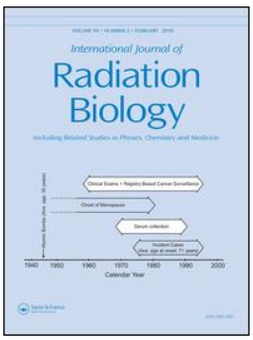

International Journal of Radiation Biology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/irab20

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To cite this article: Whitney D. Perez & Carlos J. Perez-Torres (2022): Neurocognitive and radiological changes after cranial radiation therapy in humans and rodents: a systematic review, International Journal of Radiation Biology, DOI: 10.1080/09553002.2022.2074167

To link to this article: https://doi.org/10.1080/09553002.2022.2074167

INTERNATIONAL JOURNAL OF RADIATION BIOLOGY
https://doi.org/10.1080/09553002.2022.2074167

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ORGINAL ARTICLE

Neurocognitive and radiological changes after cranial radiation therapy in humans and rodents: a systematic review

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ABSTRACT

Background: Radiation-induced brain injury is a common long-term side effect for brain cancer survivors, leading to a reduced quality of life. Although there is growing research pertaining to this topic, the relationship between cognitive and radiologically detected lesions of radiation-induced brain injury in humans remains unclear. Furthermore, clinically translatable similarities between rodent models and human findings are also undefined. The objective of this review is to then identify the current evidence of radiation-induced brain injury in humans and to compare these findings to current rodent models of radiation-induced brain injury.

Methods: This review includes an examination of the current literature on cognitive and radiological characteristics of radiation-induced brain injury in humans and rodents. A thorough search was conducted on PubMed, Web of Science, and Scopus to identify studies that performed cognitive assessments and magnetic resonance imaging techniques on either humans or rodents after cranial radiation therapy. A qualitative synthesis of the data is herein reported.

Results: A total of 153 studies pertaining to cognitively or radiologically detected radiation injury of the brain are included in this systematic review; 106 studies provided data on humans while 47 studies provided data on rodents. Cognitive deficits in humans manifest across multiple domains after brain irradiation. Radiological evidence in humans highlight various neuroimaging-detectable changes post-irradiation. It is unclear, however, whether these findings reflect ground truth or research interests. Additionally, rodent models do not comprehensively reproduce characteristics of cognitive and radiological injury currently identified in humans.

Conclusion: This systematic review demonstrates that associations between and within cognitive and radiological radiation-induced brain injuries often rely on the type of assessment. Well-designed studies that evaluate the spectrum of potential injury are required for a precise understanding of not only the clinical significance of radiation-induced brain injury in humans, but also how to replicate injury development in pre-clinical models.

ARTICLE HISTORY
Received 18 January 2022
Accepted 20 April 2022

KEYWORDS
Radiation-induced brain injury; rodent models; cognition; imaging

Introduction

Radiation therapy is a practical and critical tool to manage intracranial tumors due to its ability to non-invasively treat cases of metastatic or deeply seated brain tumors (Lee et al. 2012). As high-energy radiation particles are delivered to the tumor site, a fraction of this energy will inevitably be deposited within the healthy brain tissue along the radiation beam's path and immediately adjacent to the tumor. As a consequence of normal tissue irradiation, many patients undergoing cranial radiation therapy experience neurological side effects. Indeed, long-term side effects of cranial irradiation have been reported to occur in 50–90% of adult patients (Greene-Schloesser and Robbins 2012) and up to 50% of pediatric patients (Ajithkumar et al. 2017). It has been shown that these radiation-induced brain injuries ultimately lead to a decrease in quality of life after cancer therapy (Corn et al. 2008; Correa et al. 2012). The prognosis and severity of these side effects, however, depends on the time of clinical expression and are therefore generally categorized as acute, early-delayed, and late-delayed brain injury (Greene-Schloesser and Robbins 2012). The acute and early-delayed effects, which usually occurs from a few days up to 6 months after irradiation, are transient and typically self-resolve. Late-delayed radiation effects, which usually occurs from 6 months up to an indefinite number of years after therapy, do not self-resolve. Due to increasing survival outcomes for brain tumor patients (Siegel et al. 2018), and thus a growing population of long-term survivors, this late-delayed form of radiation induced-brain injury (RIBI) is the primary concern in terms of radiation-induced neurotoxicity.

Depending in part on the radiotherapy treatment paradigm, late-delayed RIBI can present as a focal or diffuse

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Supplemental data for this article can be accessed here

pathology (Valk and Dillon 1991; Soussain et al. 2009). Radiation necrosis presents as a focal lesion with increased vascular permeability and edema on magnetic resonance imaging (MRI; Vellayappan et al. 2018). The cognitive dysfunctions associated with radiation necrosis include seizures, focal weakness, language impairment, and blurred vision (Giglio and Gilbert 2003; Diaz and Choi 2014). Although radiation necrosis maintains high clinical relevance within late-delayed effects of RIBI, it is not the primary focus of this review as its incidence is usually small (roughly 5%). The more common form of RIBI presents as a diffuse lesion characterized by a homogeneous enhancement throughout the subcortical white matter without increased vascular permeability or edema (Zhong et al. 2015). The cognitive impairments associated with this form of RIBI include, but are not limited to, deficits in attention, memory, executive functioning, language, and psychomotor skills (Sundgren and Cao 2009; Cramer et al. 2019). Other diffuse radiological abnormalities such as cerebral volume loss, cerebral microbleeds, changes in white matter diffusion metrics, and changes in the neurometabolic profile have also been suggested to be associated with the aforementioned cognitive impairments (Robbins et al. 2012; Haller et al. 2018; Kłos et al. 2019).

The current scientific understanding behind the pathophysiology of these late-delayed forms of RIBI is built upon studies of pre-clinical animal models. Results of these experimental models, typically of healthy rodents, have revealed a multitude of dynamic processes within rodent brains after the delivery of radiation. These include, but are not limited to, the impairment of hippocampal neurogenesis (Dietrich et al. 2008; Fike et al. 2009; Capilla-Gonzalez et al. 2016), loss of neuronal function (Greene-Schloesser et al. 2013; Burns et al. 2016; Wilke et al. 2018), depletion of oligodendrocyte progenitor cells (Greene-Schloesser et al. 2013; Burns et al. 2016), chronic neuroinflammation (Lee et al. 2012; Burns et al. 2016; Lumniczky et al. 2017), and damage to microvascular endothelium (Kim et al. 2008; Warrington et al. 2013). However, it remains unclear how these biological mechanisms underlie the clinical and radiological presentations of late-delayed RIBI.

While the field of RIBI research has provided a wealth of literature on patient outcomes and animal modeling, it is important to evaluate how these findings fit together to form a complete understanding of RIBI development. The objective of this systematic review of the literature is to first establish an interdisciplinary understanding of the current clinical evidence of RIBI, and then confirm rodent model accuracy with respect to current clinical end points. Therefore, the three key questions we have set out to answer in this systematic review are:

1. What are the current cognitive and radiological assessments used to evaluate late-delayed RIBI?
2. What are the relationships between and within cognitive and radiological findings of late-delayed RIBI in humans?; and
3. How well do rodent models of RIBI replicate to the cognitive and radiological evidence observed in humans?

Methods

Search strategy

This systematic review adheres to the guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Moher et al. 2009). The initial pool of studies pertaining to clinically or radiologically detected radiation injury of the brain in humans or rodents were first collected through PubMed, Web of Science, and SCOPUS using the search string listed in S1 Appendix. The search criteria were further limited by language (English), time of publication (January 1980 to January 2022), and publication status (full text must be available). Case reports, editorials without original data, and review articles were further excluded from the pool of initial studies. Additional studies were included into this pool by manually hand-searching references of included studies.

Study selection

A preliminary screening of the titles and abstracts was performed based on the following inclusion criteria: (1) patients must be treated with cranial radiation therapy; (2) rodent models must receive a clinically relevant dose of ionizing radiation to a disease-free brain; (3) outcome is measured by a neurocognitive or neuroimaging assessment after a specified period of time post-irradiation: at least 1 month for rodents and 6 months for patients; (4) neurocognitive assessments must evaluate global cognitive functioning or one of the following domains: complex attention, executive functioning, learning and memory, perceptual-motor function, and language; (5) neuroimaging techniques must attempt to identify at least one of the following radiation-induced changes: cerebral atrophy, cerebral microbleeds, radiation-induced leukoencephalopathy, changes in diffusion metrics, and changes in metabolic profile. Respectively, these criteria function to (1) establish patient data as the ground truth; (2) verify deficits or lesions within rodent brains are exclusively due to a radiation-induced normal tissue injury; (3) ensure that the deficits or lesions measured are indeed late-delayed effects and not acute effects of RIBI; (4) limit neurocognitive outcomes to the domains in which impairments are most commonly reported; (5) limit neuroimaging outcomes to those previously reported to be associated with neurocognitive impairment.

