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Systematic Review

Changes in cortical thickness and volume after cranial radiation treatment: A systematic review

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ABSTRACT

Cognitive decline has a clear impact on quality of life in patients who have received cranial radiation treatment. The pathophysiological process is most likely multifactorial, with a possible role for decreased cortical thickness and volume. As radiotherapy treatment systems are becoming more sophisticated, precise sparing of vulnerable regions and tissue is possible. This allows radiation oncologists to make treatment more patient-tailored. A systematic search was performed to collect and review all available evidence regarding the effect of cranial radiation treatment on cortical thickness and volume. We searched the Pubmed, Embase and Cochrane databases, with an additional reference check in the Scopus database. Studies that examined cortical changes on MRI within patients as well as between treated and non-treated patients were included. The quality of the studies was assessed with a checklist specially designed for this review. No meta-analysis was performed due to the lack of randomised trials. Out of 1915 publications twenty-one papers were selected, of which fifteen observed cortical changes after radiation therapy. Two papers reported radiation-dependent decrease in cortical thickness within patients one year after radiation treatment, suggesting a clear relation between the two. However, study quality was considered mostly suboptimal, and there was great inhomogeneity between the included studies. This means that, although there has been increasing interest in the effects of radiation treatment on cortex morphology, no reliable conclusion can be drawn based on the currently available evidence. This calls for more research, preferably with a sufficiently large patient population, and adequate methodology.

It is estimated that 50–90% of patients receiving radiotherapy (RT) to the brain experience progressive cognitive disability [1,2]. The severity varies from mild impairment to symptoms similar to progressive dementia. The exact aetiology of this disabling consequence of tumour treatment remains unknown, but there are multiple hypotheses, including neuronal dysfunction, vascular damage and disturbed neurogenesis. The true cause is most likely multifactorial [1–3].

Recent advances in imaging modalities and analyses have made testing of some of these hypotheses possible [4]. Although most imaging studies focus on the relationship between radiation-induced cognitive defects and white matter (WM) [5,6] or the hippocampus [7,8], increasing attention has been given to changes in the cerebral (neo)cortex. The cerebral cortex contains a vast number of neurons, and has a thickness between 1 and 4.5 mm *in vivo*, depending on location [9]. The neurons are interconnected in an immensely complex network, and form the tissue which is essential for the execution of all cognitive processes [10]. It is comprised of both neuronal cell bodies and fibres, together with glial cells and blood vessels [11]. Both damage to neurons and vasculature can lead to disruption in the cortical network, and have been linked to changes in cognitive abilities [2,12].

Before the era of digital image analysis, macroscopic cortical atrophy as seen on routine CT or MRI had already been associated with RT and cognitive function [13–16]. But now, the exact

Abbreviations: ALL, acute lymphocytic leukaemia; CRT, conventional radiation therapy; ED, early delayed; GM, grey matter; IMRT, intensity-modulated radiation therapy; LD, late delayed; LGG, low grade glioma; NPC, nasopharyngeal carcinoma; NR, not reported; NSCLC, non-small cell lung cancer; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RT, radiation therapy; ROI, region of interest; SCLC, small cell lung cancer; WM, white matter.

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thickness of the cerebral cortex throughout the brain can be accurately computed from MR-images using specific software [9,17–23]. There are several ways to perform the morphological measurements, including deformation-based, voxel-based and surface-based morphometry (DBM, VBM and SBM), with the latter allowing for measurement of the cortical thickness [24]. In this technique, the surface of the brain is recreated as a fine mesh, and the distance between the surface and the border between the cortex and the underlying WM is calculated for each point in this mesh. The thickness is measured on a sub-millimetre level, which allows researchers to detect even microscopic changes between multiple scans. Although decrease in cortical thickness is part of the normal ageing process [25], it has also been linked with several diseases, including Alzheimer's disease [4,26], Parkinson's disease [27] and depression [28,29]. Furthermore, it has also been associated with cognitive impairments [30,31], which leads to the hypothesis that cortical thinning is a contributing factor to the impairments seen after radiation therapy. This is further supported by the fact that animal models have shown that irradiation during the pre-natal developmental period can also contribute to cortical abnormalities, including the thickness and volume of the cortex [32–34].

