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The Current Utilization of Cognitive Tests in the Research of Radiation-Induced Cognitive Dysfunction in Rodent Models

Xiao-Yang Li, Lie-Song Chen, Li-Yuan Zhang, and Ye Tian*

Department of Radiotherapy and Oncology, The Second Affiliated Hospital of Soochow University, Institute of Radiotherapy and Oncology, Soochow University, Suzhou, Jiangsu, China

Abstract

Whole brain irradiation using low LET rays has remained the mainstay to treat some primary and metastatic brain tumors. Radiation-induced cognitive dysfunction is a progressive and irreversible late side effect after whole brain irradiation and inevitably decreases the quality of life of cancer survivors. To address this negative issue, many studies have been performed to explore the mechanisms of radiation-induced cognitive dysfunction and to develop efficacious preventive and treating measures. The prerequisite and foundation of implementing a persuasive and profound study to investigate radiation-induced cognitive dysfunction is the utilization of widely acknowledged animal models and universally applied cognitive tests. In this review, articles studying radiation-induced cognitive dysfunction from 2011 to 2016 were collected. The establishment of animal models and detailed utilization of cognitive tests were analyzed and summarized. This review summarized the general range of irradiation doses and time intervals utilized and the effects of these two factors on the results of cognitive tests.

Keywords: Rodent Models; X-ray; Whole brain irradiation; Cognitive dysfunction; Cognitive test

Abbreviation: MWM: Morris Water Maze; NOR: Novel Object Recognition; NLR: Novel Location Recognition; PA: Passive and Active avoidance test.

Introduction

Whole brain irradiation (WBI) is the main modality used to treat brain metastatic tumors as well as some primary tumors, and it is sometimes the sole method to treat some pediatric tumors, such as medulloblastoma [1] and intracranial germ cell tumor [2]. Radiation-induced cognitive dysfunction is a late effect caused by WBI from several months to years' post-irradiation with incidence and severity increasing over time, and has been reported to occur in up to 50% of long-term brain tumor survivors in previous clinical studies [3]. This negative issue has seriously affected the quality of life of patients [4]. Particularly, the long-term survival of pediatric patients with marked cognitive dysfunction results in significant socioeconomic burdens [5,6].

Recent clinical studies suggest that radiation-induced damage to the hippocampus plays a considerable role in the cognitive dysfunction of patients after cranial irradiation. In particular, deficits in learning, memory, and spatial processing observed in patients who received WBI are thought to be related to hippocampal injury [7]. The mechanisms of radiation-induced cognitive dysfunction are not yet fully understood. According to the available knowledge, radiation-induced cognitive dysfunction is hypothesized to result from dynamic interactions between multiple cell types: vascular and glial clonogens, neurogenesis, neural function and neuroinflammation [8-10]. Therefore, studies into the mechanisms and preventive measures of radiation-induced cognitive dysfunction are of paramount importance to decrease the side effects of WBI and increase the quality of life of patients. To achieve this goal, widely acknowledged animal models and universally utilized cognitive tests are the prerequisite and foundation.

The Establishment of Rodent Models

Rodents, including mice and rats, are the most commonly utilized animal models in medical research given their genetic background, anatomical structure, operability, and relatively low cost of use [11]. Experimental data indicated that rodents showed similar anatomical changes and physiopathological mechanisms to human beings after cranial irradiation [12]. In addition, the effects of radiation on rodents could be assessed over relatively short time periods-weeks to months rather than years to decades. Anatomical and functional changes of rodents after cranial irradiation are dependent on age, dose, and sex, which are compatible with the risk factors in human patients [13]. Given that these observations are representative of the effects seen in patients, the rodent model would enable the efficient study of mechanisms and treatments.

The differences in rodent species, strains, age and sex could influence the results of cognitive tests. Some studies indicated that rats and mice demonstrated different strategies in spatial learning [14], and even various strains of the same species exhibited different cognition levels [15]. Possessing nearly 70% homology with humans at the genetic level, mice are relatively easy to maintain and breed, and are easily handled in the research setting. However, the small size of the brain makes it difficult to accurately locate, resulting in uneven dose distribution and damage to the respiratory and digestive system. In addition, mice are too fragile to undergo repeated anesthesia when long-term observation periods are required. Therefore, rats are utilized more frequently than mice in radiation-based studies [11]. Nonetheless, no abundant research has compared the difference of radiation-induced cognitive dysfunction between different species and strains of rodents.

