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REVIEW ARTICLE

The impact of neuroimaging advancement on neurocognitive evaluation in pediatric brain tumor survivors: A review

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ABSTRACT

Pediatric brain tumors are a type of tumors that are commonly present in children and young adults. With the improvement of treatment, the quality of life, especially the cognitive functioning, is gaining increasingly more attention. Apart from cognitive evaluations, neuroimaging studies begin to play an important part in neurocognitive functioning investigation. In this way, the brain tissue changes caused by tumor variables (including tumor location and tumor size) and treatment variables (including surgery, chemotherapy and radiotherapy) can be detected by neuroimaging. Recent advancement of neuroimaging techniques, such as functional-MRI (fMRI) and diffusion tensor imaging (DTI), made great contributions to understanding cognitive dysfunction and quantifying the effects of tumor variables and treatment variables. In recent years, laminar-fMRI provided a potentially valuable tool for examining the exact origins of neural activity and cognitive function. On the other hand, molecular fMRI might guide diagnosis and treatment of brain disease in the future by using new biomarkers, and DTI can detect white matter changes and obtain some anatomically specific information.

1 Introduction

Childhood cancers can be classified into tumors in brain, cardiac, respiratory, digestive tract, and other organs. Brain tumors, accounting for about 30% of all childhood cancers [1], are difficult to treat. Although the survival rate has reached above 60%, the decline in quality of life, especially the cognitive deficits, still presents an important issue which receives increasing attention from pediatric neurosurgeons and psychologists. There are many related factors that contribute to cognitive function, such as the tumor itself, the treatment, the patient, and environmental characteristics. In regard to psychosocial care, the Children's Oncology Group and the Psychosocial Standards of Care Project for Childhood Cancer have made great contributions [2, 3]. The National Cancer Institute Brain Tumor Progress Review Group Report suggests that routine cognitive and

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quality-of-life assessment should become the standard of care for patients with brain tumor. Many investigators began to emphasize the importance of baseline assessment for cognitive evaluation, because without it we cannot differentiate the most related factors or identify the true risks in the treatment variables [4, 5]. Although there is a number of neurocognitive examinations, neurocognitive studies have reached a state of so-called "stagnation". However, the emergence of neuroimaging studies in recent decades, which provides us with more visual and convincing demonstration, has led to increased interest in neurocognitive studies among multiple researchers.

2 Tumor variables

2.1 Tumor location

Most of pediatric brain tumors are located in deep brain areas, around the midline, such as suprasellar area, pineal gland, the 3rd ventricle, the 4th ventricle, and even the basal ganglia. Investigations imply that memory impairment is always related to these locations [5]. It has been suggested that these deficits occur due to existence of extensive connections among basal ganglia, the cerebral cortex, and the limbic cortex [5, 7]. Brain tumors can infiltrate and/or displace brain tissue, increase intracranial pressure, cause seizures, and disrupt structural and functional brain connectivity—all of these factors can contribute to cognitive deficits. Liang et al. [6] found that tumors in basal ganglia are associated with worse neuropsychological outcomes, including motor dysfunction, memory loss and emotional impairment. Tumors in suprasellar area and pineal gland may also have effect on neurocognitive function due to hormone deficiencies [8, 9], although this requires more evidence. We all know that cortical areas (such as primary motor area, somatosensory area, Wernicke's area, and Broca's area) are associated with cognition. In a diseased brain, the location of these regions needs to be discovered in order to precisely determine the resection areas [10, 11]. It has been considered that the cerebellum's function was limited to motor control and coordination. However, it has been demonstrated via diffusion tensor imaging (DTI) that the cerebellum is involved in cognitive functioning through cerebello-cerebral network [12]. It has been suggested that deep and periventricular tumors may cause memory impairment more than the superficial and frontally positioned brain tumors [5]. Sometimes, the effect of tumors' location on cognition depends on the associated complications rather than the location itself. For example, hydrocephalus secondary to posterior fossa tumor has been shown to correlate with neurocognitive deficits [13].

2.2 Tumor size

It was thought that tumor size had no correlation with cognitive function, but now studies have shown that it indeed affects the radiation field and may cause hydrocephalus, thus results in cognitive deficits [14]. A large-scale study examined the relationship between tumor size and sex, and found that boys had larger brain tumors than girls: boys have larger cranial volumes, which was assumed to be the reason for larger brain tumors in boys [15]. This finding suggests that gender should be considered as a potential risk factor on cognition assessment in pediatric brain tumor patients.