Aside from cortical thickness, cortical volume can also be derived from MR-images using the VBM method mentioned above. This is a more straightforward technique than the more complex SBM, which allows for quicker analysis. It classifies the voxels of an MRI-scan according to tissue types (grey matter, white matter or cerebrospinal fluid), quantifying the amount of each tissue type in each voxel. These values are added up to get the volume of each tissue. While the two measures are related, as the volume of the cortex changes along with its thickness, it is still recommended that both metrics should be interpreted separately due to their different genetic origins [35].

To gather all available current evidence regarding the effect of cranial RT on the cerebral cortex, we have conducted a systematic review of the literature. In this review we attempt to answer the following question: what evidence exists that changes in cortical thickness and volume occur in patients who have received cranial irradiation?

Methods

Search strategy

The systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement [36]. A search was performed in the Pubmed, Embase and Cochrane databases on the 21st of March 2018, and was constructed with help of a research librarian at Utrecht University, specialised in medical systematic reviews. The full search strings for each database are found in Appendix A. In short, we searched with terms relating to radiation therapy and cortical thickness or volume. The references of the ultimately selected studies were checked for additional studies in the Scopus database.

Study selection

After duplicate removal, all titles and abstracts of the search results were independently screened by 2 reviewers (SN and AvdB), and selected based on the inclusion criteria presented in Fig. 1. We were primarily interested in studies comparing cortical changes after RT within the same patients. However, in order to get a complete overview of the effect of RT, we also selected studies that performed a cross-sectional comparison between patients who received RT and non-RT controls. Therefore, both study designs were part of the inclusion criteria. The screening of the studies was facilitated by Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). Conflicts in screening were resolved during a consensus meeting. After screening, the full texts of the remaining manuscripts were read and the final selection of studies was made, again independently by the