The estrogen level of female rodents could exert some effects on the level of anxiety to interfere with the results of cognitive tests [16]. The age at which rodents are exposed to radiation also affects the results

*Corresponding author: Ye Tian, Department of Radiotherapy and Oncology, The Second Affiliated Hospital of Soochow University, Suzhou Key Laboratory for Radiation Oncology, Suzhou, China, Tel: 8651265225662; E-mail: dryetian@126.com

of cognitive tests. Neonatal and juvenile subjects generally have higher baseline levels of cell proliferation, caspase activity (modulating cell dysfunction and death and other important biological processes) and microglia than adults, in addition to different cytokine expression profiles [17]. This may lead to increase susceptibility to cognitive deficits and more permanent dysfunction. In fact, Forbes demonstrated deficits in object memory after juvenile irradiation, whereas no deficits were apparent in rats irradiated in middle age [18]. Older rats show cognitive impairments after irradiation with sufficient follow-uptimes [8,19]. Moreover, aging was reported to mask the detection of radiation-induced cognitive dysfunction [20]. In addition, older rats do show cognitive impairments after irradiation with a sufficient follow-up time [8,19]. Therefore, relatively young male rodents, including various strains of rats and mice, are currently utilized in studies that evaluate radiation-induced cognitive dysfunction. Ages of less than six months and three months are considered to be juveniles for rats and mice of various strains, respectively [21,22].

Whole body irradiation [23], whole brain irradiation with low [24] or high LET rays [25] and stereotactic radiosurgery [26] have all been shown to be able to induce cognitive dysfunction in rodents. Nonetheless, WBI with X-ray or γ-ray is the main modality to treat brain tumors in current clinical practice. Compared with stereotactic radiosurgery, WBI is more likely to cause radiation-induced cognitive dysfunction [27,28]. Therefore, WBI with X-ray or γ-ray on rodents could best simulate clinical scenarios in which a cognitive dysfunction was induced. In this review, we collected studies evaluating radiation-induced cognitive dysfunction using rodents of less than 6-month-old receiving WBI of low LET (Linear Energy Transfer) from 2011 to 2016 and summarized the detailed utilization of cognitive tests as well as the demonstration of radiation-induced cognitive dysfunction within one year post-irradiation (Table 1). The biological effective dose of each dosage was calculated, assuming that the α/β ratio of normal brain tissues is 3.

Cognitive Tests to Evaluate Radiation-Induced Cognitive Dysfunction

Radiation-induced cognitive dysfunction occurs in up to 90% of adult brain tumor patients who survive more than 6 months after WBI, with incidence and severity increasing over time. It is characterized by decreased verbal memory, spatial memory, attention, and novel problem-solving ability [9,24]. Cognitive dysfunction progresses to dementia in approximately 2% to 5% of long-term survivors who have received WBI, including memory loss, ataxia, and urinary incontinence. These effects can be seen without clinical or radiographic evidence of demyelination or white matter necrosis [10]. However, cognitive dysfunction could be detected by various cognitive tests with different endpoints. Cognitive tests include those that are widely thought to be hippocampal-dependent, in which irradiation impairs spatial learning in the Barnes maze, radial arm maze, novel location recognition (NLR), water maze, alternation tasks, and contextual fear conditioning. In tasks that are not clearly dependent on the hippocampus, some groups have demonstrated deficits in novel object recognition (NOR), passive avoidance, associative learning, active avoidance, and reversal learning and set shifting [19]. Among all of these cognitive tests, the open field, Morris water maze (MWM), NOR/NLR and passive and active avoidance tests are the most commonly utilized methods. The open field test is utilized to evaluate the locomotor activity and level of anxiety rather than cognition [29]. MWM consists of place navigation and spatial probing to evaluate spatial learning and reference memory, respectively [30]. NOR/NLR is used to examine recognition memory

[31,32], while the passive and active avoidance test is used to evaluate associative memory [33]. Depending on the different types of cognition evaluated, these cognitive tests are utilized separately or in various combinations (Table 2).

In each cognitive test, different endpoints are applied to evaluate cognition. In the open field test, a decreased number of crossings and total distance moved represent less locomotor activity [34,35]. In some studies, the number of stops and rearings are used to evaluate locomotor activity [36,37]. Decreased center incursions, latency to the center, percentage time in the center and distance ratio are indications of an increased level of anxiety [16,38]. In the place navigation of MWM, latency to platform, path length and total distance to the platform are the three most commonly used endpoints in research [39,40]. Latency, path length and total distance during one entire test decrease with time because animals gradually learn to find the hidden platform. Irradiated rodents exhibit much slower and shallower decreases than non-irradiated ones, indicating that spatial learning is impaired by radiation [41]. In spatial probing, journey distance of target to total, target quadrant stay time and distance to platform zone are always used [42,43]. A shorter journey distance of target to total and target quadrant stay time, a longer distance to the platform zone indicate impaired reference memory induced by radiation. In NOR, the percentage exploration time in the novel object and discrimination ratio (novel object exploration time/total exploration time with both objects) are commonly used end points [44,45]. The time to explore familiar objects was used in Lee's research to indicate impaired memory recognition [46]. Radiation-induced cognitive dysfunction is demonstrated by the decrease of exploration time in the novel object and discrimination ratio. In NLR, the exploration ratio (novel location exploration time/total exploration time with both locations) is the most frequently used endpoint to measure location novelty recognition [47-49]. Total time in exploration of the novel location, frequency of visits and latency to explore the novel location, percentage time spent in the novel location or the ratio between the time spent in the novel location and familiar location are occasionally utilized [38,44]. The decreased time spent in novel location indicates impaired cognitive function. As for the passive and active avoidance test, latency to enter the dark compartment and light compartment are the two most commonly used endpoints [50,51]. Decreased latency to enter the dark compartment and increased latency to enter the light compartment indicate impaired associative memory.

