



# Cranial irradiation induces cognitive decline associated with altered dendritic spine morphology in the young rat hippocampus

Xin Ding<sup>1</sup> · Hai-Bo Zhang<sup>1</sup> · Hui Qiu<sup>1</sup> · Xin Wen<sup>1</sup> · Long-zhen Zhang<sup>1</sup>

Received: 8 November 2021 / Accepted: 5 August 2022 / Published online: 13 August 2022  
© The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature 2022

## Abstract

**Objective** Therapeutic irradiation is commonly used to treat brain cancers but can induce cognitive dysfunction, especially in children. The mechanism is unknown but likely involves alterations in dendritic spine number and structure.

**Methods** To explore the impact of radiation exposure on the alteration of dendritic spine morphology in the hippocampus of young brains, 21-day-old Sprague–Dawley rats received cranial irradiation (10 Gy), and changes in spine density and morphology in dentate gyrus (DG) granules and CA1 pyramidal neurons were detected 1 and 3 months later by using Golgi staining. Moreover, we analyzed synapse-associated proteins within dendritic spines after irradiation.

**Result** Our data showed that cognitive deficits were detected in young rats at both time points postirradiation, accompanied by morphological changes in dendritic spines. Our results revealed significant reductions in spine density in the DG at both 1 month (40.58%) and 3 months (28.92%) postirradiation. However, there was a decrease in spine density only at 1 month (33.29%) postirradiation in the basal dendrites of CA1 neurons and no significant changes in the apical dendrites of CA1 neurons at either time point. Notably, among our findings were the significant dynamic changes in spine morphology that persisted 3 months following cranial irradiation. Meanwhile, we found that depletion of the synapse-associated proteins PSD95 and Drebrin coincided with alterations in dendritic spines.

**Conclusion** These data suggest that the decreased levels of PSD95 and Drebrin after ionizing radiation may cause changes in synaptic plasticity by affecting the morphological structure of dendritic spines, blocking the functional connectivity pathways of the brain and leading to cognitive impairment. Although the mechanism involved is unclear, understanding how ionizing radiation affects young brain hippocampal tissue may be useful to gain new mechanistic insights into radiation-induced cognitive dysfunction.

**Keywords** Irradiation · Hippocampus · Neurogenesis · Dendritic spine · PSD95

## Introduction

Cranial irradiation has been regarded as a standard treatment protocol that increases survival rates of pediatric brain tumors but may lead to progressive cognitive impairments. Approximately 50 to 60% of children will be at risk of cognitive dysfunction, resulting from cranial irradiation treatment [1]. Radiation-induced cognitive injury has diverse characteristics but often includes decreased hippocampus-dependent learning, memory and spatial processing abilities [2]; moreover,

younger children at diagnosis have demonstrated higher intelligence quotients and functional deficits [3, 4]. At present, more than 60% of pediatric cancer patients are expected to survive into adulthood [4], and cognitive impairment is one of the most debilitating late effects, expressed as learning disabilities, social difficulties, long-term education and vocational limitations [5]. Consequently, understanding how ionizing radiation affects young brain hippocampal tissue may be useful to gain new mechanistic insights into irradiation-induced cognitive dysfunction.

Synaptic plasticity contributes to acquiring new information, adapting to environmental influences and repairing damage. Changes in spine structure and density correlate with synaptic plasticity, which in turn positively correlates with cognition [6–8]. If dendritic spines are regarded as the material foundation of memory, dendritic spine stabilization

✉ Xin Ding  
dingxin81@163.com

<sup>1</sup> Department of Radiotherapy and Oncology, Affiliated Hospital of Xuzhou Medical University, Xuzhou, Jiangsu, China

is proposed to be very important for long-term memory [9]. Although previous research has shown that irradiation compromises neuronal architecture in adult mice [10, 11], much less is known regarding the impact of cranial irradiation on dendritic spines in the hippocampus of young animals. The brain tissue in children is far more sensitive to radiation than the adult brain [12]. The incidence of brain cancers in children is higher than that in adults, and multimodality treatments increase the probability of long-term survival [13]. Thus, neuropsychological and behavioral outcomes of pediatric patients are receiving increasing attention. However, to the best of our knowledge, there have been few reports with respect to the temporal and region-specific effects on spine density and morphology after irradiation in young animals, which are roughly equivalent in age to young children (i.e., <5 years old).

In the current study, we addressed the effects of cranial irradiation on dendritic spine morphology, synaptic density and synaptic proteins associated with cognitive dysfunction in young rats to provide more detailed morphological evidence and investigation of hippocampal deficit.

## Materials and methods

### Animals

Twenty-one-day-old male Sprague–Dawley rats (50–60 g) were obtained from the Medical Experimental Animal Center of Soochow University (Suzhou, China). The rats were kept in a temperature- and light-controlled environment, provided with food and water, and then randomly divided into two groups: the control group and the irradiation group. The Animal Care and Ethics Committee at Soochow University, China, approved all experimental procedures.

### Irradiation

During the administration of radiation, the rats were anesthetized with 3.6% chloral hydrate (360 mg/kg), and the control rats were treated similarly. The rats were placed in a prone position in a linear accelerator (SL 18, Philips, UK) as described previously [14, 15]. Each rat received a single dose of 0 Gy or 10 Gy of 4 MeV electron beam cranial irradiation.