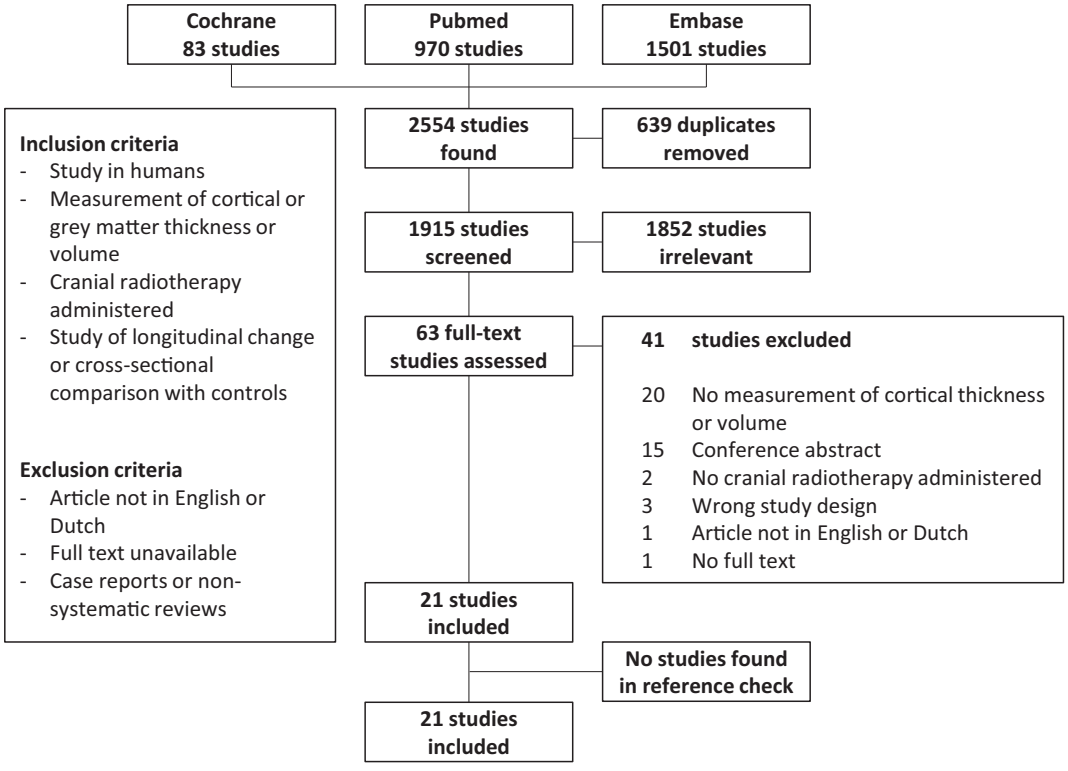

Fig. 1. Flow-chart of article selection, and overview of inclusion and exclusion criteria.

two screening authors, followed by another consensus meeting to resolve conflicts.

Data extraction

Data were extracted by the first author using a standard data collection form. We collected any analyses of changes or differences in either cortical thickness or volume after RT. If present, the relation between RT dose and cortical changes was also collected. Additionally, data on population, sample size, type of RT and length of follow-up were collected. When only part of the population of a study received RT, and no RT-subgroup analysis was reported, data from the entire population were extracted. Finally, if a study analysed the volume of the entire grey matter instead of the cerebral cortex, this difference in grey matter volume was extracted.

Data quality and relevancy

A checklist was constructed to assess data quality and relevancy of the papers. The domains of this checklist included case selection, study design and analysis quality. A complete overview of the assessment checklist, and the criteria that needed to be met for a positive score, are shown in Table 1.

The criteria in the domain "case selection" were mainly chosen to reflect on the risk of selection bias in the studies. The description of the way cases are selected, whether a random or consecutive sample was used, and a description of excluded and non-participating subjects allow us to verify that all eligible patients were included in the study. A comprehensive case description allows readers to see how the patients and controls relate to each other, and whether or not other treatments have been given to one or all groups.

The study design was evaluated by determining whether a priori brain regions were analysed. The use of these regions of interest (ROIs) means that the researchers identified brain regions where cortical changes are expected to occur. They were selected because these areas are related to certain cognitive functions or these areas have been shown to be vulnerable in earlier research. Using a limited number of a priori brain regions also negates the problem of multiple comparisons, whereby a significant result is more easily obtained when analysing many different brain regions simultaneously. Dividing the cortex into regions for analysis, as opposed to complete brain or lobes, means smaller areas of cortical thickness and volume change can be found. Similarly, only an analysis of the complete brain results in finding all possible regions of cortical change. Studying the relation between cortical change and dose shows that the observed changes are more likely to be related to radiation therapy, and are less likely to be caused by other factors, like ageing, which is well described [25].

Finally, the quality of the imaging and processing procedures and the quality of analysis and its description gives an indication of the methodological and statistical validity, and thereby the risk of bias by confounding or multiple comparisons.

Results

After duplicate removal, the search yielded a total of 1915 unique studies. After screening of title and abstract, 63 studies were selected for full text evaluation. After reading the full text, 21 studies were included for this review. A reference check in Scopus revealed no additional studies. The flow-chart of study selection is shown in Fig. 1.

Of the selected studies, 7 reported on cortical thickness after radiation therapy. Thirteen measured either cortical or grey matter volume after RT, and one studied both thickness and volume. An overview of the studies is found in Tables 2 and 3, and the assessment of bias and relevancy are found in Table 4. As none of the found studies are randomized controlled trials, meta-analysis of the study results is not advised [37]. Therefore, the findings of the found references will be presented in a narrative manner.

Cortical thickness

Eight studies presented data on the effect of radiation therapy on cortical thickness. Of those, three studies registered longitudi-

Table 1
Criteria for assessing risk of bias and study relevancy.