The Irradiation Dose and Time Intervals Post-Irradiation Used to Evaluate Cognitive Dysfunction in Cognitive Tests

Although most experiments indicated cognitive dysfunction following cranial irradiation in rodent models, there are also some studies have shown normal and even improved cognition after irradiation. Factors that influence the detection of cognitive dysfunction include the specific behavioral domain assessed, sensitivity of the assay, age at which the radiation is initiated, time after irradiation that cognition is assessed, gender of the subject, region irradiated (i.e., whole-body, whole-brain or specific brain regions), total dose of radiation administered and if the radiation is administered as a single dose or in multiple fractions [19]. In this review, the irradiation dose and time interval post-irradiation are emphasized.

Irradiation dose in cognitive tests

Open field test: Irradiation doses from 2 Gy/1f [35,51,52] to 30 Gy/1f [51] (BED=3.33 Gy and 330 Gy respectively) were used in various studies, among which 2 Gy/1 f [35,51,52], 5 Gy/1 f [34], 8 Gy/1 f

Publishing Date	First Author/ Correspondent Author	Affiliation	Irradiation and Rodents	Observation time	Cognitive Tests
2011 [47]	Acharya/Limoli	University of California, USA	10 Gy/1 f Athymic Nude rats	1 and 4 Months	NLR
2014 [48]	Acharya/Limoli	University of California, USA	10 Gy/1 f Athymic Nude rats	1 and 8 Months	NLR
2015 [49]	Acharya/Limoli	University of California, USA	10 Gy/1 f Athymic Nude rats	2 Months	NLR
2011 [44]	Raber/Raber	University of California, USA	10 Gy/1 f C57BL/6J mice	3 Months	MWM, NOR, NLR, Rotorod, Conditioned fear
2012 [62]	Zou/Huang TT	University of California, USA	5 Gy/1 f C57BL/6J mice	3 Months	Radical arm water maze NOR, NLR
2013 [42]	Belarbi/Rosi	University of California, USA	10 Gy/1 f C57BL/6J mice	2.5 Months	MWM, NOR
2014 [18]	Forbes/Riddle	Wake Forest School of Medicine, USA	40 Gy/8 f F344xBN rats	3, 6 and 12 Months	NOR, NLR
2010 [64]	Conner/ Riddle	Wake Forest School of Medicine, USA	40 Gy/8 f F344xBN rats	6.5 and 13 Months	NOR
2014 [60]	Greene-Schloesser/ Greene-Schloesser	Wake Forest School of Medicine, USA	40 Gy/8 f F344xBN rats	6.5-7 Months	MWM, NOR
2011 [20]	Shi/Robbins	Wake Forest School of Medicine, USA	40 Gy/8 f F344xBN rats	14 Months	MWM
2012 [46]	Lee/Robbins	Wake Forest School of Medicine, USA	40 Gy/8 f F344xBN rats	6.5 and 7 Months	NOR
2014 [65]	Peiffer/Peiffer	Wake Forest School of Medicine, USA	30 Gy/6 f, 39 Gy/6 f F344xBN rats	10-11 Months	MWM
2012 [50]	Warrington/Sonntag	University of Oklahoma, USA	36 Gy/8 f C57BL/6J mice	1 and 3 Months	PA, Barnes Maze
2013 [61]	Jenrow/Jenrow	Henry Ford Hospital, USA	10 Gy/1 f F344xBN rats	6 Months	NOR
2011 [38]	Rao/Wetmore	Mayo Clinic, USA.	20 Gy/5 f C57BL/6J mice	1 and 5 Months	Open Field, NOR, NLR, Elevated Plus Maze, Rotorod
2015 [53]	Tome/Tome	Albert Einstein College of Medicine	C57BL/6J mice 10 Gy/1f	7 to 16 Days	Open Field (7 Days), Elevated Plus Maze (12 Days), NLR (8 and 11 days), NOR (15 and 16 Days)
2015 [45]	Piao/Tabar	Memorial Sloan Kettering Cancer Center, USA	SD rats 50 Gy/10 f	10 Weeks	MWM, NOR, NLR, Rotorod
2013 [37]	Kalm/Blomgren	University of Gothenburg, Sweden	8 Gy/1 f C57BL/6J mice	1 Year	Open Field, IntelliCage
2011 [36]	Karlsson/Blomgren	University of Gothenburg, Sweden	8 Gy/1 f C57BL/6J mice	3.5 Months	Open Field, IntelliCage, Trace Fear Conditioning
2012 [16]	Roughton/Blomgren	University of Gothenburg, Sweden	8 Gy/1 f C57BL/6J mice	4 Months	Open Field, IntelliCage
2010 [66]	Caceres/Guelman	University of Buenos Aires, Argentina	5 Gy/1 f Wistar rats	1 Month	Open Field, NOR, PA
2011 [34]	Caceres/Guelman	University of Buenos Aires, Argentina	5 Gy/1 f Wistar rats	1 Month	Open Field, PA, Elevated Plus Maze
2010 [67]	Liu/Liu	Sun Yat-sen University, China	10 Gy/1 f, 20 Gy/1 f, 40 Gy/1 f SD rats	7, 20 Days and 2 Months	MWM
2011 [40]	Zhou/Liu	Sun Yat-sen University, China	20 Gy/4 f, 40 Gy/8 f SD rats	1, 2, 3 Months	MWM
2014 [41]	Peng/Tang	Sun Yat-sen University, China	30 Gy/1 f Balb/c mice	2 Months	MWM
2015 [58]	Xu/Tang	Sun Yat-sen University, China	30 Gy/1 f Balb/c mice	2 Months	MWM
2014 [55]	Ji/Tian	Soochow University, China	20 Gy/1 f SD rats	2 Months	Open Field, MWM
2014 [51]	Ji/Tian	Soochow University, China	10 Gy/1f, 30 Gy/1 f SD rats	1 Month	Open Field, MWM, PA
2013 [35]	Zhang/Tian	Soochow University, China	10 Gy/1 f, 20 Gy/1 f SD rats	2 Months	Open Field, MWM, PA