### Cognitive test

The Morris water maze and novel object recognition tests were used to determine behavioral effects of irradiation. Experiments were performed at the Institute of Neuroscience, Soochow University. All testing occurred during 08:00–16:00. The Morris water maze test was used to examine hippocampal-dependent spatial learning and memory

function, as described previously [15]. The novel object recognition task is based on the concept that rodents will spend more time exploring novel objects than familiar objects. During the trial phase, rats were first placed into a rectangular box (505 mm height × 410 mm length × 410 mm width) and presented with two identical objects for 3 min. During the test phase (performed 1 h later), one familiar object was changed to a novel object, and the rats were placed in the box for 3 min. The exploration time for the familiar or novel object during the test phase was recorded.

### Analysis of dendritic spine density and morphology

Golgi staining was performed for spine analyses using the FD Rapid GolgiStain™ Kit (FD Neurotechnologies Inc., Baltimore, MD) following the manufacturer's guidelines. The neurons that satisfied the following criteria were chosen for analysis: (1) presence of untruncated dendrites; (2) consistent and dark Golgi staining along the entire extent of the dendrites; and (3) relative isolation from neighboring neurons to avoid interference with analysis [16]. Three to five dendritic segments, each at least 30 μm in length per neuron, and 10–11 neurons were analyzed per brain. Neurons that met the staining conditions were imaged under a Zeiss Axio Imager microscope with a 40× objective.

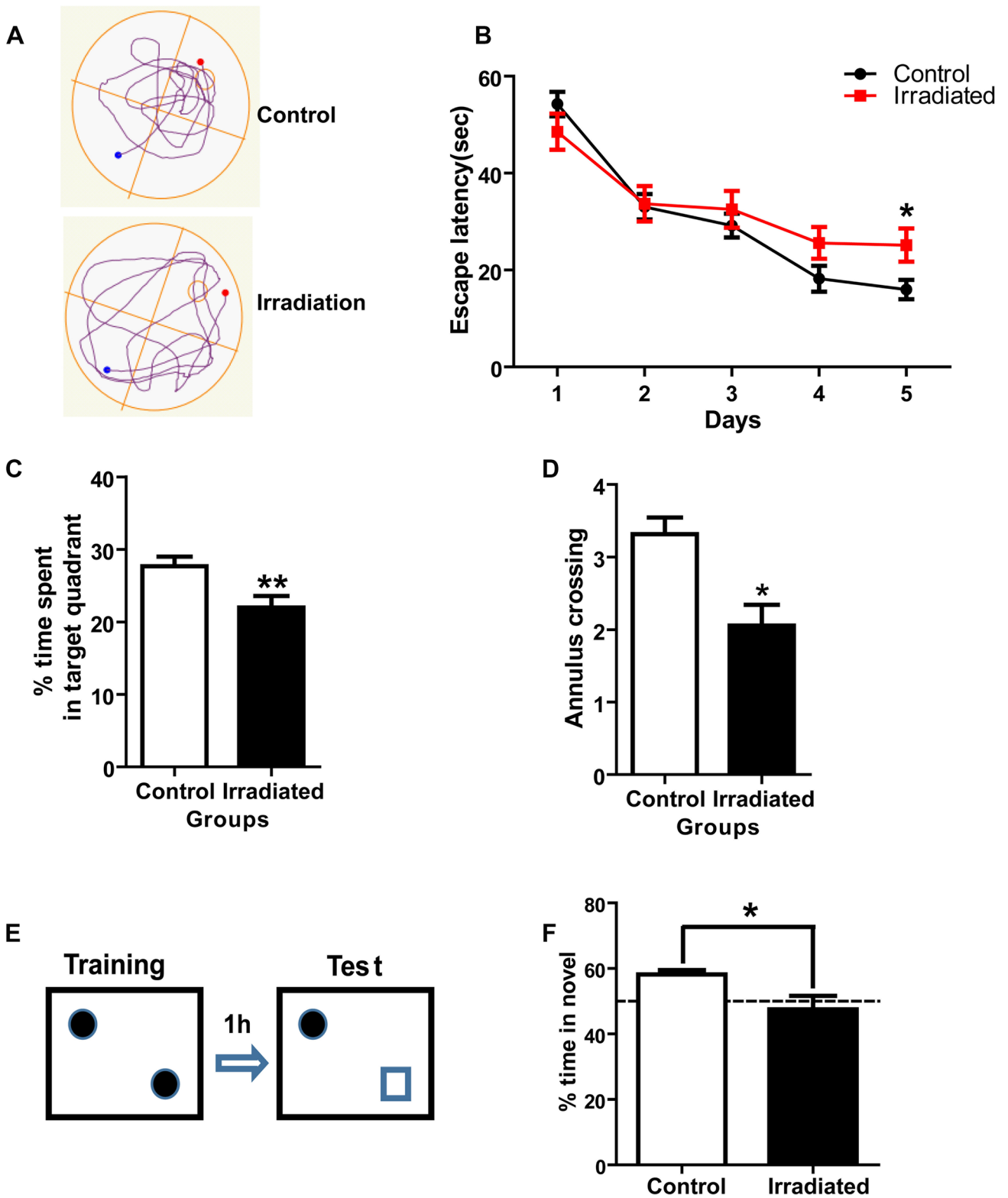
Dendritic spines can be classified into the following categories: (1) thin: a long neck and a small head; (2) mushroom: a small neck and a large head; and (3) stubby: a very short spine without a distinguishable neck [16]. The dendritic segments were imaged under a Zeiss Axio imager microscope with a 100× oil immersion objective. ImageJ software was used to quantify the spine density, which was presented as the number of spines per 10 μm of dendrite length.

### Western blotting

In brief, protein samples were separated using SDS-PAGE gels and transferred to PVDF membranes. The sample loading quantity was 25–40 μg, and membranes were incubated with primary antibodies at 4 °C overnight. After washing with TBS-T, membranes were incubated with secondary antibody for 1 h at room temperature. Visualization was performed with chemiluminescence detection reagent.