This limitation in neurocognitive and neuroimaging outcomes was performed due to the wide range of possible albeit infrequent side effects that could potentially occur after radiation treatment. Neurocognitive assessments therefore focused on changes in the domains of language, executive function, learning and memory, complex attention, perceptual-motor function, and general cognitive ability according to previously reported guidelines (Sachdev et al.

2014; Janss et al. 2019). Furthermore, neuroimaging outcomes are focused on those that have been shown to be related to neurocognitive impairment, such as cerebral atrophy, cerebral microbleeds, radiation-induced leukoencephalopathy, changes in diffusion metrics, and changes in metabolic profile (Greene-Schloesser et al. 2012; Robbins et al. 2012; Lupo and Nelson 2014). All evidence and definitions of neurocognitive or radiological RIBI have been left to the interpretation of the original authors.

Accepted studies based on this title and abstract screening were retrieved and saved to Zotero, our reference management database of choice. The full text of these studies was then read to ensure quality of study methodology and to confirm adherence to inclusion criteria.

Data extraction and analysis

Data were extracted from the studies that fulfilled the inclusion and exclusion criteria. Details of study characteristics were extracted, which included species, age, sex, sample size, health status, irradiated volume, total dose, and dose per fraction. Details of the relevant findings were extracted, which included outcome measurement techniques, time of outcome detection, and classification of outcome. For studies that contain groups with an experimental treatment arm, only the group that has received solely radiation is considered for this review. Some studies may set forth the objective of measuring both cognitive and radiological RIBI, however fail to find evidence of either one or the other; only the successfully detected form of RIBI will be incorporated as evidence in this review. Studies that do not provide the techniques for cognitive or radiological RIBI assessment will not be considered in our results. These collected data were then organized and combined according to the authors' categorization of evidence (cognitive or radiological RIBI, rodent or human) in order to visualize their relationships and diversity (Lex et al. 2014).

Results

Description of search results

The literature search identified a total of 2647 studies. After the removal of duplicates, 1722 studies remained. Abstract screening based on the inclusion criteria excluded 1562 studies, leaving a remaining total of 158 studies to undergo full-text assessment. Five studies were excluded due to either insufficient evidence of RIBI or omission of RIBI assessment protocols, leaving a final group of 153 studies included in this systematic review. A summary of this systematic search of the literature, as well as the enumeration of included studies, is provided in Figure 1. The comprehensive collection of details extracted from these studies, such as patient demographics and treatment protocols, can be found in S1 Table (for human studies) and S2 Table (for rodent studies).

It is unclear whether the various relationships between domains of cognitive impairment in human studies reflect ground truth or research interests

We found a total of 49 studies that sought to investigate cognitive RIBI within a human cohort. The following trends

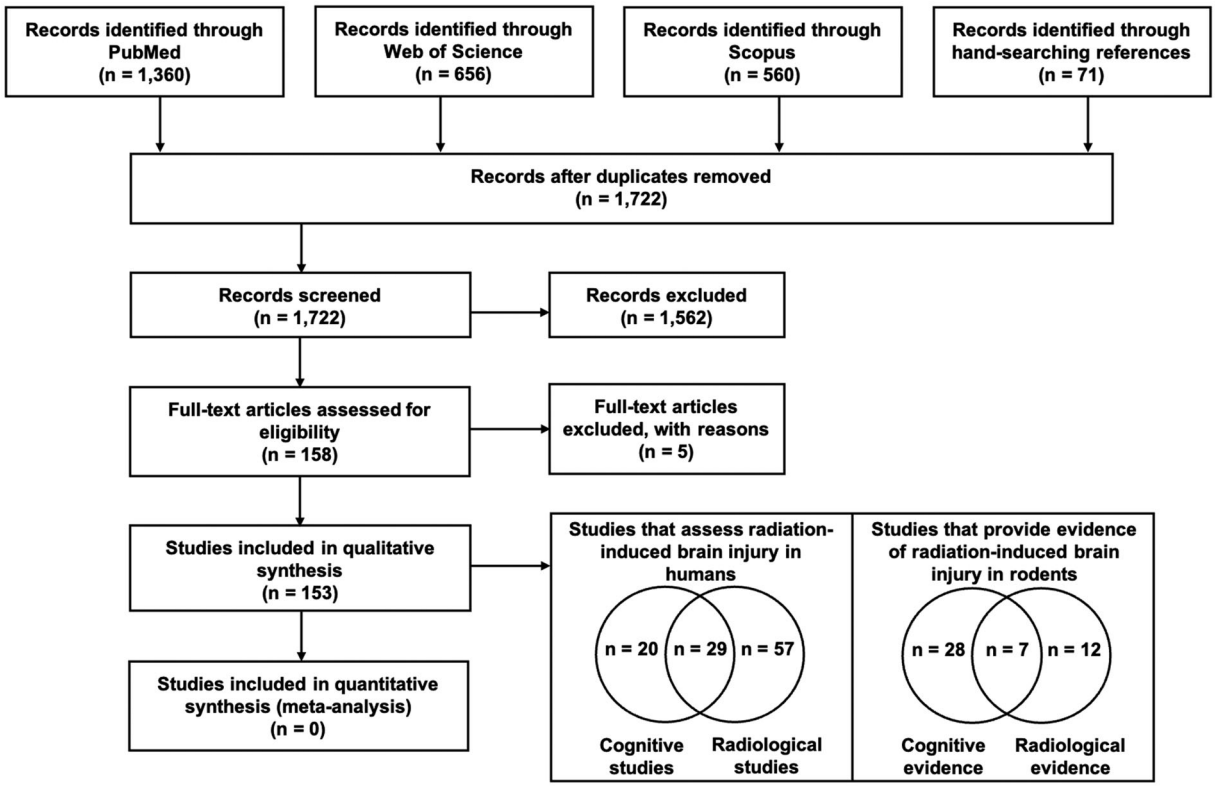

Figure 1. PRISMA flowchart for the identification and selection of studies.

were found in patients receiving cranial radiation therapy: (1) impaired cognitive functioning occurs in the domains of complex attention (Anderson et al. 1997; Schatz et al. 2000; Mulhern et al. 2001; Armstrong et al. 2002; Reddick et al. 2003; Schatz et al. 2004; Mulhern et al. 2004; Moretti et al. 2005; Douw et al. 2009; Correa et al. 2012; Krull et al. 2013; Schuitema et al. 2013; Butler et al. 2013; Reddick et al. 2014; Edelmann et al. 2014; Schuitema et al. 2015; Chapman et al. 2016; Simó et al. 2016; Roddy et al. 2016; Follin et al. 2016; Rashid et al. 2017; Bompaire et al. 2018), learning and memory (Mulhern et al. 1992; Mulhern et al. 2001; Armstrong et al. 2002; Reddick et al. 2003; Chang et al. 2009; Chapman et al. 2012; Correa et al. 2012; Krull et al. 2013; Riggs et al. 2014; Edelmann et al. 2014; Chapman et al. 2016; Simó et al. 2016; Armstrong et al. 2016; Roddy et al. 2016; Follin et al. 2016; Bompaire et al. 2018; Tringale et al. 2019; Brown et al. 2020; Morrison et al. 2021), executive function (Anderson et al. 1997; Schatz et al. 2000; Douw et al. 2009; Correa et al. 2012; Krull et al. 2013; Schuitema et al. 2013; Schuitema et al. 2013; Edelmann et al. 2014; Simó et al. 2016; Roddy et al. 2016; Follin et al. 2016; Rashid et al. 2017; Bompaire et al. 2018), perceptual-motor function (Douw et al. 2009; Correa et al. 2012; Roddy et al. 2016; Follin et al. 2016; Rashid et al. 2017; Redmond et al. 2018), or language (MacLean et al. 1995; Chapman et al. 2012; Simó et al. 2016; Follin et al. 2016; Tibbs et al. 2020); (2) reduced aptitude occurs for general cognitive abilities such as academic achievement, intellectual ability, and neurocognitive functioning (Twaddle et al. 1983; Mulhern et al. 1992; Radcliffe et al. 1994; Anderson et al. 1997; Schatz et al. 2000; Davidson et al. 2000; Mulhern et al. 2001; Reddick et al. 2003; Mulhern et al. 2004; Moretti et al. 2005; Omuro et al. 2005; Khong et al. 2006; Aoyama et al. 2007; Corn et al. 2008; Tang et al. 2012; Krull et al. 2013; Schuitema et al. 2013; Butler et al. 2013; Reddick et al. 2014; Edelmann et al. 2014; Merchant et al. 2014; King et al. 2015; Schuitema et al. 2015; Simó et al. 2016; Bompaire et al. 2018; Roth et al. 2020; Alirezaei et al. 2021; Lin et al. 2021); and 3) cognitive impairment does not occur in isolation, but rather spans across multiple cognitive domains.