2014 [54]	Zhang/Tian	Soochow University, China	20 Gy/1 f	2 Months	Open Field, MWM
			SD rats		
2016 [52]	Sun/Tian	Soochow University, China	2 Gy/1 f, 10 Gy/1 f,	1, 2, 3, 6 Months	Open Field, MWM, NOR, NLR
			20 Gy/1 f, 30 Gy/1 f		
2015 [39]	Dong/Wu	Tongji Medical College, China	2 Gy/1 f, 10 Gy/1 f C57BL/6J mice	1.5 Months	MWM
2013 [56]	Semmler/Linnebank	University Zurich, Switzerland	20 Gy/4 f, 40 Gy/4 f	14 Days, 1.5 Months	Open Field, MWM
			Wistar rats		
2011 [63]	Jahanshahi/Khoshnazar	Golestan University of Medical Sciences, Iran	10 Gy/1 f, 10 Gy/5 f	2 Days	PA
			Wistar rats		
2010 [68]	Motomura/ Natsume	Nagoya University School of Medicine, Japan	10 Gy/1 f,	2 Days	MWM, NOR
			C57BL/6J mice		
2012 [43]	Joo/Lee/Nam	Seoul National University College of Medicine, Korea	20 Gy/4 f,	2 Months	MWM
			C57BL/6J mice		
2013 [59]	Oh/Lee	Pusan National University, Korea	5 Gy/1 f	Right after IR 17 Days	MWM (Right after IR) PA (17 Days)
			C57BL/6J mice		

MWM: Morris Water Maze; NOR: Novel Object Recognition; NLR: Novel Location Recognition; PA Passive and Active avoidance test.
Some research groups are dedicated to the study of radiation-induced cognitive dysfunction, including University of California, Wake Forest School of Medicine, University of Gothenburg, University of Buenos Aires, Sun Yat-Sen University and Soochow University. Different research groups utilized different rodent species, irradiation dose and time intervals to evaluate cognition. Cognitive tests were utilized separately or with various combinations.

Table 1: Summary of recent researches studying radiation-induced cognitive tests.