### Statistical analysis

All data are expressed as the mean ± SEM and were analyzed with SPSS 17.0 software (SPSS, Seattle, USA). Independent sample t-test was used to analyze the mean comparison between two groups. Where behavioral data were nonnormally distributed, a Mann–Whitney *U*-test was used. \**p* < 0.05; \*\**p* < 0.01; \*\*\**p* < 0.001.



**Fig. 1** Cranial irradiation-induced cognitive deficits in young rats. **A** The swim tracks of the rats during Morris water maze testing. **B** Comparison of the latency to find the platform between the control and irradiated groups. **C** The percentage of target quadrant exploring

time between the two groups in probe test. **D** Number of crossings in the original location of the platform. **E** Diagram of the object recognition task. **F** The times spent exploring a novel object is shown as a ratio of the total times at 1 month after irradiation

## Results

### Impaired hippocampus-dependent behaviors in young rats after cranial irradiation

Learning and memory tasks were performed in young rats to evaluate cognitive dysfunction 1 and 3 months following cranial radiation. One month after irradiation, there was no significant difference in the place navigation and the spatial probe test (data not shown) between the two groups. However, the control rats found the platform faster than the 3-month postirradiation rats (Fig. 1A). All rats improved their performance on days 1–4 during the place navigation test, while on day 5, the radiation group had a longer latency time than the control ( $25.59 \pm 3.27$  s vs.  $15.98 \pm 2.01$  s;  $n = 15\text{--}20$ ,  $p = 0.013$ ; Fig. 1B). In the spatial probe test, the control rats spent significantly more time in the target quadrant compared to the treated rats ( $27.75 \pm 1.27\%$  vs.  $21.95 \pm 1.50\%$ ;  $n = 20$ ,  $p = 0.002$ ; Fig. 1C). The control rats crossed the target annulus nearly four times, whereas the irradiated rats crossed only twice (Fig. 1D).

A novel object recognition test was used to evaluate hippocampus-dependent nonspatial learning and memory (Fig. 1E). During the 3-min training session, sham and irradiated rats showed no significant difference in exploration time of the objects (data not shown). One hour after the training trial, rats were tested for novel object recognition. Sham rats spent more time exploring the novel object than the familiar object at 1 month after 10 Gy (control:  $58.19 \pm 1.33\%$ , irradiated:  $47.51 \pm 4.15\%$ ;  $n = 20$ ,  $p = 0.035$ ; Fig. 1F), but there were no group differences at 3 months postirradiation ( $p > 0.05$ ; not shown).

### Changes in dendritic spine density after radiation exposure

In this study, we showed that there were significant reductions in spine density at both 1 month (40.58%,  $p < 0.001$ ) and 3 months (28.92%,  $p < 0.001$ ) postirradiation in the DG (Fig. 2A, B). However, in the basal dendrites of CA1 neurons, there was a significant reduction (33.29%,  $p < 0.001$ ) in spine density only at 1 month postirradiation (Fig. 2C). Meanwhile, we found that cranial irradiation did not significantly alter spine density in the CA1 apical neurons at either time point (Fig. 2D).

### Changes in dendritic spine morphology after radiation exposure

The research above showed that radiation exposure greatly reduces the overall spine density in the DG. When we analyzed the types of dendritic spines, we found that the

**Fig. 2** Irradiation-induced time and region-specific changes in dendritic spine density in the DG and CA1 area. **A** Quantitative analysis showing dendritic spines/10  $\mu$ m in the DG neurons; irradiation rats exhibit a significant reduction than in control rats. Right: Representative dendrites in the DG granule neurons. **B** Cranial irradiation effects the numbers of dendritic spines/10  $\mu$ m in the pyramidal neurons in the CA1 region. Right: Representative basal dendrites. **C** No changes in spine density are observed after cranial irradiation in the CA1. Right: Representative apical dendrites. The scale bar indicates 5  $\mu$ m