	Yes	No
Case and control selection	Setting, time frame and eligibility criteria for recruitment provided, and adequate matching in cross-sectional studies	Data on setting, method of selection and eligibility criteria for recruitment incomplete, and insufficient matching
Random or consecutive sample	Consecutive or random participant sampling	No consecutive or random participant sampling or unclearly described
Non-participants	Data on non-participating (excluded patients in case of retrospective study, eligible but non-participating in case of prospective study) subjects given, including reason for non-participating	Data on non-participating subjects not reported or incomplete
Case description	Information on participants complete (demographics, primary disease, received treatments)	Data on participants incomplete
A priori brain regions	Pre-defined brain regions of interest studied	No pre-defined brain regions of interest studied
Discrete RT patient group	Results are available of a group of patients that all received RT	Data available only of combined treatment group
Changes in cortex regions	Changes in cerebral cortical regions measured and reported	Changes in total cerebral lobes, total cortex or total grey matter measured
Relation to dose	Changes in cortex are relation to RT dose and location	Dose and location of RT is not related to cortical changes
Complete brain analysed	Cortical changes measured in entire brain, or entire brain with tumour regions censored	Cortical changes not measured in entire brain, e.g. in one cerebral lobe
Imaging and processing	Measurements performed on MR-images of sufficient quality and resolution, with adequate tumour area censoring (if necessary) and documented use of appropriate software	Poor image quality, insufficient tumour area censoring and/or incomplete information on software used
Analysis described	Methods of image analysis and computation adequately described, including imaging parameters and software used	Methods unclearly or incompletely described
Analysis quality	Use of correction for multiple comparisons, nonparametric statistical inference and controlling for possible confounding factors	One or more items missing; or the description is unclear

Table 2
Study characteristics of papers on cortical thickness.

Paper	Adults	Study design	Patient diagnosis	Total patients	Patients treated with RT	Chemotherapy in RT group	Controls (*n*)	RT type (total dose in Gy)	Mean time after RT
Correa (2013)	Yes	Both	Hematopoietic stem cell recipients	28	9	9	Healthy controls (10)	Full-dose total body irradiation (12.0–13.75)	1 year
Karunamuni (2016)	Yes	Longitudinal	High-grade glioma	15	15	15	–	Fractionated partial brain irradiation (60)	1 year
Kundu (2017)	No	Longitudinal	Medulloblastoma	14	14	14	Juvenile pilocytic astrocytoma (36)	Craniospinal irradiation (mean total 24.6 Gy)	376 days
Lin (2017)	Yes	Cross-sectional	Nasopharyngeal carcinoma	42	42	40	Pre-RT NPC patients (22)	2D-CRT (66–76), IMRT (58–70)	3.32 months (ED) and 10.90 months (LD)
Liu (2007)	No	Cross-sectional	Medulloblastoma	9	9	9	Healthy controls (9)	Craniospinal irradiation (25.7)	2.8 years
Nieman (2015)[*]	No	Cross-sectional	Various tumours	19	19	17	Healthy controls (32), surgical controls (9)	Cranial-spinal radiation (23.40–36.00)	1.51 and 1.70 years
Seibert (2017)	Yes	Longitudinal	Primary brain tumour	54	54	53	–	Fractionated partial brain irradiation (57.9)	1 year
Tamnes (2015)	No	Cross-sectional	All	130[**]	18	18	Healthy controls (130)	Cranial irradiation (20.0)	23 years

ALL = acute lymphocytic leukaemia, CRT = conventional radiation therapy, ED = early delayed, IMRT = intensity-modulated radiation therapy, LD = Late delayed, NPC = nasopharyngeal carcinoma, RT = radiation therapy.
[*] Same study as Nieman (2015) in Table 3.
[**] Same study population as Zeller (2013) in Table 3.

Table 3
Study characteristics of papers on cortical volume.