3 Treatment

3.1 Surgery

The effect of surgery on cognitive function depends on the neurosurgeon's experience, surgical intervention itself (type of surgical intervention),

surgical approach, and eventual complications. The advances in neurosurgical techniques in the past few decades have decreased the morbidity and mortality. Few studies have explored the isolated effect of surgery on neurocognition, due to the fact that most pediatric brain tumors are treated by surgery in combination with chemotherapy and radiotherapy, but rarely alone. According to some researchers, transient deficits always occur after surgery (e.g. memory declining and posterior fossa syndrome) [16–18]. Memory and attention, which are crucial in new knowledge attaining, are likely to be affected the most after surgery [19].

3.2 Chemotherapy

There is also little understanding on the effect of chemotherapy on neurocognition in pediatric patients with brain tumor. However, knowledge about chemotherapy for other cancers can serve as reference for its treatment. Some researchers suggest that chemotherapy has no significant medical impact, while others insist that there is a decrease in neurocognition in survivors. Chemotherapy may lead to cognitive deficits in acute phase, without as many long-term negative effects as seen in radiotherapy [20]. And it was reported that high-dose chemotherapy regimens were associated with transient, treatment-related white matter changes, lasting for about 6 months at most [21]. However, investigation on the effects of standard-dose chemotherapy on cognitive function is still lacking, and more research is needed to clarify if the effect of chemotherapy is reversible or causes long-term delayed damage. Investigations show that some chemotherapy agents can carry direct and indirect risks for cognitive impairment [22–26]. Particular agents can damage not only the brain parenchyma but also the white matter by crossing the blood–brain barrier (BBB) [27]. For example, the frequently used chemotherapeutic agent, 5-fluorouracil, can cross BBB simply by diffusion [27]. The neurocognitive declines often depend on the components of those agents. In other words, it has been suggested that the chemotherapy agents, which is applied to the pediatric brain tumor patients, may have little effect on restoring cognitive functioning, although we still need more evidence. Additionally, the changes in grey and white matter are usually reversible after chemotherapy treatment [17].

3.3 Radiotherapy

Radiotherapy is accepted as the most deleterious treatment that has the highest risk for cognitive deficit in pediatric patients [28, 29]. White matter and the hippocampus are especially sensitive to damage caused by radiotherapy [30–35], and some studies also indicate that memory loss is caused by global brain dysfunction after cranial irradiation [2, 31].

Injuries resulting from radiation can be seen in three phases. In the acute phase, disruption of BBB can induce some common symptoms, such as nausea, headache, and worsening of neurologic deficits. Cognitive problems existing in early-delayed phase are reversible in most cases, however, some may indeed develop into radiation somnolence syndrome or focal encephalopathy. This might be caused by BBB disruption or oligodendrocyte injuries. Effects in late-delayed phase are always irreversible and progressive, and appear as a result of ischemia, demyelination of white matter, and necrosis. Related risk factors include the radiated tissue volume, the total dose of radiation, and concomitant chemotherapy [36].

Cranial radiation therapy and chemotherapy have synergistic action via vascular changes, cerebral calcifications, demyelination, and BBB permeability. Radiotherapy and chemotherapy can affect attention due to white matter loss [20].

4 Neuroimaging advancement

In contrast to the relatively large amount of researches that used cognitive assessments, such as the Wechsler Intelligence Scale, the neuroimaging studies are much less prevalent. However, neuroimages have great value in identifying subtle neural structural changes and/or circuits [20]. This may help uncover the neural basis for cognitive deficits. In the late 20th century, the development of neuroimaging methodologies was crucial for cognitive function assessment in cortical motor regions [37]. Functional brain mapping was used as a tool to determine the boundaries between brain tumors with variable tumor site and healthy brain tissue [10]. Direct electrical stimulation (DES) may be the oldest mapping technique. It is the "golden standard" at present, however, it's still being criticized for its invasiveness [38] and its possibility to induce seizures [10]. Older studies have demonstrated that structural brain changes affect its function. New imaging techniques, such as positron emission computed tomography (PET) and functional-MRI (fMRI), greatly promote our understanding about the relationship between anatomy and cognitive function. PET uses radioactive agents as tracer, such as ^{15}O. Deoxygenated hemoglobin is more sensitive to the magnetic field. fMRI measures the ratio of hemoglobin and deoxygenated hemoglobin, which is called blood oxygenation level-dependent (BOLD) effect. Compared to PET, fMRI has some advantages. Firstly, it can be more commonly used in clinics. Secondly, without radioactive elements, fMRI can be measured repeatedly, in order to obtain whole data and comprehensive understanding. Lastly, fMRI can detect about 3 cubic millimeter voxel, in this way, high spatial resolution can be obtained.