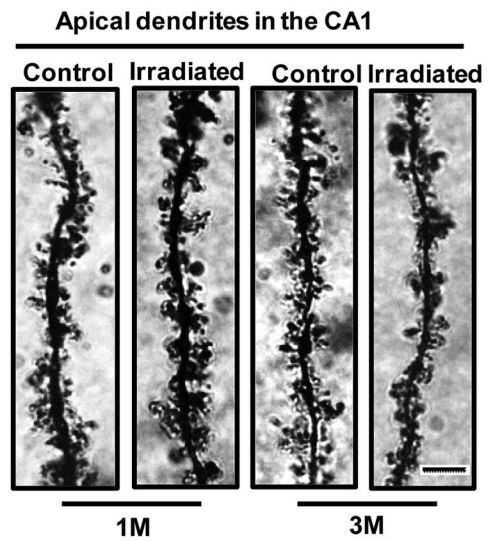
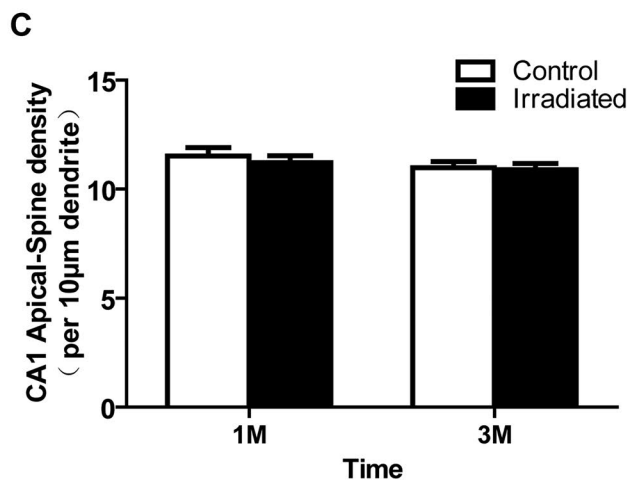
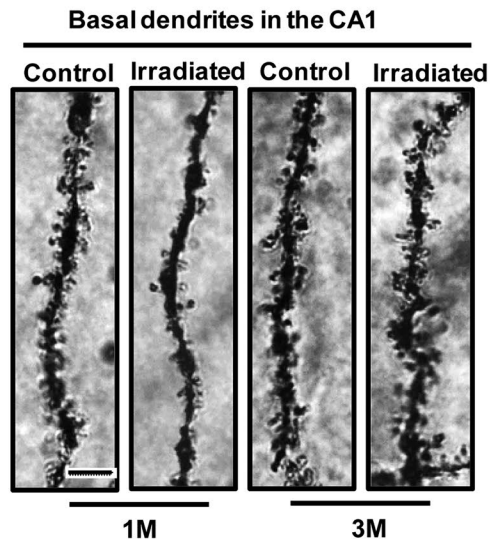
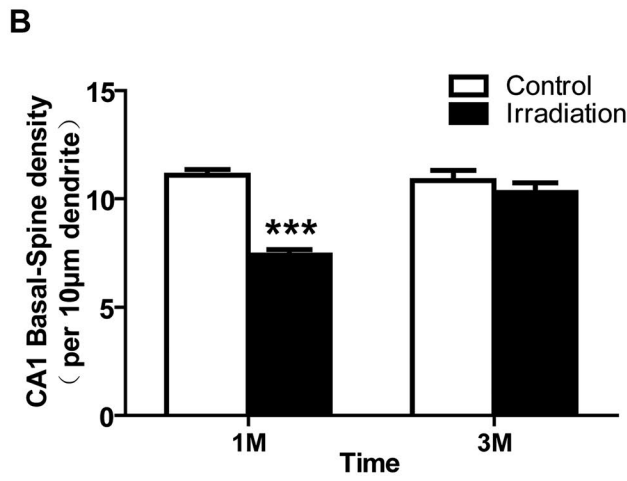
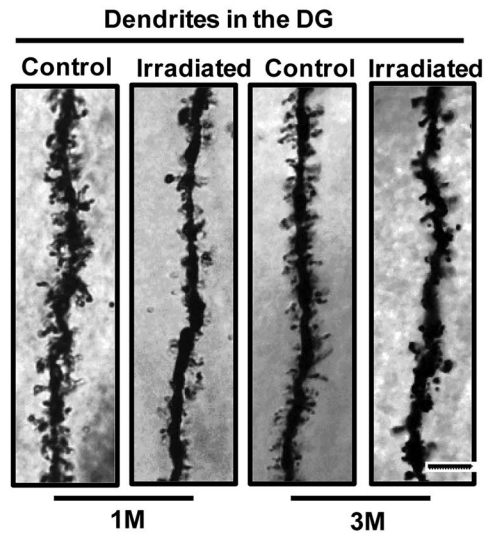
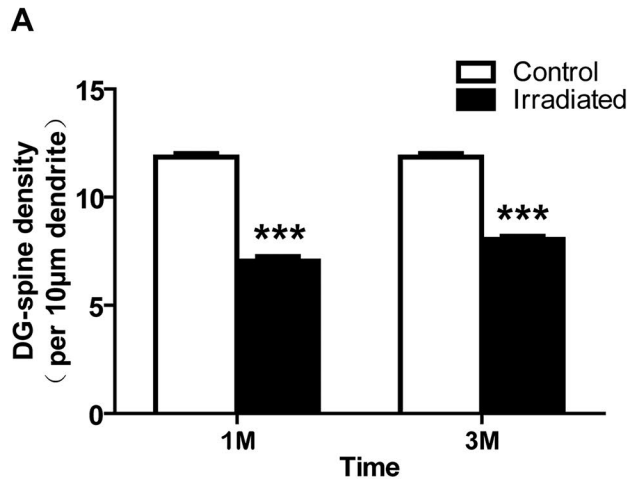
irradiated rats had reductions in the density of mushroom spines by approximately 7.17% and 9.29% at 1 and 3 months postirradiation, respectively, relative to the controls (Fig. 3A, B). The proportion of thin spines was decreased (7.86%,  $p < 0.01$ ) only at 3 months, while the changes were not statistically significant at 1 month (Fig. 3A, B). However, a remarkable increase in the proportion of stubby spines was only observed at 1 month (Fig. 3A, B).