	Open Field	**Morris Water Maze**	**Novel Objective Recognition**	**Passive and Active Avoidance**
			Novel Location Recognition	
Cognition to evaluate	Locomotor activity	Spatial learning	Recognition memory	Associative memory
	Level of anxiety	Reference memory	Spatial Memory	
Endpoints commonly used	a. Number of lines crossings	a. Latency, path length and total distance to the platform (Place navigation)	a. Discrimination ratio	a. Latency to enter the dark compartment
	b. Total distance moved	b. Target quadrant stay time (Spatial probe)	b. % time exploration time in novel objects (NOR)	b. Latency to enter light
	c. Frequency or total time of rearing or leaning		c. Total time, Frequency of visits and Latency to explore the novel spatial location (NLR)	c. Step-through latency
	d. Grooming			
Dose range commonly used	2 Gy/1 f (BED=3.33 Gy) to 30 Gy/1 f (BED=330 Gy)	2 Gy/1 f (BED=3.33 Gy) to 30 Gy/1 f (330 Gy)	2 Gy/1 f (BED=3.33 Gy) to 30 Gy/1 f (330 Gy)	2 Gy/1 f (BED=3.33 Gy) to 30 Gy/1 f (330 Gy)
Time intervals to evaluate cognitive dysfunction	7 days to 1 year	Few hours to 14 months	NOR: 0.5 month to 1 year	1 months to 3 months
			NLR: 1 month to 1 year	

Open field, Morris water maze, Novel Object/Location Recognition (NOR/NLR) and passive and active avoidance test are most frequently utilized cognitive tests with a view to evaluating locomotor activity and level of anxiety, spatial learning and reference memory, recognition memory, associative memory respectively. Each test undertakes various endpoints to evaluate cognition quantitatively. In open field, Morris water maze and passive and active avoidance test, dosage ranging from 2 Gy/1 f to 30 Gy/1 f was commonly used. Dosage used in NOR and NLR
varied from 5 Gy/1 f to 40 Gy/8 f. Most cognitive tests undertook few days to 1 year to observe radiation-induced cognitive dysfunction, except that passive and active avoidance tests always used 1 month to 3 months. Time intervals of less than half a year were the most frequently utilized

Table 2: Summary of cognitive tests.

[16,36,37], 10 Gy/1 f [35,51-53] and 20 Gy/1 f [35,52,54,55] (BED=3.33 Gy, 13.33 Gy, 29.33 Gy, 43.33 Gy and 153.33 Gy respectively) were the most commonly used. At these dosages, WBI did not influence the locomotor activity, as demonstrated by the unchanged number of linings crossed and distance moved, except for the dosage of 8 Gy/1f [16], 20 Gy/ 4 f and 40 Gy/4 f [56] in some studies. The results of current studies utilizing a dosage of 8 Gy/1 f were not in accordance. In Roughton's study, 14-day-old C57BL/6J mice showed more locomotor activity 4 months after receiving whole brain irradiation of 8 Gy/1 f [16]. However, in Karlsson's study, there was no change in locomotor activity for 14-day-old C57BL/6J mice after 3.5 months after receiving 8 Gy/1 f irradiation [36]. In Semmler's research, Wistar rats were irradiated with 20 Gy/4 f and 40 Gy/4 f, and showed decreased locomotor activity than the control groups [56]. As for the level of anxiety demonstrated by center incursions, latency to center and percentage time or distance traveled in the center, the effects of radiation in various studies were not in consistent. In Caceres's research, a dosage of 5 Gy/1 f decreased the level of anxiety by increasing the total time spent in the center [57]. However, the results of Roughton's research were the opposite by

decreasing the total time in the center, which indicated that a dosage of 8 Gy/1 f increased the level of anxiety [16]. In addition, the research work undertaken by Zhang and Sun indicated that dosages of 2 Gy/1 f, 10 Gy/1 f, 20 Gy/1 f and 30 Gy/1 f had no effects on the level of anxiety by exerting no influence on the total time or distance spent in the center [35,52].

Morris water maze: The irradiation dose used in recent studies varied over a large range from 2 Gy/1 f [35,39,51,52] to 30 Gy/1 f [41,51,52,58] (BED=3.33 Gy and 330 Gy respectively), among which dosages of 10 Gy/1 f [35,39,42,44,51,52], 20 Gy/1 f [35,52,54,55] and 30 Gy/1 f [41,51,52,58] (BED=43.33 Gy, 153.33 Gy and 330 Gy respectively) were the most frequently used. A dosage of 2 Gy/1 f did not impair cognition, and 5 Gy/1 f [59], 20 Gy/4 f [40,43,56], 40 Gy/8 f [20,40,60] and 40 Gy/4 f [56] (BED=13.33 Gy, 53.33 Gy, 106.67 Gy and 173.33 Gy respectively) were used to induce impairment in cognition. The longer latency to the platform, path length and total distance to the platform in place navigation, shorter journey distance of target to total and target quadrant stay time and longer distance to platform zone indicated impairment of spatial learning and reference memory