4.1 Electroencephalogram (EEG) and electrocorticography (ECoG)

EEG records bioelectrical activity of the brain through electrodes placed on the scalp. It was first applied by a British physician, Richard Caton, who tried to observe electrical impulses from the living brains of rabbits and monkeys in 1875. EEG is known for its portability, affordability and high temporal resolution, but has problems of attenuation and distortion of signals. On the contrary, ECoG can also detect the electrical discharges of the cortex with better signal accuracy. Both of these techniques can be used for epileptogenic mapping and speech and motor mapping, but ECoG is an invasive technique [10].

4.2 fMRI

fMRI is used for language lateralization and preoperative mapping of higher cortical regions, and has a high validity against DES, which is the "golden standard" for brain function mapping.

Neurons acquire energy from the adjacent capillaries via oxygen and nutrient diffusion from blood, which can be visualized by fMRI images obtained by blood oxygen level-dependent (BOLD) technique [39]. But in order to exclude false positive results, large numbers of image samples are needed in cognitive studies [40]. As a measurement of cognitive functioning, EEG has advantage in temporal resolution, while fMRI has superiority in spatial resolution. Efforts have been made to combine these two, but it is too difficult to realize due to sophisticated signal processing and high software requirements [41–43]. fMRI has excellent whole brain coverage, and it shows more visual structure than EEG, therefore, is more commonly used than EEG in cognitive neuroscience research [44]. To analyze fMRI images, functional segregation and functional integration focus on specific brain regions and

the relationship or connectivity between them, respectively [39].

Resting-state fMRI is based on spontaneous BOLD signal fluctuation without task requirement. So it is often used in neurological and neurosurgical conditions, especially for pediatric patients [45]. In task-based fMRI, the changes associated with specific tasks can provide brain function mapping. For example, fMRI plus the Sternberg task can reveal the necessary functional regions responsible for normal working memory performance, or sometimes for other working memory paradigms [11].

Laminar fMRI is a kind of fMRI method to record neural activity. Neural activity is highly inter-connective in each brain area, sending commands by top-down signals and receiving sensory signals by bottom-up signals [46–49]. Traditional fMRI is able to detect both top-down and bottom-up responses. To distinguish these two kinds of signals, invasive form of EEG has been used in animals before. But for human beings, recent development of laminar-fMRI provides an opportunity to acquire the same information without the use of invasive procedures [49–51]. The feed forward, feedback and horizontal responses can be shown by means of laminar fMRI, an *in vivo* measurement for neural activity [52]. However, this is not a direct tool, instead, it identifies the BOLD response towards the cortical surface [53]. The neocortex, a massively recurrent network that occupies around 90% of the brain cortex, consists of 6 layers of grey matter [54–58]. Also, the brain function depends on inter-area and inter-laminar communication [47, 59]. By using laminar fMRI, the origins of neural activity can be examined, and information in all domains of cognitive neuroscience may be acquired [52].

Molecular fMRI is another form of fMRI used to examine the neural activity. It uses fluorescent dyes and proteins that can reach deep brain regions. These specific dyes and proteins influence magnetic signals but not the visible light, therefore they are perfectly suited for deep brain scanning [60, 61]. Molecular fMRI achieves great progress in animal research, and it can be applied to human in order to study cognitive functioning. Moreover, molecular fMRI may guide diagnosis and treatment of brain diseases by defining new biomarkers or mechanically significant hallmarks of neural processing [62]. The application of molecular fMRI mainly lies not only in examining neural correlations with cognitive process, but also in guiding diagnosis and treatment of brain diseases.