Author	Adults	Study design	Patient diagnosis	Total patients	Patients treated with RT	Chemotherapy in RT group	Controls (*n*)	RT type (total dose in Gy)	Mean time after RT
Edelmann (2014)	No	Cross-sectional	All	79	39	39	Healthy controls (23)	Cranial radiation (20)	23.9 years
Follin (2016)	No	Cross-sectional	All	33	33	33	Healthy controls (29)	Cranial radiation (18–25)	34 years
Gommlich (2018)	Yes	Longitudinal	Glioma (grade II and III)	26	26	NR	–	Partial brain irradiation (54)	12 months
Hu (2014)	Yes	Cross-sectional	Nasopharyngeal carcinoma	30	30	NR	Pre-RT NPC patients (20)	NR	NR
Leng (2017)	Yes	Cross-sectional	Nasopharyngeal carcinoma	46	46	NR	Pre-RT NPC patients (24)	IMRT (66–74)	NR (range from 1 week to 4 years)
Lv (2014)	Yes	Cross-sectional	Nasopharyngeal carcinoma	30	30	27	Pre-RT NPC patients (15)	2D-CRT or IMRT (58–76)	7.6 months
Nieman (2015)[*]	No	Cross-sectional	Various tumours	28	19	17	Healthy controls (32), surgical controls (9)	Cranial-spinal radiation (total 23.40–36.00)	1.51 and 1.70 years
Petr (2018)	Yes	Longitudinal	Glioblastoma	41	41	41	Proton-RT treated (16)	3DCRT or IMRT (50–60)	6 months
Porto (2008)	No	Cross-sectional	All	20	10	10	Healthy controls (21)	Preventative cranial irradiation (12–24)	14.5 years
Prust (2015)	Yes	Longitudinal	Glioblastoma	14	14	14	–	Partial brain irradiation (60)	6 months
Reddick (1998)	No	Cross-sectional	Medulloblastoma	15	15	NR[***]	LGG treated with surgery only (15)	Whole brain and focal irradiation (55–65)	5.1 years
Riggs (2014)	No	Cross-sectional	Medulloblastoma (19), astrocytoma (1)	20	20	20	Healthy controls (13)	Cranial-spinal irradiation (23.4–41.4, boost 54.0–59.4)	5.1 years
Simó (2016)	Yes	Both	SCLC	22	22	22	Healthy controls (21), Non-SCLC (13)	Prophylactic cranial irradiation (25)	3 months
Zeller (2013)	No	Cross-sectional	All	130[**]	18	18	Healthy controls (130)	Prophylactic cranial irradiation (20)	22.5 years

ALL = acute lymphocytic leukaemia, CRT = conventional radiation therapy, IMRT = intensity-modulated radiation therapy, LGG = low grade glioma, NPC = nasopharyngeal carcinoma, NR = not reported, RT = radiation therapy, SCLC = small cell lung cancer.
[*] Same study as Nieman (2015) in Table 2.
[**] Same study population as Tamnes (2013) in Table 2.
[***] Group composed of both surgery + RT and surgery + RT + chemo group, ratio not specified.

Table 4
Assessment of bias and relevancy.

Paper	Case selection					Study design				Analysis		
	Case and control selection	Random or consecutive sample	Non-participants	Case description	A priori brain regions	Discrete RT patient group	Changes in cortex regions	Relation to dose	Complete brain analysed	Imaging and processing	Analysis described	Analysis quality
Correa (2013)	–	–	–	✓	–	–	✓	–	✓	✓	✓	–
Edelmann (2014)	–	✓	✓	✓	–	✓	–	–	✓	–	✓	–
Follin (2016)	✓	✓	✓	✓	–	✓	–	–	✓	✓	✓	–
Gommlich (2018)	✓	–	✓	–	–	✓	–	–	✓	–	✓	–
Hu (2014)	–	–	–	–	–	✓	✓	–	✓	✓	✓	–
Karunamuni (2016)	✓	✓	✓	✓	–	✓	–	✓	✓	✓	✓	–
Kundu (2017)	✓	✓	✓	✓	–	✓	✓	–	–	–	✓	–
Leng (2017)	–	–	–	–	–	✓	–	–	✓	✓	✓	–
Lin (2017)	–	–	–	✓	✓	✓	✓	–	✓	✓	✓	–
Liu (2007)	✓	–	–	✓	–	✓	✓	–	✓	✓	✓	–
Lv (2014)	–	–	–	–	–	✓	✓	✓	✓	✓	✓	–
Nieman (2015)	–	–	–	✓	–	✓	–	–	✓	✓	✓	–
Petr (2018)	✓	–	✓	✓	–	✓	–	✓	✓	✓	✓	–
Porto (2008)	–	–	–	✓	–	✓	✓	–	✓	✓	✓	–
Prust (2015)	–	–	–	✓	–	✓	–	–	✓	✓	✓	–
Reddick (1998)	–	–	–	–	–	✓	–	–	–	–	✓	–
Riggs (2014)	–	–	–	✓	–	✓	–	–	✓	✓	✓	–
Seibert (2017)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	–
Simó (2016)	✓	✓	–	✓	–	✓	✓	–	✓	✓	✓	–
Tamnes (2015)	✓	✓	✓	✓	–	–	✓	–	✓	✓	✓	–
Zeller (2013)	✓	✓	✓	✓	–	–	–	–	✓	✓	✓	–