respectively. In some studies, the effects of radiation on spatial learning and reference memory were dose-dependent. In Sun's research group, a dosage of 20 Gy/ 1 f and 30 Gy/ 1 f, but not 10 Gy/1 f and 2 Gy/1 f jeopardized spatial learning and reference memory [52]. However, a dosage of 10 Gy/1 f was able to impair spatial learning and reference memory in some studies. In Raber's and Dong's research, a dosage of 10 Gy/1 f increased the latency to the platform after 48 hours and 3 months post-irradiation respectively [39,44]. The spatial learning and reference memory of Sprague–Dawley rats was impaired by dosage of 40 Gy/8 f for 1 and 2 months and recovered after 3 months post-irradiation [40]. At approximately 7 months post-irradiation, spatial learning and reference memory were not influenced by dosage of 40 Gy/8 f for F344xBN rats [60]. As for the dosage of 20 Gy/4 f, it increased the latency to the platform and decreased target quadrant stay time for C57BL/6J mice 2 months post-irradiation [43], but it made no difference for Sprague–Dawley rats and Wistar rats after nearly the same time interval after irradiation [40,56]. A dosage of 40 Gy/4 f did not impair spatial learning and reference memory of Wistar rats after 14 days and 6 weeks post-irradiation [56]. In addition, a dosage of 50 Gy/10 f was unable to impair the reference memory of Sprague–Dawley rats in 10 weeks post-irradiation [45].

Novel object recognition and novel location recognition: In NOR and NLR, there was a broad dose range from 2 Gy/1 f to 30 Gy/1 f [52] (BED=3.33 Gy and 330 Gy respectively), among which dosages of 10 Gy/1 f [42,44,52,53,61] and 40 Gy/8 f [18,46] (BED=43.33 Gy and 106.67 Gy respectively) were the most frequently used. Dosages of 5 Gy/1 f [62], 20 Gy/5 f [38] and 50 Gy/10 f [45] (BED=13.33 Gy,46.67 Gy and 133.33 Gy respectively) were also utilized in some studies. Radiation-induced cognitive dysfunction detected by NOR was demonstrated by the decrease of exploration time in the novel object or decreased discrimination ratio and they were dose-dependent in some studies. According to the results of available studies, a dosage of 2 Gy/1 f could not impair recognition memory [52]. The effects of 10 Gy/1 f irradiation on recognition memory were not consistent, which may impair [44,61] or exert no effects [42,53] on recognition memory in different studies for both rats and mice. A dosage of 20 Gy/5 f of which the BED is nearly equivalent to that of 10 Gy/1 f was also reported to be incapable of impairing recognition memory [38]. Other dosages of 40 Gy/8 f [18,46], 50 Gy/10 f [45], 20 Gy/1 f and 30 Gy/1 f [52] in various studies jeopardized recognition memory. In NLR, radiation-induced cognitive dysfunction was demonstrated by the decrease of exploration time in the novel location or decreased discrimination ratio. In Sun's research, dosage of 20 Gy/1 f and 30 Gy/1 f, but not 2 Gy/1 f and 10 Gy/1 f impaired recognition memory by decreasing the exploration time in the novel location [52]. However, in the series studies by Acharya on stem cell transplantation [47-49] and the research undertaken by Tome [53], a dosage of 10 Gy/1 f could decrease the exploration time in the novel location. Dosages of 20 Gy/5 f [38] and 50 Gy/10 f [45] impaired recognition memory by decreasing the exploration time in the novel location. In addition, a dosage of 40 Gy/8 f could not impair recognition memory detected by NLR in 3, 6 and 12 months post-irradiation in Forbes's research [18].

Passive and active avoidance test: The irradiation doses utilized ranged from 2 Gy/1f [35,51] to 30 Gy/1f [51] (BED=3.33 Gy and 330Gy respectively), among which 5 Gy/1 f [34,59] and 10 Gy/1 f [35,51,63] (BED=13.33 Gy and 43.33Gy respectively) were the most frequently used. Decreased latency to enter the dark compartment and increased latency to enter the light compartment indicated impaired associative memory. However, the effect of dose on associative memory has not always been negative. A dosage of 2 Gy/ 1 f was used in Ji's research