Within this pool of 49 studies, there were 120 cumulative attempts to measure cognitive domain deficits after cranial radiotherapy. Only 94 of these 120 efforts were successful; the majority of viable evidence lies within the domains of complex attention, learning and memory, and general cognitive ability, while the minority lies within executive function, language, and perceptual-motor function (Figure 2(a)). Interestingly, some studies that attempt to comprehensively assess multiple cognitive domains detected little to no forms of cognitive impairment from their battery of assessments (Waber et al. 2004; Chapman et al. 2016; Agbahiwe et al. 2017; Bian et al. 2019; Phillips et al. 2020). Other comprehensive studies had more success in measuring cognitive impairments and were able to detect deficits using at least half of their battery of assessments (Anderson et al. 1997; Douw et al. 2009; Simó et al. 2016). Pooling together these 94 cases of successfully detected deficits, about 90% of the current viable evidence of cognitive impairment in human studies are composed of changes in general cognitive ability, complex attention, learning and memory, or executive function with little consideration for the assessment of language and perceptual-motor function (Figure 2(b)). Furthermore, it can be observed that these 94 cases of cognitive deficits do not occur in isolation, but rather encompasses multiple domains (Figure 2(c)). Studies that show cognitive deficits occurring in a single domain did not attempt to measure changes in any other cognitive domains. This is relevant for all isolated cases of general cognitive ability but excludes one case of memory and learning and one case of complex attention.

While there is a multitude of evidence for the impairment of cognitive domains, these results differ due to their heterogeneity of assessments (Figure 3). In our dataset, for example, we find that 24% of all human cognitive impairments are related to complex attention, which are measured by 9 different types of assessments. Even if these deficits in cognition are summarized and categorized into domains, the type of assessment used to detect injury only provides a fraction of the overall answer. For instance, Correa et al. uses the Digit Span test to measure selective attention while Edelmann et al. uses the Grooved Pegboard test to measure processing speed. These measurements of selective attention and processing speed both fall under the category of complex attention, but they describe different aspects of the attention domain. Although we can picture general relationships about the types of cognitive RIBI cases and their interconnections, we cannot be sure whether these trends represent the inherent characteristics of RIBI or are rather a reflection of the field's vested interest in particular RIBI subcategories.

Trends can be easily deduced from human studies of MRI-detectable radiation injuries due to the generality of neuroimaging techniques

We found a total of 86 studies that sought to investigate radiological RIBI within a single human cohort. The following trends were found in patients receiving cranial radiation therapy: (1) changes in diffusion present as decreases in fractional anisotropy and increases in mean diffusivity, longitudinal diffusivity, or perpendicular diffusivity within global white matter (WM) or WM regions such as the fornix, cingulum bundle, corpus callosum, uncinate fasciculus, ventral cingulum, genu, and splenium (Khong et al. 2006; Nagesh et al. 2008; Haris et al. 2008; Rueckriegel et al. 2010; Chapman et al. 2012; Xiong et al. 2013; Schuitema et al. 2013; Edelmann et al. 2014; Hope et al. 2015; King et al. 2015; Simó et al. 2016; Connor et al. 2016; Duan et al. 2016; Connor et al. 2017; Leng et al. 2017; Makola et al. 2017; Redmond et al. 2018; Bompaire et al. 2018; Follin et al. 2019; Morrison et al. 2019; Bian et al. 2019); (2) the majority of cerebral atrophy studies measure the change in WM volumes, which are shown to decrease post-irradiation (Usenius et al. 1995; Reddick et al. 1998; Davidson et al. 2000; Mulhern et al. 2001; Armstrong et al. 2002; Reddick et al. 2003; Mulhern et al. 2004; Reddick et al. 2005; Faraci

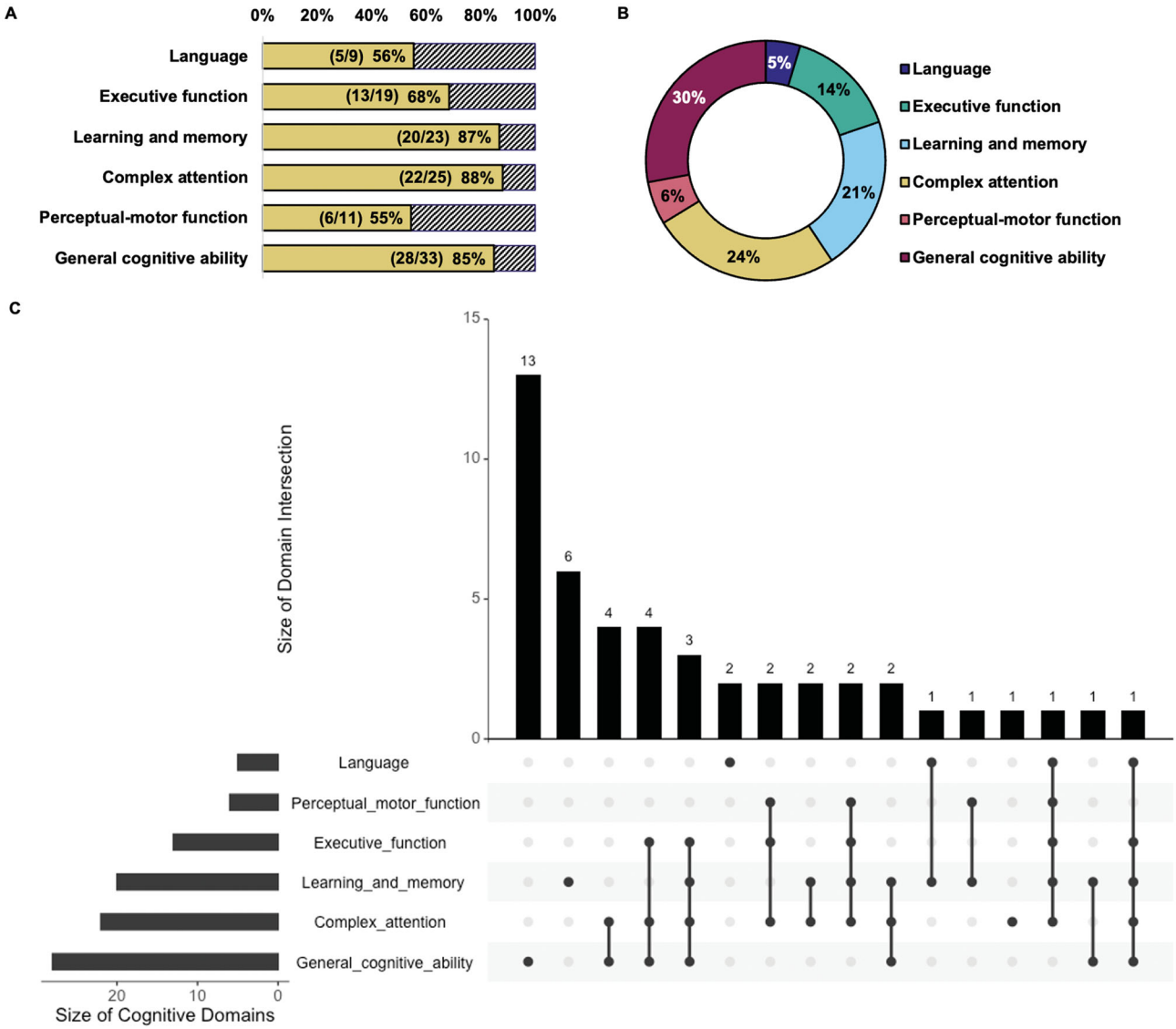

Figure 2. Current evidence on radiation-induced cognitive impairment in human studies. (a) Number of attempts and success rate for specific cognitive deficits associated with brain irradiation. Each domain-specific success rate is determined by comparing the number of cases that *successfully* detects cognitive deficits within its respective domain to the number of cases that *sought out* with the objective of detecting cognitive deficits within its respective domain. Studies may have multiple cases of domain-specific cognitive deficits. (b) Domain-specific prevalence rates as determined by comparing the number of cases that successfully detects cognitive deficits *within its respective domain* to the number of cases that successfully detects cognitive deficits *for all domains*. (c) Interaction between cognitive domains. The 'Size of Domain Intersection' enumerates the studies that present evidence of their respective combination of cognitive deficit cases. The 'Size of Cognitive Domains' enumerates the successfully detected cases of cognitive deficits within its respective domain.

et al. 2011; Riggs et al. 2014; Reddick et al. 2014; Edelmann et al. 2014; Follin et al. 2016; Tibbs et al. 2020; Lin et al. 2021); (3) the total number of cerebral microbleeds detected within a patient increases with time after cranial irradiation (Lupo et al. 2012; Peters et al. 2013; Varon et al. 2014; Lupo et al. 2016; Kralik et al. 2018; Morrison et al. 2019; Morrison et al. 2021); (4) WM hyperintensities, also known as leukoencephalopathy, localizes within the periventricular regions of the brain (Matsumoto et al. 1995; Andersen et al. 2003; Johannesen et al. 2003; Moretti et al. 2005; Omuro et al. 2005; Belliveau et al. 2017; Bompaire et al. 2018); and (5) a loss of neuronal density and/or function, reflected by a decrease in N-acetylaspartate normalized to creatine (NAA/Cr) in MR spectroscopy (MRS; Usenius et al. 1995; Virta et al. 2000; Rutkowski et al. 2003; Sundgren et al. 2009; Rueckriegel et al. 2012; Wang et al. 2012; Xiong et al. 2013; Follin et al. 2016; Alirezaei et al. 2021).