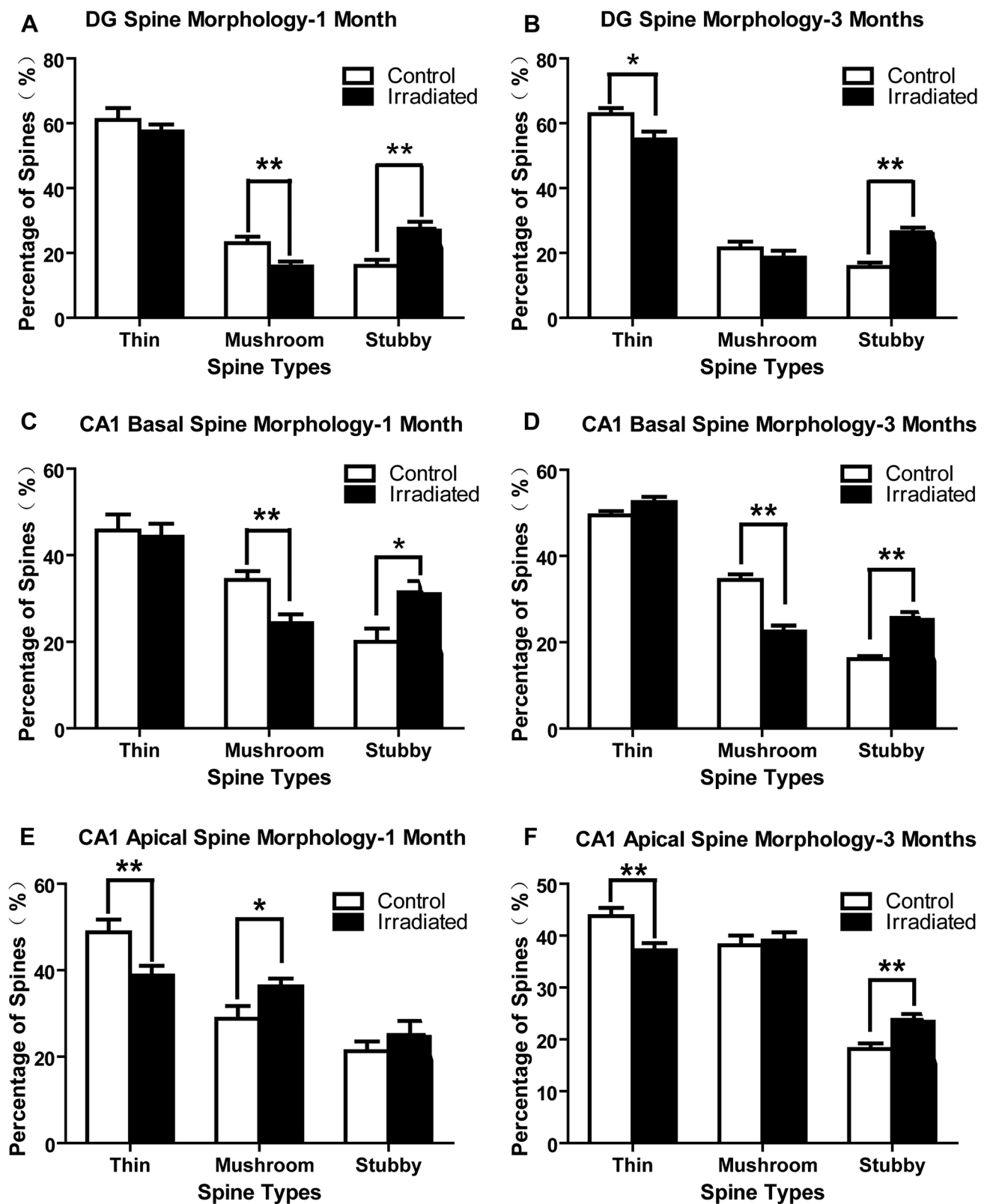
In the basal dendrites of CA1 neurons, our analysis showed no significant changes in thin spines at either time point (Fig. 3C, D). On the other hand, we found that the density of mushroom spines decreased dramatically at both 1 month (10.01%,  $p < 0.01$ ) and 3 months (11.94%,  $p < 0.01$ ) (Fig. 3C, D) after treatment. Surprisingly, there was a trend toward a significant increase in stubby spines at both 1 month (11.43%,  $p < 0.01$ ) and 3 months (9.51%,  $p < 0.01$ ) (Fig. 3C, D).

In the apical pyramidal dendrites of CA1 neurons, there were no significant changes in the overall density of spines at either time point. When analyzed by spine type, we found differences in thin, mushroom, and stubby spines between the control and irradiated groups (Fig. 3E, F). There was a significant decrease in thin spines (10.01%,  $p < 0.01$ ) and a trend toward an increase in mushroom spines (7.50%,  $p < 0.01$ ) compared to the control group at 1 month (Fig. 3E). Although no significant differences were observed in the proportion of mushroom spines between the sham and irradiated groups at 3 months, there were significant differences in the proportion of thin (6.56%,  $p < 0.01$ ) and stubby spine subtypes at 3 months postirradiation (Fig. 3F).

### Radiation exposure resulted in a significant decrease in synapse-associated protein levels in the hippocampus

Postsynaptic density protein (PSD95) plays an important role in regulating synaptic plasticity and is associated with synapse number or synaptic loss. The developmentally regulated brain protein (Drebrin) is a developmental regulatory protein that has been shown to be important in the remodeling and regulation of dendritic spines and synapses. Therefore, we further examined the effects of ionizing radiation on the levels of PSD95 and Drebrin proteins in rat hippocampal tissues. The results showed that the PSD95 protein content