4.3 DTI

White matter plays an important role in interconnecting different brain regions and information transfer. Therefore, the integrity of brain white matter pathways contributes a lot to the complex cognitive tasks [26]. MRI is a common, clinically used neuroimaging tool, which can not only provide images of superior quality but also avoid damages caused by ionizing radiation (e.g. in CT scan) or radioactive tracers (e.g. in PET). Until now, DTI has been the only technique available for white matter tract imaging. DTI is important in pre-operative planning and post-operative follow-up [10]. It provides an opportunity to detect microstructural white matter changes, and detect associations between functional and structural abnormalities [63]. With sufficient sensitivity, DTI may be good at investigating neuronal substrate of therapy-induced cognitive deficits [27]. DTI has also been demonstrated to be valid for language mapping, when compared to DES [10]. DTI can provide a non-invasive assessment of white matter construction. Sometimes, it may be even more sensitive to subtle changes in the microstructure of white matter fiber tracts and shows more detailed information than the

cognitive scales [14, 64]. In this way, DTI can be used to analyze whether white matter damage is involved in cognitive decline.

With the help of DTI, various measures can be applied clinically, including mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD). MD reflects the overall diffusion magnitude, while RD and AD reflect the average diffusion. Reduced FA values are found in cases of demyelination [65, 66], edema [67, 68], gliosis [69], inflammation [70, 71], increased axon diameter [72], lower axonal packing density [73], tortuosity [74], and increased membrane permeability [75].

The analysis of DTI data also consists of voxel-based analysis (VBA), region-of-interest (RIO) analysis, histogram, and fiber tractography (FT). VBA can be used to detect potential group differences without prior knowledge or hypothesis on the extent and location of the tumor. It is a fully-automatic procedure, which requires well-aligned brain tissue. We could analyze tissue density or volume differences through VBA quantitation in T1 or DTI. The techniques can divide the brain into grey matter, white matter and cerebrospinal fluid. RIO analysis is commonly used to acquire the underlying data value but it takes much time to get the results, so it is not suitable for large data. Histogram is sensitive and automatic, while it is fit for dealing with global diffuse effect, not indicating the lesion site. FT provides virtual reconstruction of white matter pathways by integrating the DTI measurements anatomically. However, FT needs high quality diffusion weighted imaging (DWI) data to minimize the error accumulation [26].

DTI is a very sensitive integrity detector of white matter. A promising approach of fiber tractography can obtain some specific information anatomically. Complementary data gained by tractometry represent a proposed multi-modal way to quantify specific microstructural properties along white matter fibers.

However, the use of DTI is also being discussed due to its drawbacks as it is based on the measurement of diffusion of water molecules. Brain tumors can influence the diffusion properties, changing the apparent anatomy of fiber tracts. In addition, intraoperative brain shift may lower the accuracy of DTI [10]. Although there are numerous pitfalls for acquiring, processing, analyzing and interpreting the data, DTI is still valuable, especially when it is combined with fMRI or trans-cranial magnetic stimulation, etc.

It is suggested to combine fMRI and DTI as this combination can provide precise cortical mapping and white matter tract mapping at the same time, allowing for greater accuracy [10].

5 Conclusion

Pediatric brain tumors account for about 30% of all childhood cancers. Neurocognitive function, an important aspect of quality of life, used to be assessed only by cognitive scale. However, new neuroimaging techniques have been shown as excellent tools for cognitive function analysis because they can help us distinguish subtle changes in brain tissue. Furthermore, laminar fMRI can help provide information and help us understand all domains of cognitive neuroscience, which couldn't be explored by traditional fMRI. Apart from that, molecular fMRI can visualize deep brain regions by using special fluorescent dyes and proteins which can help us to examine neural correlations in cognitive processes. DTI is sensitive to fiber changes in white matter, therefore, can help analyze cognitive decline caused by white matter injury (induced by tumor itself or treatment variables). All mentioned neuroimaging techniques provide us with qualitative and quantitative measurements and,

if applied in neurocognitive functioning analysis, will make a great contribution to neurocognitive defect analysis.

Ethical approval

This article does not contain any studies with human participants or animal performed by any of the authors.

Conflict of interests

All the authors declare that they have no conflict of interests.

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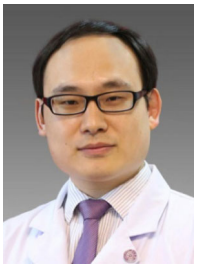

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