Further studies provide findings of radiological RIBI development that do not fit within these trends. One of such observations is that while many studies suggest cerebral atrophy mainly affects the loss of WM volume, other studies describe cerebral atrophy as a loss of cortical thickness (Karunamuni et al. 2016; Seibert et al. 2017), a reduction of gray matter volume (Leng et al. 2017; Shi et al. 2018; Nagtegaal et al. 2021), or a decrease in whole brain volume without a change in WM volume (Prust et al. 2015). Furthermore, one study reports that there was no significant difference in cerebral volume between the patients and controls over time (Agbahiwe et al. 2017). Another observation pertains to the conflicting evidence in the permanence of

Figure 3. Assessments performed in human studies to measure changes in cognition after cranial radiotherapy. Illustrated in each subfigure are techniques that successfully detected changes in cognition for the domains of: (a) language, (b) executive function, (c) learning and memory, (d) complex attention, (e) perceptual-motor function, (f) general cognitive ability.

microbleeds. Indeed, it has been shown that microbleeds may disappear during clinical follow-up (Belliveau et al. 2017; Morrison et al. 2019) or that microbleeds could be detected at all follow-up examinations upon appearance (Peters et al. 2013; Lupo et al. 2016; Morrison et al. 2021). Finally, there are still discrepancies in establishing a

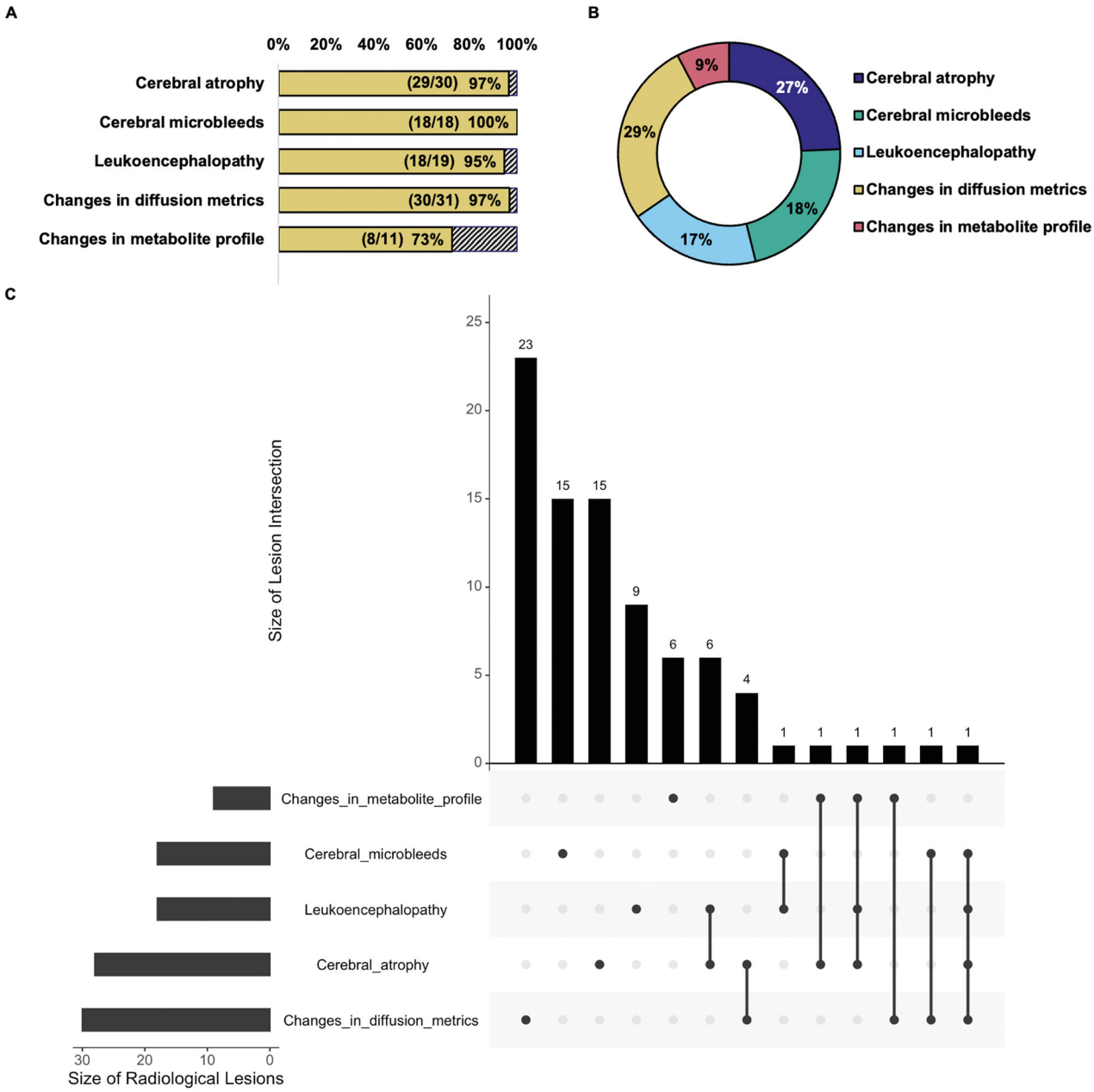

Figure 4. Current evidence on radiation-induced abnormalities as detected by magnetic resonance imaging in human studies. (a) Number of attempts and success rate for specific radiological lesions associated with brain irradiation. Each lesion-specific success rate is determined by comparing the number of cases that *successfully* detected its respective radiological lesion to the number of cases that *sought out* with the objective of detecting its respective radiological lesion. Studies may have multiple cases of radiologically detected lesions. (b) Lesion prevalence rates as determined by comparing the number of cases for *each* successfully detected radiological lesion to the number of cases for *all* successfully detected radiological lesions. (c) Interaction between types of radiological lesions. The 'Size of Lesion Intersection' enumerates the studies that present evidence of their respective combination of radiologically detected cases. The 'Size of Radiological Lesions' enumerates the successfully detected cases of the respective radiologically detected lesions.

clinically feasible metabolic characteristic for RIBI. As previously mentioned, many MRS studies show that NAA/Cr decreases after cranial irradiation with the assumption that Cr remains stable over time. Due to a limited number of studies, however, the change in Cr has yet to be determined. A handful of studies show that it decreases within the irradiated brain (Virta et al. 2000; Rueckriegel et al. 2012), however it is uncertain whether this is due to increasing age or irradiation. Due to a limited number of studies, the change in myoinositol normalized to creatine has yet to be determined. However, one study (Rutkowski et al. 2003) shows that it increases within the irradiated brain. Due to conflicting results, the effect of choline normalized to creatine remains inconclusive. Indeed, studies have reported increases (Rutkowski et al. 2003), decreases (Virta et al. 2000; Sundgren et al. 2009; Alirezaei et al. 2021), or no changes (Usenius et al. 1995; Davidson et al. 2000; Wang et al. 2012; Xiong et al. 2013) in choline normalized to creatine post-irradiation.

