the dentate nuclei. Taken together, these studies show that cerebellar damage leads to cognitive deficits.

Children with medulloblastomas have cognitive defects due to pretreatment factors (such as tumor growth, hydrocephalus, and compression and invasion of the brainstem and adjacent structures) and posttreatment factors (such as operation, radiation therapy, and chemotherapy) or a combination of these factors.11,61 Survivors with cerebellar medulloblastomas have more cognitive difficulties than children with cerebellar pilocytic astrocytomas (resection alone) who did not receive additional radiation therapy and chemotherapy. In other cases, children treated using radiation therapy and chemotherapy for malignant tumors such as acute lymphoblastic leukemia without cerebellar damage due to surgery have cognitive performances higher than survivors with medulloblastomas. Therefore, the cognitive impairments of patients with medulloblastomas might be due to a combination of pretherapeutic and posttherapeutic factors, including their potential interactions. To better understand the precise causes of cognitive deficits, experimental studies should take into account the focal change of the cerebellum (tumor and resection location), the regional changes of the cerebellum (radiation therapy), and the overall changes of the CNS (chemotherapy). Moreover, neuroplasticity before and after the treatment should also be considered, including the potential confounding effects of the age of the subject and the duration of the disease. Because ethical considerations may limit experimental investigations, a combination of clinical and neuroimaging studies are further needed, including clinical-based evidence approaches. Recognition of the critical cognitive contributions of the cerebellum might lead to improved cognitive outcome and quality of life for this patient population.

Memory Disorders

Several clinical studies on cerebellar damage have demonstrated the role of the cerebellum in cognitive function. Exner et al.25 reported that lesions to the posterior inferior cerebellar artery region lead to cognitive and affective deficits, but lesions to the superior cerebellar artery region do not, suggesting that the posterior cerebellar regions play a dominant role in cognitive and affective processing. On the other hand, working memory and verbal fluency deficits can result from a local cerebellar lesion. Similarly, in a study of patients presenting with cerebellar lesions, Bailleul et al.3 have shown that memory, attention, and cognitive function deficits were the most common signs in these patients. Patients who have undergone resection of a tumor involving the left cerebellar hemisphere displayed visuospatial impairment. A general impairment of working memory accompanied by visual memory and/or auditory memory impairment with no functional predominance has been observed in children undergoing operations for cerebellar tumors.12 Cognitive deficits following treatment for pediatric cerebellar tumors have been shown to affect visual working memory in particular.38 In children treated for a malignant posterior fossa tumor, Puget et al.64 showed that damage to the dentate nuclei and the inferior vermis could predict the degree of impairment of neurological and neuropsychological functions in these children. The IQ scores in these children were inversely correlated with the severity of the damage to the dentate nuclei. Taken together, these studies show that cerebellar damage leads to cognitive deficits.

J Neurosurg: Pediatrics / Volume 14 / August 2014
Remediation in Childhood Cancer Survivors

Thanks to advanced treatment, the number of childhood cancer survivors has significantly increased. It has become evident that these survivors are experiencing long-term neurocognitive deficits. Many efforts in treatment have been presented to reduce cognitive deficits for patients with medulloblastomas. These efforts have involved using chemotherapy to reduce the radiation dose in these patients and even completely eliminate craniospinal radiation therapy in infants with medulloblastomas. To our knowledge, no clinical study has demonstrated that specific cerebellar damages may result in cognitive disorders. However, a deeper understanding of functional topography in the human cerebellum may guide surgeons in the precise localization of critical areas of the brain in relation to the tumor, allowing them to perform more complete tumor resections while reducing the potential for neurocognitive morbidity. Currently, efforts to remediate cognitive deficits are crucial. With a pilot study, Butler and Copeland proposed the cognitive remediation program for childhood cancer survivors, including 3 approaches: brain injury rehabilitation, educational psychology, and child clinical psychology. This program also needs to be discussed because there have been a limited number of studies in patients treated for brain tumors, but it also suggested some positive effects. Butler and Copeland found that childhood cancer survivors who participated in cognitive training improved significantly in all attentional measures. In another study by Callu et al., rehabilitation allowed a child treated for a medulloblastoma to have fluent progression at school. The program encourages various groups, including the rehabilitation team, psychotherapists, parents, and teachers, to work together to improve cognitive function for these children. The communication between them is very important to quickly remediate a child’s cognitive difficulties. The remediation helps children to not only improve cognitive functions, but also to prevent uneasiness in the social and psychological domains to ameliorate their quality of life.

Conclusions

The important role played by the cerebellum in cognition, and in memory in particular, has been highlighted in this paper. Different cerebellar regions appear to be engaged depending on the cognitive tasks involved. Functional neuroimaging allows the anatomo-functional role of the cerebellum to be studied noninvasively and should make it possible to gain a better understanding of the cognitive disorders observed in children treated for medulloblastoma and other cerebellar tumors. Based on neuroimaging and clinical studies, attention should be paid to avoid or limit the damage of the posterior cerebellar lobes to minimize cognitive deficits. However, more research is needed on functional neuroimaging to better clarify the relationship between the cerebellum, the impact of additional treatments, and cognitive disorders, to choose the best therapeutic approach and improve the quality of life for children.

References


Disclosure

This work was supported by grants from the French Society for Childhood Cancer (SFCE) and the Hospital Clinical Research Program (PHRC) in Grenoble, France. Dr. Hoang received clinical or research support for this study from Grenoble University Hospital. Author contributions to the study and manuscript preparation include the following. Conception and design: Kramnik, Hoang. Acquisition of data: Kramnik, Hoang, Cousin. Analysis and interpretation of data: Kramnik, Hoang. Drafting the article: Kramnik, Hoang. Pagnier, Lyard, Cousin. Critically revising the article: Kramnik, Hoang, Pagnier, Guichardet, Dubois-Teklali, Lyard. Reviewed submitted version of manuscript: Kramnik, Hoang, Pagnier, Guichardet, Dubois-Teklali, Schiff. Statistical analysis: Kramnik, Hoang. Administrative/technical/material support: Kramnik, Hoang, Schiff. Study supervision: Kramnik, Hoang.
Cognitive disorders in pediatric medulloblastoma


49. Mulhern RK, Palmer SL, Reddick WE, Glass JO, Kun LE,


D. H. Hoang et al.