and Zhang's research, and did not induce any impairment of associative memory [35,51]. In Caceres's research, whole brain irradiation of 5 Gy/1f in Wistar rats improved the associative memory by increasing the latency to enter the dark compartment [34]. On the contrary, a dosage of 5 Gy/1 f in Oh's research impaired the associative memory of C57BL/6J mice 17 days post-irradiation by decreasing the latency to enter the dark compartment [59]. Larger doses, such as 10 Gy/5 f [63], 10 Gy/1 f [51], 36 Gy/ 8 f [50] and 30 Gy/1f [51] (BED=16.67 Gy, 43.33 Gy, 90 Gy and 330 Gy respectively), induced the impairment of associative memory by decreasing the latency to enter the dark compartment, except that 10 Gy/1 f and 20 Gy/1 f did not change the latency to enter the dark compartment after two months post-irradiation [35]. Different fractionations may yield different results in the passive and active avoidance test. Jahanshahi irradiated Wistar rats with 10 Gy/1 f and 10 Gy/5 f and found that 10 Gy/5 f but not 10 Gy/1 f impaired the associative memory by decreasing the latency to enter the dark compartment [63]. This indicated that fractionated radiation was more effective at impairing associative memory by decreasing the latency.

Time intervals post-irradiation to evaluate cognitive dysfunction

Open field: Time intervals post-irradiation were used to evaluate locomotor activity and the level of anxiety in open field and varied from 7 days [53] to 1 year [37], among which the utilized time intervals were mostly less than half a year, such as 1 [34,38,51,52] to 4 months [16,36]. In one study by Kalm, the time interval was 1 year post-irradiation [37]. In those time intervals, WBI from 2 Gy/1 f to 30 Gy/1 f (BED=3.33 Gy and 330 Gy respectively) did not impair locomotor activity [38,52] and may have changed the level of anxiety: increased [57], decreased it [16] or exerted no effects [35,52].

Morris water maze: Time intervals post-irradiation used in the Morris water maze ranged from a few hours [59] to 14 months [20], among which the most common time intervals were less than 3 months [39,42,44,51], and 2 months was the most frequently utilized [35,40,41,43,52,54,55,58]. The time interval of 14 months was only used in Shi's study [20]. For C57BL/6J mice approximately 2-month-old, WBI of 5 Gy/1 f [59], 10 Gy/1 f [39,44] and 20 Gy/4 f [43], but not 2 Gy/1 f [39], impaired spatial learning and reference memory within 2 months post-irradiation except in Belarbi's research [42]. For Sprague-Dawley rats approximately 2-month-old, WBI of 20 Gy/4 f [40], 40 Gy/8 f [40], 20 Gy/1 f [35,52,54,55] and 30 Gy/1 f [51,52] (BED=53.33 Gy, 106.67 Gy, 153.33 Gy and 330 Gy respectively) decreased spatial learning and reference memory within 6 months post-irradiation, except for 50 Gy/10 f in Piao's research [45]. WBI of 2 Gy/1 f and 10 Gy/1 f (BED=3.33 Gy and 43.33 Gy respectively) did not change the rats' performance in place navigation and spatial probing in all the collected studies [35,51]. For Balb/c mice approximately 2-month-old, WBI of 30 Gy/1 f (BED=330 Gy) induced cognitive dysfunction in 2 months post-irradiation [41,58].

Novel object recognition and novel location recognition: Time intervals post-irradiation utilized in NOR varied from half a month [53] to one year [18], among which most time intervals were less than half a year [46,61]. Time intervals of 3 months [18,42,44,45,52,62] and 6 months [18,38,52,61] were the most frequently utilized and 7 months [46] as well as 1 year were used in one study each [18]. Time intervals post-irradiation in NLR ranged from 1 month [38] to 1 year [18]. Most studies utilized time intervals of 1 month [38,47,48,52], 3 months [18,44,45,52,62] and 4 months [47] and some studies also used 5 months [38], 6 months [18,52] and 8 months [48] to evaluate

recognition memory in NLR. For F344xBN rats approximately 3-month-old, WBI of 10 Gy/1 f [61] and 40 Gy/8 f [46] (BED=43.33 Gy and 106.67 Gy) decreased recognition memory in NOR between 3 months to 13 months. For Sprague–Dawley rats approximately 1-month-old, WBI of 50 Gy/10 f [45], 20 Gy/1 f [52] and 30 Gy/1 f [52] (BED=133.33 Gy, 153.33 Gy and 330 Gy respectively) jeopardized cognition evaluated by NOR and NLR in approximately 3 months post-irradiation. For C57BL/6J mice of less than 4-month-old, WBI of 10 Gy/1 f did not impair recognition memory in NOR until 3 months post-irradiation [42,44,53].

Passive and active avoidance test: The time intervals post-irradiation utilized in passive and active avoidance tests were 1 month [50,51,63], 2 months [54] and 3 months [50], among which 1 month was the most frequently utilized. For Wistar rats of 24 to 48-hour-old, WBI of 5 Gy/1 f impaired associative memory in 1 month post-irradiation [34]. For Sprague-Dawley rats approximately 1-month-old, WBI of 30 Gy/1 f, but not 10 Gy/1 f and 2 Gy/1 f, decreased associative memory in 1 month post-irradiation [51].