Within this pool of 86 studies, there were 109 cumulative attempts to measure MRI-detectable changes after cranial radiotherapy from which 103 were successful in detecting radiation-induced changes (Figure 4(a)). Pooling together these 103 cases of successfully detected lesions, about 90% of

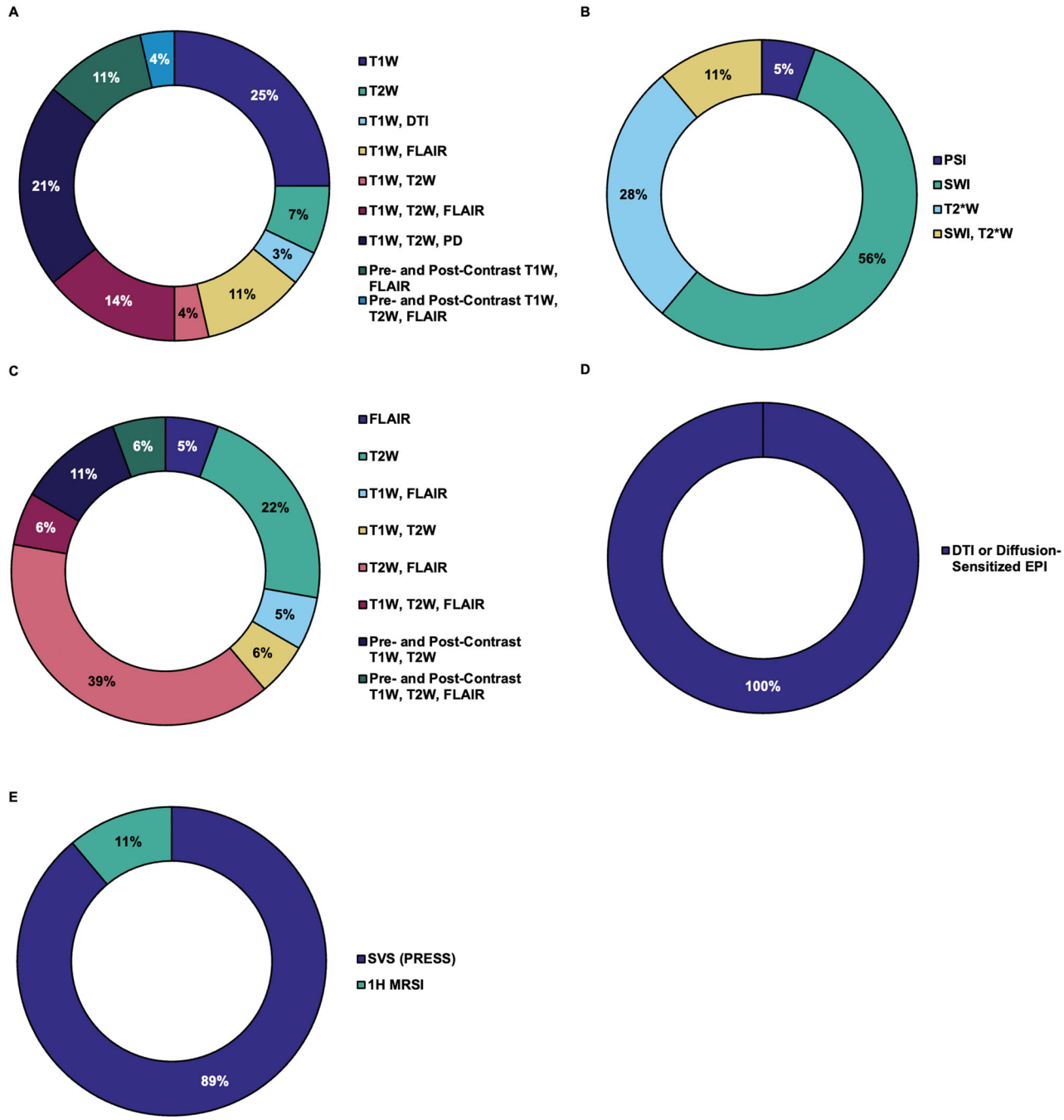

Figure 5. Magnetic resonance imaging techniques performed in human studies to detect lesions after cranial radiotherapy. Illustrated in each subfigure are techniques that successfully detected lesion types such as: (a) cerebral atrophy, (b) cerebral microbleeds, (c) leukoencephalopathy, (d) changes in diffusion metrics, (e) changes in metabolic profile.

the current viable evidence of MRI-detectable injuries in human studies are composed of changes in cerebral atrophy, cerebral microbleeds, leukoencephalopathy, changes in diffusion metrics with minor evidence for the assessment of changes in metabolite profile (Figure 4(b)). Furthermore, the relationships between different forms of radiological RIBI are more discrete than cognitive RIBI: most of these cases of radiologically detected lesions occur in isolation (Figure 4(c)). The studies in which these radiological lesions are shown to occur by themselves did not attempt to measure other MRI-detectable changes.

While there is a multitude of evidence for radiological RIBI, these results do not differ as much in the heterogeneity of assessments as compared to cognitive RIBI (Figure 5). In our dataset, for example, we find that 27% of all radiologically detected lesions in humans are related to cerebral atrophy, which are measured by 9 different types of assessments. However, these variations in assessment types are different from those used for cognitive RIBI. The assessment types for radiological RIBI differ by level of detail provided compared to assessment types for cognitive RIBI. For instance, 25% of cerebral atrophy studies used only

T1-weighted imaging while 21% used a combination of T1-weighted, T2-weighted, and proton density images. Volume loss will still be measured in these two circumstances, regardless of which combination of MRI protocols is used. The difference, however, is that the accuracy ascribed to cerebral volume loss is strengthened as more techniques are used. In other words, the different types of cognitive RIBI assessments measures different aspects of cognitive domain impairment while different types of radiological RIBI assessments measure the same result with different levels of exactness. While we can form a general deduction about the types of radiological RIBI cases (Figure 4(b)) and connections of radiological RIBI (Figure 4(c)), firm numerical end points cannot be concluded for all aforementioned studies due to discrepancies in study methodology and data presentation.

There is an association between cognitive and radiological radiation-induced brain injury, but their causative relationship remains unclear

We found a total of 29 studies that provided evidence of both cognitive and radiological RIBI within a single human cohort. The design, evidence type, and results of each study are provided in S3 Table. The following relationships between radiological lesions and cognitive impairments were found in these patients that underwent cranial radiation therapy: (1) loss of intracranial volume is associated with poor cognitive status (Davidson et al. 2000; Mulhern et al. 2001; Reddick et al. 2003; Mulhern et al. 2004; Douw et al. 2009; Riggs et al. 2014; Reddick et al. 2014; Edelmann et al. 2014; Rashid et al. 2017; Bompaire et al. 2018; Tringale et al. 2019; Lin et al. 2021); (2) abnormalities in diffusion imaging is associated with poor cognitive status (Khong et al. 2006; Chapman et al. 2012; Schuitema et al. 2013; Edelmann et al. 2014; King et al. 2015; Chapman et al. 2016; Simó et al. 2016; Redmond et al. 2018; Bompaire et al. 2018; Tringale et al. 2019; Tibbs et al. 2020); (3) WM hyperintensities (leukoencephalopathy) are associated with poor cognitive status (Davidson et al. 2000; Douw et al. 2009; Correa et al. 2012; Bompaire et al. 2018); and (4) cerebral microbleeds are associated with cognitive decline (Roddy et al. 2016; Bompaire et al. 2018; Morrison et al. 2021).

While these general relationships have been elucidated, it is imperative to also consider other findings of cognitive and radiological RIBI development from the systematic review that do not fit within these trends. While there is evidence that cerebral microbleeds are associated with worse cognitive function, three other similar studies included in this systematic review report that there were no clinical or neurocognitive symptoms related to cerebral microbleeds (Varon et al. 2014; Passos et al. 2015; Phillips et al. 2020). For leukoencephalopathy, the study by Aoyama et al. reports that only patients with severe white matter injury show clinically meaningful signs of cognitive deterioration. However, this cognitive outcome was assessed using the mini-mental state examination, which is not as sensitive toward post-treatment changes in cognition compared to comprehensive neuropsychological tests (Cramer et al. 2019). Most importantly, many of these studies do not investigate the temporal relationship between cognitive and radiological RIBI. There are four studies that focus on teasing apart this temporal relationship by describing it from an imaging biomarker perspective, showing that changes in diffusion metrics precede and predict cognitive outcomes (Khong et al. 2006; Chapman et al. 2012; Chapman et al. 2016; Tringale et al. 2019). In addition, one study provides evidence that white matter hyperintensities precede the onset of cognitive decline over a period of 6 years post-irradiation (Armstrong et al. 2002). Due to a lack of further evidence on the temporal relationship between cognitive and radiological RIBI, in addition to a lack of large studies with well-designed methodologies, there remains to be a consensus on whether radiologically detected injuries develop in tandem, precede, or follow cognitive impairment.