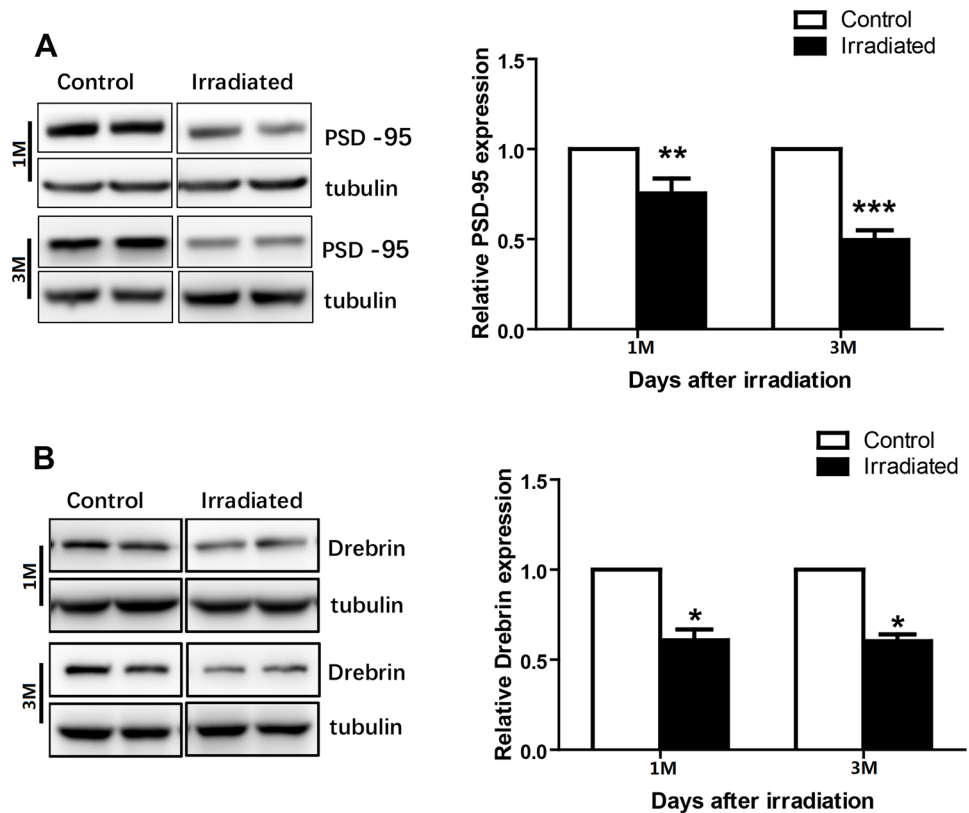




**Fig. 3** Irradiation-induced time and region-specific changes in the dendritic spine morphology in the hippocampal DG and CA1 area. 1) the proportion of spine morphological sub types in the DG-neurons at 1 (A) and 3 months (B). 2) The proportion of spine morphologi-

cal subtypes in the CA1 region basal density at 1 (C) and 3 months (D). 3) The proportion of spine morphological sub-types in the CA1 region apical density at 1 (E) and 3 months (F)

**Fig. 4** Effect of cranial irradiation on PSD95 and Drebrin expression in the hippocampus. **A** The results showed that the content of PSD95 protein in the hippocampus of rats decreased by 24.6% ( $p < 0.01$ ) 1 month after ionizing radiation and further decreased by 50.5% ( $p < 0.001$ ) 3 months. **B** Western blot quantification shows that Drebrin expression was decreased by 39.6% and 39.2% at 1 and 3 months postirradiation



in the hippocampus of rats decreased by 24.6% ( $p < 0.01$ ) 1 month after ionizing radiation and further decreased by 50.5% ( $p < 0.001$ ) 3 months after radiation (Fig. 4A). Drebrin is involved in brain development and affects the formation of dendritic spines. In this study, Drebrin protein expression was decreased by 39.6% and 39.2% at 1 month and 3 months after irradiation, respectively ( $p < 0.05$ ) (Fig. 4B).

## Discussion

Many research studies on radiation-induced cognitive deficits have largely focused on adult animals. In these studies, radiation-induced cognitive dysfunctions were generally detected after higher doses of radiation and much longer follow-up times [17, 18]. Previous reports have suggested that younger age at the time of irradiation exposure is one of the highest risk factors associated with cognitive impairment [19–21]. Our behavioral study showed that young rats (21 days old) exhibited early-occurring cognitive deficits at 1 month postirradiation in the novel object recognition test. Moreover, performance in the probe trials during the Morris water maze was impaired 3 months after irradiation. To our knowledge, radiation-induced cognitive impairment has not been observed in adult rats after the same dose and at the same time point after irradiation [22, 23]. These

results support the notion that young rats are particularly susceptible to irradiation exposure.

Theoretically speaking, there must be some anatomical and functional changes concomitant with cognitive impairment after cranial irradiation. It has been reported that cognitive function strongly correlates with synaptic plasticity [24, 25], and changes in the density and morphology of dendritic spines are a structural correlate of synaptic plasticity. The hippocampus plays an important role in learning and memory, and there have also been reports of differences in responses between CA1 pyramidal cells and DG granule cells after injury [26]. In the current study, analysis of Golgi-stained neurons showed that radiation exposure led to a significant decrease in spine density in the DG region over time and a significant reduction in the basal dendrites of CA1 pyramidal neurons at 1 month. In contrast to previous studies performed on adult animals [10], our data suggest that a relatively severe decrease in the extent of dendritic spines persisted for a long time after irradiation, and such changes induced by irradiation may have a more profound effect in young animals than in older animals.

Recent advanced technologies in molecular biology have demonstrated a close relationship between spine morphology and synaptic function [24]. Most notable among our findings were the significant dynamic changes in spine morphology that persisted 3 months following cranial irradiation, although no changes in spine density were observed

in the CA1 region at either time point. Meanwhile, our data showed that in both DG and CA1 dendrites, the proportions of mushroom spines were particularly affected by irradiation exposure. Thin spines have been shown to be highly motile and transient. Similar phenomena were also found in other studies [10, 27]. Mushroom spines have larger postsynaptic densities and contain more  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors that are important in conferring postsynaptic cell excitability, representing more stable “memory spines” [27, 28]. Thus, the loss of mushroom spines, as seen here, may have a more profound effect on neuronal function. Thin spines maintain structural flexibility to enlarge and stabilize after long-term potentiation and can accommodate new, enhanced or recently weakened inputs, making them candidate “learning spines” [29]. Radiation may reduce the neuron’s ability to form new synapses and changes in activity. Conversely, a significant increase in the proportion of stubby spines was detected in both the DG and CA1 regions after irradiation. Although less is known about these stubby structures, some scholars speculate that the proportion of stubby spines changed by radiation exposure might regulate cognitive function through alterations in dopaminergic signaling [10]. Previous studies confirmed that changes in spine morphology and density can alter the wiring and functioning of a brain region [30]. It seems that the structural changes we observed in spine morphology varied, suggesting a strong association with cognitive dysfunction after irradiation in young rats.