The time interval post-irradiation influenced the results of cognitive tests. In most cognitive tests, radiation-induced cognitive dysfunction became pronounced gradually with the time post-irradiation, reached the peak at some time and finally recovered. In the open field test in the study by Kalm and Karlsson, C57BL/6J mice receiving irradiation of 8 Gy/1f demonstrated no change of locomotor activity 3.5 months post-irradiation and more rearings and stops 1 year post-irradiation [36,37]. In Zhou's study, SD male rats demonstrated impaired cognition by demonstrating longer latency to target and total distance in the Morris water maze in 4 weeks after 20 Gy/4 f irradiation and began to recover 8 weeks post-irradiation. As for the dosage of 40 Gy/8 f irradiation, rats required 12 weeks to recover [40]. These results indicate not only that the results of cognitive tests change with the time intervals post-irradiation, but also that longer recovery time is needed to repair the cognitive dysfunction induced by larger doses. The time interval after irradiation could also affect the results of NOR and NLR. Irradiation of 10 Gy/1 f on C57BL/6J mice did not change the time spent on familiar objects and novel objects 10 to 11 weeks [42] post-irradiation, while it decreased the time spent on novel objects 12 weeks post-irradiation. Acharya implemented a series of studies evaluating the effects of neural stem cells transplantation on brain injury with the use of novel location recognition test [64-68]. After receiving irradiation of 10 Gy/1 f, two-month-old athymic nude rats demonstrated a decrease of exploration ratio 1 to 4 months post-irradiation and no significant change of exploration ratio 8 months post-irradiation [47-49]. As for the passive and active avoidance test in Warrington's research, C57BL/6J mice irradiated with 36 Gy/8 f exhibited longer latency to enter the light compartment 1 month post-irradiation and the latency began to decrease 3 months post-irradiation [50].

Conclusions

In this review, we demonstrated the establishment of rodent models, the utilization of cognitive tests in the studies and evidence of radiation-induced cognitive dysfunction. We drew several conclusions as follows: (I) Various strains of rats and mice receiving whole brain irradiation (WBI) served as appropriate models to simulate clinical scenarios where cognitive dysfunction is induced by WBI for the treatment of primary and metastatic brain tumors. (II) Among all of those cognitive tests, the open field, MWM, NOR/NLR and passive and active avoidance tests are the most utilized methods. These cognitive tests are utilized for the evaluation of locomotor activity and the level of anxiety, spatial learning and reference memory, recognition memory

and associative memory respectively. (III) Many factors influenced the detection of cognitive dysfunction, including animal species, age and weight upon receiving irradiation, irradiation dose and time intervals post-irradiation. (IV) Dosages ranging from 2 Gy/1 f (BED=3.33 Gy) to 30 Gy/1 f (330 Gy) were the most frequently utilized. These dosages did not change locomotor activity, and the effects on the level of anxiety were not definite in the open field. (V) Dosages of 2 Gy/1 f (BED=3.33 Gy) did not definitely impair cognition. Dosage of 5 Gy/1 f (BED=13.33 Gy), 10 Gy/1 f (BED=43.33 Gy), 20 Gy/5 f (BED=46.67 Gy) and 20 Gy/4 f (BED=53.33 Gy), with the BED less than 100 Gy, may not have consistently impaired cognition, especially in rats. By contrast, dosages with BED greater than 100 Gy including 40 Gy/8 f (BED=106.67 Gy), 40 Gy/4 f (BED=173.33 Gy), 20 Gy/1 f (BED=153.33 Gy), 30 Gy/1 f (BED=330 Gy) and 40 Gy/1 f (BED=573.33 Gy) jeopardized cognition. However, BED of 100 Gy should by no means be considered to be the cutoff value to induce cognitive dysfunction. (VI) In a single study utilizing different dosages, cognitive dysfunction was detected in a dose-dependent manner. (VII) From a few hours to one year post-irradiation, cognitive dysfunction was detected.

While many studies have utilized cognitive tests to evaluate radiation-induced cognitive dysfunction, the lack of uniform criteria for animal species, age and weight upon receiving irradiation, irradiation dose and time intervals post-irradiation makes it difficult to compare between studies. The heterogeneity of cognitive tests and presentation of data between studies did not allow for a quantitative dose–response evaluation across studies. It was also difficult to delineate a dose-effect curve and to ascertain a cutoff dose to induce cognitive dysfunction. Therefore, it is necessary to establish uniform criteria for the future implementation of cognitive tests, which could enable better comparisons between studies and provide a better understanding of dose-effect relationships to facilitate the understanding of the mechanisms of radiation-induced cognitive dysfunction and promote the development of preventive and treatment measures.

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