While many components of cognitive and radiological RIBI have been shown to be interconnected, there are certain relationships that draw more interest from the research field than others. A large proportion of evidence on the association between cognitive and radiological RIBI stems from cerebral atrophy and its relationship to the domain of complex attention (Figure 6(a)). However, this trend may not be reflective of the true etiology of RIBI. That is, these number of papers may also reflect the research field's current interest in studying cerebral atrophy and its relationship to different cognitive domains. Similar thinking can be applied to other types of radiological RIBI, such as radiation-induced leukoencephalopathy and changes in diffusion metrics, and their respective relationships with cognitive outcomes. Upon controlling for collaborative groups, a change in distribution of associations between cognitive and radiological RIBI can be found; interestingly, the largest proportion now stems from changes in diffusion metrics and its relationship to the domain of learning and memory (Figure 6(b)). However, the inherent issue of inhomogeneous assessments of the connection between cognitive and radiological RIBI still remains, making it unclear whether one relationship is inherently more important than the other. Therefore, further comprehensive assessment of the cognitive and radiological RIBI relationship is needed to elucidate their role in causation of neurological deterioration.

Clinical findings are not fully represented in rodent models

We found a total of 35 studies that provided evidence of cognitive RIBI within a rodent sample. These rodent studies exclusively reflect either learning and memory (Yoneoka et al. 1999; Raber et al. 2004; Rola et al. 2004; Shi et al. 2006; Zhao et al. 2007; Brown et al. 2007, p. 200; Atwood et al. 2007; Robbins et al. 2009; Acharya et al. 2009; Caceres et al. 2010; Acharya et al. 2011; Nageswara Rao et al. 2011; Warrington et al. 2012; Acharya et al. 2013; Belarbi et al. 2013; Jenrow et al. 2013; Parihar et al. 2014; Greene-Schloesser et al. 2014; Forbes et al. 2014; Peiffer et al. 2014; Acharya et al. 2014; Baulch et al. 2016; Acharya et al. 2016;

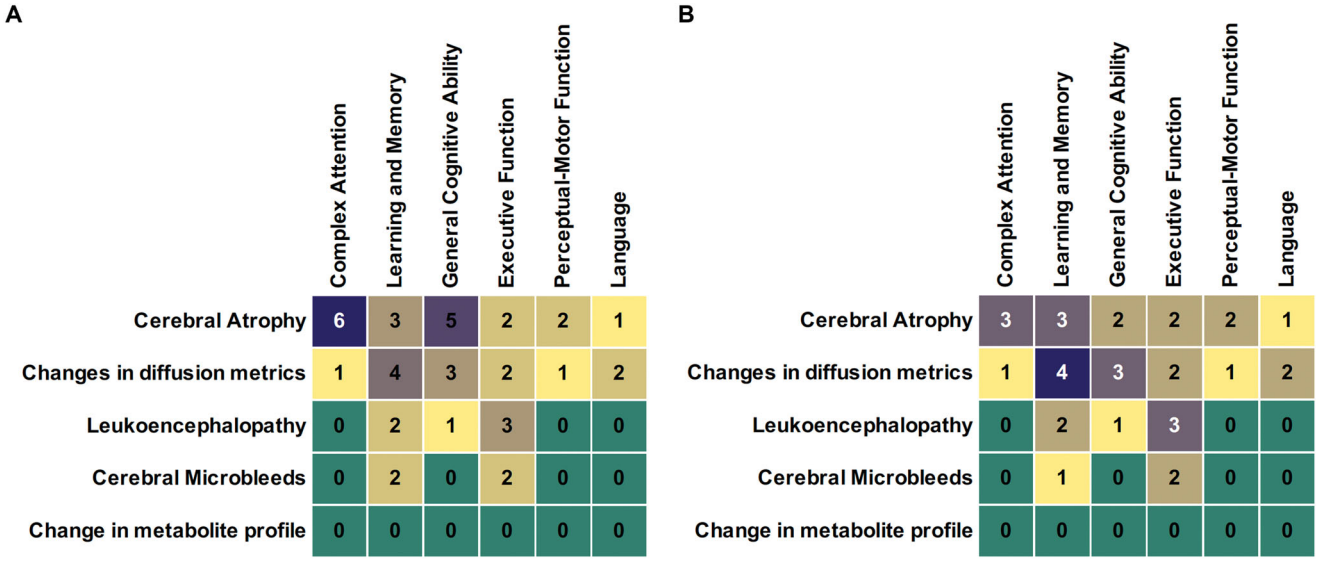

Figure 6. Associations between human studies containing evidence of both cognitive and radiological radiation-induced brain injuries. Number of (a) studies and (b) research groups that have shown both cognitive and radiological RIBI in the same cohort. Dark blue values indicate a higher number of studies with respect to the entire distribution while teal values indicate a lower number of studies.

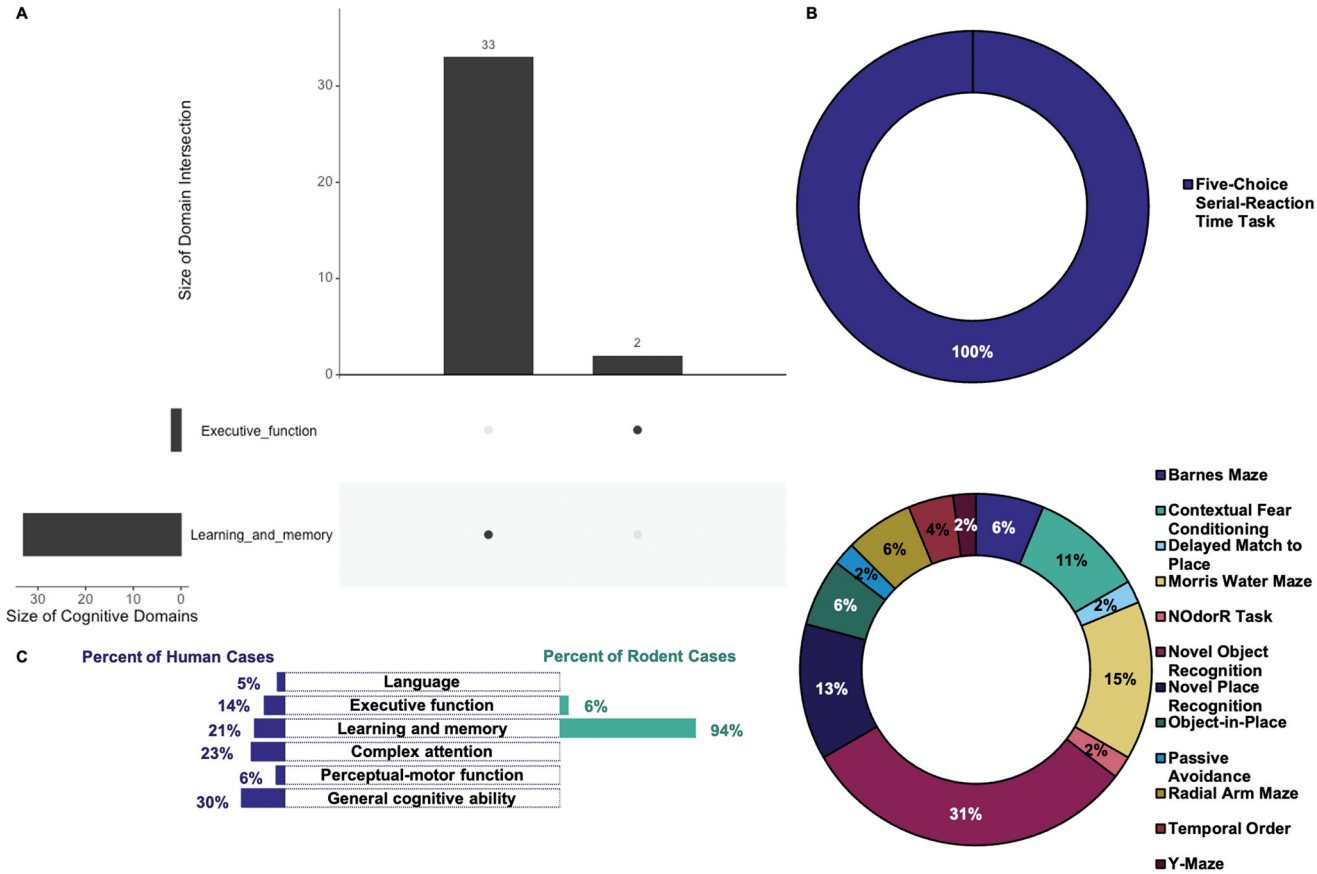

Figure 7. Current evidence on radiation-induced cognitive impairment in rodent studies. (a) Interaction between cognitive domains. The 'Size of Domain Intersection' enumerates the studies that present evidence of their respective combination of cognitive deficit cases. The 'Size of Cognitive Domains' enumerates the successfully detected cases of cognitive deficits within its respective domain. (b) Techniques that successfully detected changes in cognition for the domains of (top) executive function and (bottom) learning and memory. (c) Distribution of cognitive domains assessed in rodents and humans after brain irradiation.