PSD95 is a major scaffold protein that determines the size and strength of dendritic spines; in particular, the loss of PSD95 is likely to partly underlie dysfunction in learning and memory processes [31, 32]. In this study, we found that irradiation decreased the accumulation of PSD95, which may result in changes in dendritic spines. However, previous studies showed that X-ray irradiation decreased the levels of cytoskeletal proteins in dendritic spines but PSD95 levels were not reduced in mature neuron dendritic spines in vitro [33] and significantly increased along dendrites in adult transgenic mice (2 months old) after irradiation [11]. Such discrepancies among studies may be due to differences in the irradiation source or dose. More importantly, age-induced alterations in PSD95 protein expression levels may result in the differences described above [32]. Further studies are necessary to elaborate on the associations between radiation and alterations in PSD95 protein levels at different ages at the time of treatment. In addition, the decrease in Drebrin levels may be another reason for the loss of plasticity of dendritic spines, which may cause changes in synapses by affecting the morphological structure of dendritic spines, block the functional connectivity pathways of the brain, and cause cognitive dysfunction [34]. However, the mechanism remains to be fully elucidated.

In conclusion, cranial irradiation resulted in persistent cognitive deficits, caused alterations in spine density and morphology in the young hippocampus in a time-dependent and region-specific manner, and reduced PSD95 and Drebrin levels that coincided with the onset of memory impairment, suggesting that a disturbance in neuronal circuitry function may be caused by massive simultaneous synaptic dysfunction underlying radiation-induced cognitive deficits. Our study shows a possible association but not causative role in the pathogenesis of cognitive impairments. Further research is needed to validate the molecular mechanisms behind learning and memory deficits after ionizing radiation in young rats. In this study, our present data and those from other studies in adult animals create a basis to elucidate radiation-induced cognitive impairments.

**Acknowledgements** We would like to thank the (Institute of Neuroscience, Soochow University) for technical support.

**Funding** This work was supported by the Science Foundation of Jiangsu Commission of Health (H2018116), Jiangsu Planned Projects for Postdoctoral Research Funds (2018K259C).

## Declarations

**Competing Interest** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## References

- Landier W, Skinner R, Wallace WH, Hjorth L, Mulder RL, Wong FL, Yasui Y, Bhakta N, Constine LS, Bhatia S, Kremer LC, Hudson MM (2018) Surveillance for late effects in childhood cancer survivors. *J Clin Oncol* 36:2216–2222
- Goldsby RE, Liu Q, Nathan PC, Bowers DC, Yeaton-Massey A, Raber SH, Hill D, Armstrong GT, Yasui Y, Zeltzer L, Robison LL, Packer RJ (2010) Late-occurring neurologic sequelae in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *J Clin Oncol* 28:324–331
- Cekanaviciute E, Rosi S, Costes SV (2018) Central nervous system responses to simulated galactic cosmic rays. *Int J Mol Sci* 19:3669
- Wagner AP, Carroll C, White SR, Watson P, Spoudeas HA, Hawkins MM, Walker DA, Clare ICH, Holland AJ, Ring H (2020) Long-term cognitive outcome in adult survivors of an early childhood posterior fossa brain tumour. *Int J Clin Oncol* 25:1763–1773
- Loganovsky KN, Bomko MO, Abramenko IV, Kuts KV, Belous NI, Masiuk SV, Gresko MV, Loganovska TK, Antypchuk KY, Perchuk IV, Kreinis GY, Chumak SA (2018) Neuropsychobiological mechanisms of affective and cognitive disorders in the chernobyl clean-up workers taking into account the specific gene polymorphisms. *Probl Radiac Med Radiobiol* 23:373–409
- Fuenzalida M, Chiu CQ, Chávez AE (2021) Muscarinic regulation of spike timing dependent synaptic plasticity in the hippocampus. *Neuroscience* 456:50–59
- Guo Y, Zou G, Qi K, Jin J, Yao L, Pan Y, Xiong W (2021) Simvastatin impairs hippocampal synaptic plasticity and cognitive function in mice. *Mol Brain* 14:41