Sun et al. 2016; Acharya et al. 2016; Brown et al. 2016; Feng et al. 2016; Bazyar et al. 2017; Allen et al. 2018; Bálentová et al. 2018; Alexander et al. 2018; Perez et al. 2018; He et al. 2021) or executive function (Sahnoune et al. 2018; Tang et al. 2019); they do not replicate the interconnection of cognitive impairments measured in humans (Figure 7(a)). Much like in the human studies, a variety of behavioral assays are used to evaluate impairment in

hippocampal-dependent learning and memory (Figure 7(b)). While this cognitive domain is found to be impaired in human patients, there is a clear mismatch between the focus of cognitive assessment in human studies versus rodent studies (Figure 7(c)). Similar to the issues that emerged in human studies, it is unclear whether these trends are a result of either (1) the true characteristic of cognitive impairment in rodents, or (2) the inherent interests of researchers modeling cognitive RIBI in humans. In other words, it is uncertain whether our findings originate from the assumption that either (1) rodent brains can only produce hippocampal-dependent learning and memory impairments post-irradiation, or (2) we only see hippocampal-dependent learning and memory impairments post-irradiation in rodents because that is the only area of injury that we are measuring. As at least one group has found non-hippocampal-dependent cognitive deficits in rodent RIBI models, the latter assumption is more likely than the former.

We found a total of 19 studies that provided evidence of radiological RIBI within a rodent sample. These rodent studies identified radiologically detectable lesions such as changes in metabolite profile (Atwood et al. 2007; Rodgers et al. 2016; Brown et al. 2016; Chen et al. 2017; Bálentová et al. 2017; Pérès et al. 2018; Hnilicová et al. 2019; Bálentová et al. 2019; Bálentová et al. 2021), cerebral atrophy (Peiffer et al. 2014; Sahnoune et al. 2018; Beera et al. 2018; Perez et al. 2018; Pérès et al. 2018; de Guzman et al. 2019; Tang et al. 2019; He et al. 2021), and changes in diffusion metrics (Wang et al. 2009; Wang et al. 2013; Liu et al. 2015; Sahnoune et al. 2018; Pérès et al. 2018; Tang et al. 2019); the majority of these lesions are detected in isolation (Figure 8(a)). Furthermore, although the imaging techniques used to detect these changes are similar to the protocols used for humans (Figure 8(b)), the distribution of MRI-detectable lesions in rodent models do not fully reflect the human injury (Figure 8(c)). While neuroimaging studies of successful models of cognition show evidence of cerebral atrophy using anatomical MRI (Peiffer et al. 2014; Beera et al. 2018; Pérès et al. 2018; de Guzman et al. 2019) and DTI techniques (Sahnoune et al. 2018; Perez et al. 2018; Tang et al. 2019), there are currently no rodent models that provide evidence of radiation-induced leukoencephalopathy after undergoing similar neuroimaging protocols as RIBI patients. Likewise, there are no studies that perform neuroimaging protocols to detect cerebral microbleeds within the rodent brain, likely due to the increased susceptibility artifacts when scanning rodent brains. With respect to rodent models measuring microstructural and metabolic changes, evidence is limited in number and remains inconclusive. While some rodent models show a post-treatment decrease in FA, others show FA remain unchanged post-treatment (Peiffer et al. 2014; Rodgers et al. 2016; Sahnoune et al. 2018; Perez et al.

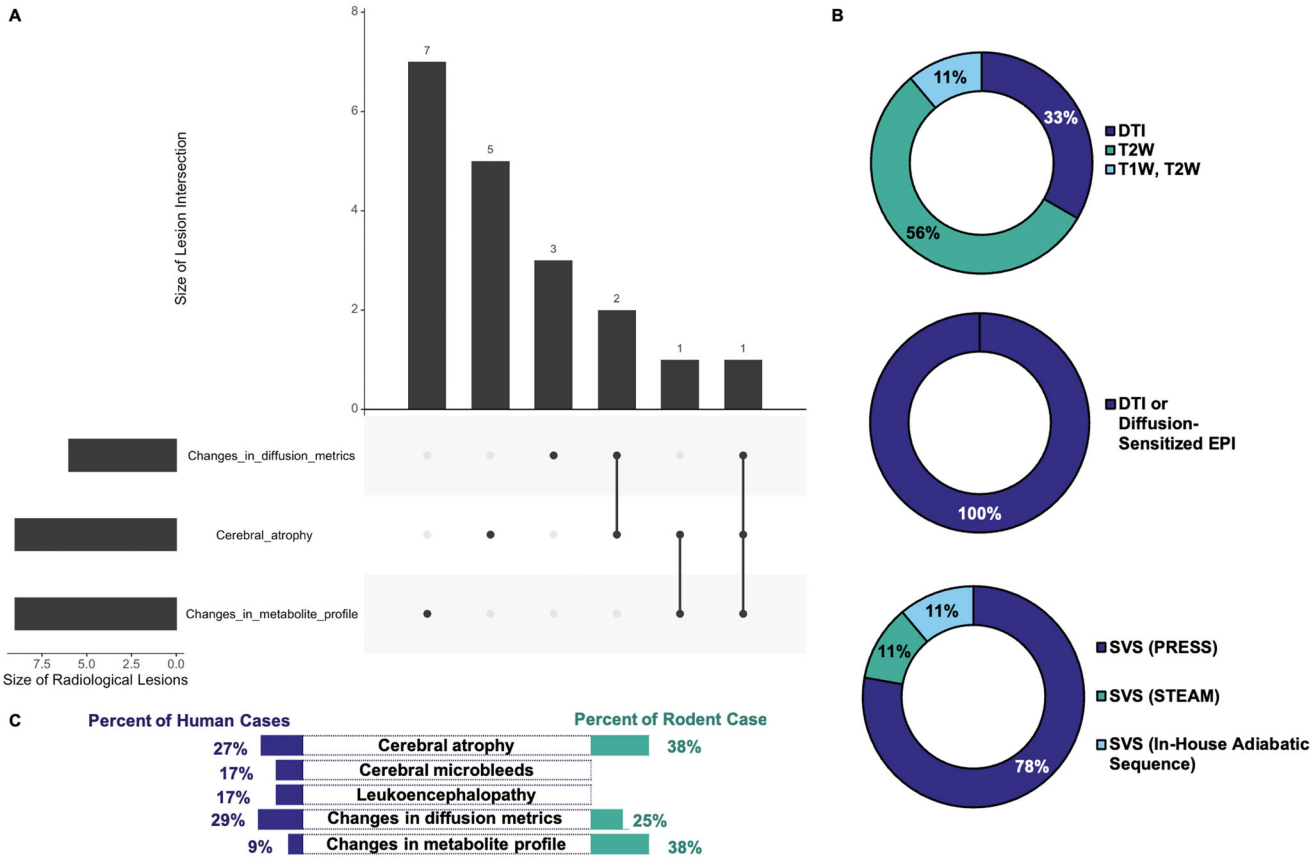

Figure 8. Current evidence on radiation-induced lesions detectable by magnetic resonance imaging in rodent studies. (a) Interaction between types of radiological lesions. The 'Size of Lesion Intersection' enumerates the studies that present evidence of their respective combination of radiologically detected cases. The 'Size of Radiological Lesions' enumerates the successfully detected cases of the respective radiologically detected lesions. (b) Techniques that successfully detected changes in (top) cerebral atrophy, (middle) diffusion metrics, and (bottom) metabolite profile. (c) Distribution of radiological lesions assessed in rodents and humans after brain irradiation.

2018) despite the occurrence of other cognitive changes within the same cohort. Furthermore, while there is evidence of metabolic-related changes in rodent brains, the evidence contains many discrepancies. Neuroimaging assessments in models of cognition show conflicting evidence of metabolic changes within the rodent brain post-irradiation. NAA/Cr has been shown to increase (Atwood et al. 2007; Rodgers et al. 2016), decrease (Brown et al. 2016, p. 201; Chen et al. 2017; Bálentová et al. 2017; Hnilicová et al. 2019; Bálentová et al. 2019; Bálentová et al. 2021), or have no change post-irradiation (Robbins et al. 2009). Glutamate and glutamine normalized to creatine have been shown to increase (Atwood et al. 2007), decrease (Brown et al. 2016; Bálentová et al. 2021), or have no change post-irradiation (Robbins et al. 2009; Bálentová et al. 2017). Choline normalized to creatine has been shown to increase (Bálentová et al. 2021), decrease (Chen et al. 2017; Bálentová et al. 2019), or have no change post-irradiation (Bálentová et al. 2017; Hnilicová et al. 2019). Myoinositol normalized to creatine has been shown to increase (Hnilicová et al. 2019; Bálentová et al. 2021), decrease (Atwood et al. 2007; Rodgers et al. 2016), or have no change (Robbins et al. 2009) post-irradiation.

We found seven studies that provided evidence of both cognitive and radiological RIBI within a rodent sample. The design, evidence type, and results of each study are presented in S4 Table. Two studies describe the relationship between changes in executive functioning and diffusion metrics within rodents (Sahnoune et al. 2018; Tang et al. 2019) while the other five studies present the connection between learning and memory impairments and either cerebral atrophy (Peiffer et al. 2014; Perez et al. 2018; He et al. 2021) or changes in metabolite profile (Atwood et al. 2007; Brown et al. 2016). While these rodent studies have successfully detected cognitive and radiological changes post-irradiation, the current rodent models of RIBI do not holistically replicate the research findings currently exhibited in human cases.

Discussion

This systematic review of the literature was conducted to evaluate the characteristics of current late-delayed RIBI studies, elucidate the connections between cognitive and radiological forms of late-delayed RIBI, and report the accuracy of current rodent models. Regarding the features of human cognitive RIBI, there are many attempts to measure deficits within the domains of general cognitive ability, complex attention, or learning and memory. In comparison, there are not as many attempts to measure changes in language, perceptual-motor function, or executive function. Additionally, the success rate of cognitive domain deficit detection generally reflects the number of attempts to measure cognitive domain deficits. That is, the domain deficits that contribute the entirety of cognitive RIBI consist of those that are more widely sought out to assessed, such as general cognitive ability and complex attention. Regarding the features of human radiological RIBI, there are many attempts to measure cerebral atrophy, cerebral microbleeds, leukoencephalopathy, and changes in diffusion metrics. However, there are not as many attempts to measure changes in metabolite profile. Additionally, each type of radiological lesion has a perfect success rate except for cerebral atrophy.

With respect to the trends between cognitive and radiological RIBI, our results show that there is a high distribution of studies that focus on the association between cerebral atrophy and complex attention. However, certain associations between cognitive domain deficits (e.g., perceptual-motor function and language) and radiologically detected lesions (e.g. leukoencephalopathy, cerebral microbleeds, and changes in metabolite profile) remain largely undefined. It is thus unclear whether these trends are due to implicit relationships between cognitive and radiological RIBI or to predispositions in research interests.

Incongruency is further reflected in the current preclinical models of RIBI. Results from rodent studies show that there are a limited number of models that have successfully replicated characteristics of cognitive and radiological RIBI as it would occur in a human. In the case of cognitive impairment, it is shown in this review that most rodent models of cognition replicate hippocampal-dependent learning and memory – only one of the many aspects of human cognitive impairment. Further consideration of cognitive assessments performed in rodent studies suggests that the high number of results for hippocampal-dependent memory impairment may be driven by a lack of comprehensive assays in rodent models of RIBI. In addition, results from rodent models of neuroimaging are not completely consistent with what is observed in humans. Most of the evidence for radiological RIBI in rodents is derived from cases of cerebral atrophy and changes in metabolite profile, with a minor contribution from changes in diffusion metrics. While these radiological lesions are also present in humans, there is no current evidence that rodents are capable of exhibiting further characteristic lesions observed in humans, such as radiation-induced leukoencephalopathy and cerebral microbleeds. However, the lack of cerebral microbleed detection may be driven by a lack of MR techniques and hardware compatible with small animals.

The primary limitation of our systematic review is a lack of quantitative analysis of our results. However, a meta-analysis could not be performed due to the heterogeneity of study methodology and data presentation. There was a wide variety of study designs, patient demographics, outcome measurement techniques, and follow-up times after treatment. In some studies, particular components of methodology were completely omitted. Furthermore, other study characteristics such as irradiated volume, total dose, number of treatment fractions, and raw outcome scores were not consistently provided within the methods. Regarding heterogeneity in the presentation of data, many human studies with mixed patient demographics (e.g. mixed treatment cohorts of radiotherapy only and radiotherapy with chemotherapy) present results in an unstratified manner such that it was difficult to deduce which side effects were derived solely from radiotherapy. Additionally, some studies reported wide ranges of

outcome measurement (e.g. 6–60 months post-treatment) without stratification of results in regard to its specific time point of presentation. Due to these challenges in combining and comparing the collected data in a systematic fashion, it became clear that a meta-analysis would not provide an accurate insight into the current data.

A limitation of our qualitative analysis of the literature is that patient demographics, irradiated volume, and radiation dose were not considered in the analysis of late-delayed effects of RIBI. This is because treatment effects were not given with respect to patient age or sex, but rather as an entire cohort. Additionally, there were high variations in treatment protocols, which are unique to the patient's disease presentation and progression. For these reasons, the late-delayed effects of RIBI were investigated holistically based on the evidence made available by a systematic review of the literature. In addition, we do not know how many inconclusive or negative findings have been discovered but not published. It is also possible that other studies concerning the late-delayed effects of RIBI in humans and rodents were published but were not within the scope of our search strategy.

Evidence from our review shows that rodent models are limited in replicating the multitude of cognitive impairments observed in humans due to constraints in the availability of verified cognitive assessments. A suggestion would be to consider the use of additional cognitive assessments for rodent models that have been performed outside the field of rodent RIBI models. For instance, rodent studies of space radiation-induced cognitive impairment have successfully modeled metacognitive and hypothesis-generating tasks that were previously assumed to be primate-specific (Britten et al. 2021). Aside from rodent models, intermediate animal models may also have the potential to replicate human outcomes. Notably, non-human primates (Robbins et al. 2011; Hanbury et al. 2015; Andrews et al. 2019), swine (Athanasiadi et al. 2021), and dogs (Benczik et al. 2002) have been shown to be feasible large animal models of RIBI. Overall, it may be ideal to consider either alternative cognitive assessments for rodent models or different model systems in order to replicate the human characteristics of cognitive and radiological RIBI more closely.

An additional suggestion for future research is to create a protocol of standardized assessments in order to maintain reproducible results in multi-center clinical trials of RIBI therapeutics. Our systematic review shows there are many successful methods to assess impairment within a neurocognitive domain: 5 different tests identified language impairment, 9 for executive function, 13 for learning and memory, 9 for complex attention, 6 for perceptual-motor function, and 11 for general cognitive ability. While this diversity in assessment type allows for different facets of cognitive impairment to be measured and analyzed, it also creates issues in maintaining consistency within the field of RIBI. Along with standardization, it is also important that these assessments accommodate the practicalities of clinical follow-up procedures. For instance, these evaluations should be simple without sacrificing sensitivity and able to be quickly performed by non-specialists (Durand et al. 2015).

Lastly, it is important to begin incorporating the use of more functional rather than structural MRI techniques in studies of RIBI, such as functional MRI (van den Heuvel and Hulshoff Pol 2010) and functional connectivity (Zhao et al. 2021). As noted above, cognitive deficits have been identified in rodent space radiation models at doses much lower than those explored for RIBI. These deficits are believed to occur without overt structural changes. Similarly, some rodent RIBI reports indicate cognitive deficits without corresponding structural changes (Shi et al. 2009; Rancilio et al. 2017). However, as we noted in our section regarding the relationship between cognitive and radiological deficits, no human study of RIBI that has evaluated both cognitive and radiological changes have found cognitive deficits without corresponding radiological changes. There are multiple possible explanations for this discrepancy between human cases and rodent models. But if the thought is that the cognitive deficits that characterize RIBI are due to functional changes that precede the structural changes, then the use of functional imaging can help make that clearer. Together, the use of more sensitive imaging techniques and standardized neurocognitive assessments would provide a greatly needed holistic approach to understanding the complete spectrum of late-delayed RIBI in brain cancer survivors.

In summary, the associations between and within cognitive and radiological RIBI often rely on the type of assessment chosen to detect it. Indeed, inhomogeneous assessments of RIBI subcomponents can result in inhomogeneous manifestations of RIBI subcomponents. This theme of heterogeneity eventually pervades into preclinical animal modeling, creating rodent studies that assay only certain subcomponents of RIBI. Rather than placing consideration for only certain subcomponents of RIBI, perhaps it is just as important to evaluate the totality of known effects to realize the full consequence of RIBI.

Disclosure statement

The authors report there are no competing interests to declare.

Funding

This publication was made possible, in part, thanks to financial support from the Ralph W. and Grace M. Showalter Research Trust at Purdue University.

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