8. Segal M (2017) Dendritic spines: Morphological building blocks of memory. *Neurobiol Learn Mem* 138:3–9
9. Sala C, Segal M (2014) Dendritic spines: the locus of structural and functional plasticity. *Physiol Rev* 94:141–188
10. Son Y, Yang M, Wang H, Moon C (2015) Hippocampal dysfunctions caused by cranial irradiation: a review of the experimental evidence. *Brain Behav Immun* 45:287–296
11. Parihar VK, Limoli CL (2013) Cranial irradiation compromises neuronal architecture in the hippocampus. *P Natl Acad Sci U S A* 110:12822–12827
12. Dropcho EJ (2010) Neurotoxicity of radiation therapy. *Neurol Clin* 28:217–234
13. Ostrom QT, Patil N, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS (2020) CBTRUS Statistical report: Primary brain and other central nervous system tumors diagnosed in the United States in 2013–2017. *Neuro Oncol* 22:iv1–iv96
14. Ji JF, Ji SJ, Sun R, Li K, Zhang Y, Zhang LY, Tian Y (2014) Forced running exercise attenuates hippocampal neurogenesis impairment and the neurocognitive deficits induced by whole-brain irradiation via the BDNF-mediated pathway. *Biochem Biophys Res Commun* 443:646–651
15. Ding X, Wu HH, Ji SJ, Cai S, Dai PW, Xu ML, Zhang JJ, Zhang QX, Tian Y, Ma QH (2017) The p75 neurotrophin receptor regulates cranial irradiation-induced hippocampus-dependent cognitive dysfunction. *Oncotarget* 8:40544–40557
16. Titus AD, Shankaranarayana Rao BS, Harsha HN, Ramkumar K, Srikumar BN, Singh SB, Chattarji S, Raju TR (2007) Hypobaric hypoxia-induced dendritic atrophy of hippocampal neurons is associated with cognitive impairment in adult rats. *Neuroscience* 145:265–278
17. Ueno H, Suemitsu S, Murakami S, Kitamura N, Wani K, Matsumoto Y, Okamoto M, Ishihara T (2019) Region-specific reduction of parvalbumin neurons and behavioral changes in adult mice following single exposure to cranial irradiation. *Int J Radiat Biol* 95:611–625
18. Forbes ME, Paitsel M, Bourland JD, Riddle DR (2014) Early-delayed, radiation-induced cognitive deficits in adult rats are heterogeneous and age-dependent. *Radiat Res* 182:60–71
19. Wlodarek L, Cao F, Alibhai FJ, Fekete A, Noyan N, Tobin SW, Marvasti TB, Wu J, Li SH, Weisel RD, Wang LY, Jia Z, Li RK (2020) Rectification of radiotherapy-induced cognitive impairments in aged mice by reconstituted Sca-1(+) stem cells from young donors. *J Neuroinflammation* 17:51
20. Das MM, Godoy M, Chen S, Moser VA, Avalos P, Roxas KM, Dang I, Yáñez A, Zhang W, Bresee C, Arditi M, Liu GY, Svendsen CN, Goodridge HS (2019) Young bone marrow transplantation preserves learning and memory in old mice. *Commun Biol* 2:73
21. Netson KL, Conklin HM, Wu S, Xiong X, Merchant TE (2013) Longitudinal investigation of adaptive functioning following conformal irradiation for pediatric craniopharyngioma and low-grade glioma. *Int J Radiat Oncol Biol Phys* 85:1301–1306
22. Raber J, Rola R, LeFevour A, Morhardt D, Curley J, Mizumatsu S, VandenBerg SR, Fike JR (2004) Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. *Radiat Res* 162:39–47
23. Zhang LY, Chen LS, Sun R, Ji SJ, Ding YY, Wu J, Tian Y (2013) Effects of expression level of DNA repair-related genes involved in the NHEJ pathway on radiation-induced cognitive impairment. *J Radiat Res* 54:235–242
24. Raven F, Van der Zee EA, Meerlo P, Havekes R (2018) The role of sleep in regulating structural plasticity and synaptic strength: Implications for memory and cognitive function. *Sleep Med Rev* 39:3–11
25. Moczulska KE, Tinter-Thiede J, Peter M, Ushakova L, Wernle T, Bathellier B, Rumpel S (2013) Dynamics of dendritic spines in the mouse auditory cortex during memory formation and memory recall. *Proc Natl Acad Sci U S A* 110:18315–18320
26. Alkadhi KA (2019) Cellular and molecular differences between area CA1 and the dentate gyrus of the hippocampus. *Mol Neurobiol* 56:6566–6580
27. Allen AR, Raber J, Chakraborti A, Sharma S, Fike JR (2015) Fe-56 irradiation alters spine density and dendritic complexity in the mouse hippocampus. *Radiat Res* 184:586–594
28. Avila JA, Alliger AA, Carvajal B, Zanca RM, Serrano PA, Luine VN (2017) Estradiol rapidly increases GluA2-mushroom spines and decreases GluA2-filopodia spines in hippocampus CA1. *Hippocampus* 27:1224–1229
29. Tackenberg C, Ghori A, Brandt R (2009) Thin, stubby or mushroom: Spine pathology in Alzheimer's disease. *Curr Alzheimer Res* 6:261–268
30. Fox ME, Chandra R, Menken MS, Larkin EJ, Nam H, Engeln M, Francis TC, Lobo MK (2020) Dendritic remodeling of D1 neurons by RhoA/Rho-kinase mediates depression-like behavior. *Mol Psychiatry* 25:1022–1034
31. Erli F, Palmos AB, Raval P, Mukherjee J, Sellers KJ, Gattford NJF, Moss SJ, Brandon NJ, Penzes P, Srivastava DP (2020) Estradiol reverses excitatory synapse loss in a cellular model of neuropsychiatric disorders. *Transl Psychiatry* 10:16
32. Dore K, Malinow R (2021) Elevated PSD-95 blocks ion-flux independent LTD: A potential new role for PSD-95 in synaptic plasticity. *Neuroscience* 456:43–49
33. Shirai K, Mizui T, Suzuki Y, Okamoto M, Hanamura K, Yoshida Y, Hino M, Noda SE, Al-jahdari WS, Chakravarti A, Shirao T, Nakano T (2013) X irradiation changes dendritic spine morphology and density through reduction of cytoskeletal proteins in mature neurons. *Radiat Res* 179:630–636
34. Koganezawa N, Hanamura K, Sekino Y, Shirao T (2017) The role of drebrin in dendritic spines. *Mol Cell Neurosci* 84:85–92

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.