nal changes within patients, four cross-sectional studies compared RT patients with non-RT controls (either matched healthy controls or patients who received other cancer treatments), and one study combined a longitudinal and a cross-sectional design.

Longitudinal studies

Two studies scored highest in our assessment tool and both investigated dose-dependent cortical thinning in a longitudinal design by comparing pre-RT MR images with those made one year after treatment.

Karunamuni et al. retrospectively studied 15 high grade glioma patients who underwent fractionated partial brain RT and chemotherapy [38]. They concluded that total cortical thickness decreased more with increasing doses of administered RT. With every additional Gy the cortex showed thinning of 1.3 μm, up to a total dose of 34.6 Gy. Above this dose, thinning increased to 7.2 μm/Gy. They further analysed the cortical thickness per lobe, and found that the parietal, limbic and temporal lobes were most susceptible to cortical thinning after RT, the latter being the most vulnerable.

Seibert et al. conducted a similar study, but used a pre-specified ROI analysis [39]. They selected 54 patients treated with RT for primary brain tumours, and looked at the effect of regional dose on cortical thickness. They focussed their attention on cortical regions associated with higher cognitive functions: the inferior parietal cortex and the entorhinal cortex (see Fig. 2). These two ROIs were compared with two regions representing the primary cortex: the pericalcarine cortex and the paracentral lobule. They found a significant correlation between radiation dose and the amount of thinning in their two regions of interest, whereas no such correlation was found in the two reference regions. When assessing whether cortical reduction appears in areas receiving either low (<20 Gy) or high (>40 Gy) mean dose, they found that the two ROIs combined showed significant loss of thickness of 0.19 mm (6%) after receiving the high dose. Again, this was not found in the primary cortex. Additionally, they used a linear mixed-effects model to test the effect of regional radiation dose to cortical thinning for each of the 34 cortical regions of the Desikan–Killiany brain atlas. This showed radiation vulnerability in 9 brain regions, with cortical thinning ranging from 1.8 μm to 6.5 μm per Gy.

Two other studies exploring longitudinal change in cortical thickness were performed by Correa et al. and Kundu et al. [40,41]. They both had a paediatric study population, with hematopoietic stem cell transplantation recipients and medulloblastoma patients respectively. Kundu et al. found an increase in temporal cortical thickness 1 year after RT. They compared this to juvenile pilocytic astrocytoma patients who received only surgical treatment, who showed cortical thinning normal for their age. Correa et al. saw a significant cortical thinning in the left and right middle frontal gyrus in their subjects. However, they used a study population that was largely comprised of patients who received only chemotherapy, with only some receiving chemoradiation. There was not enough statistical power to analyse the effect of RT alone. Analysing the chemotherapy group revealed decrease in the left middle frontal gyrus, but no significant changes in the right middle frontal gyrus.

Cross-sectional studies

Of the cross-sectional studies, the one by Lin et al. measured post-RT cortical thickness in adult patients [42]. They divided a cohort of nasopharyngeal carcinoma patients into three: pre-RT, 1–6 months post-RT (named ED: early delayed) and 7–18 months

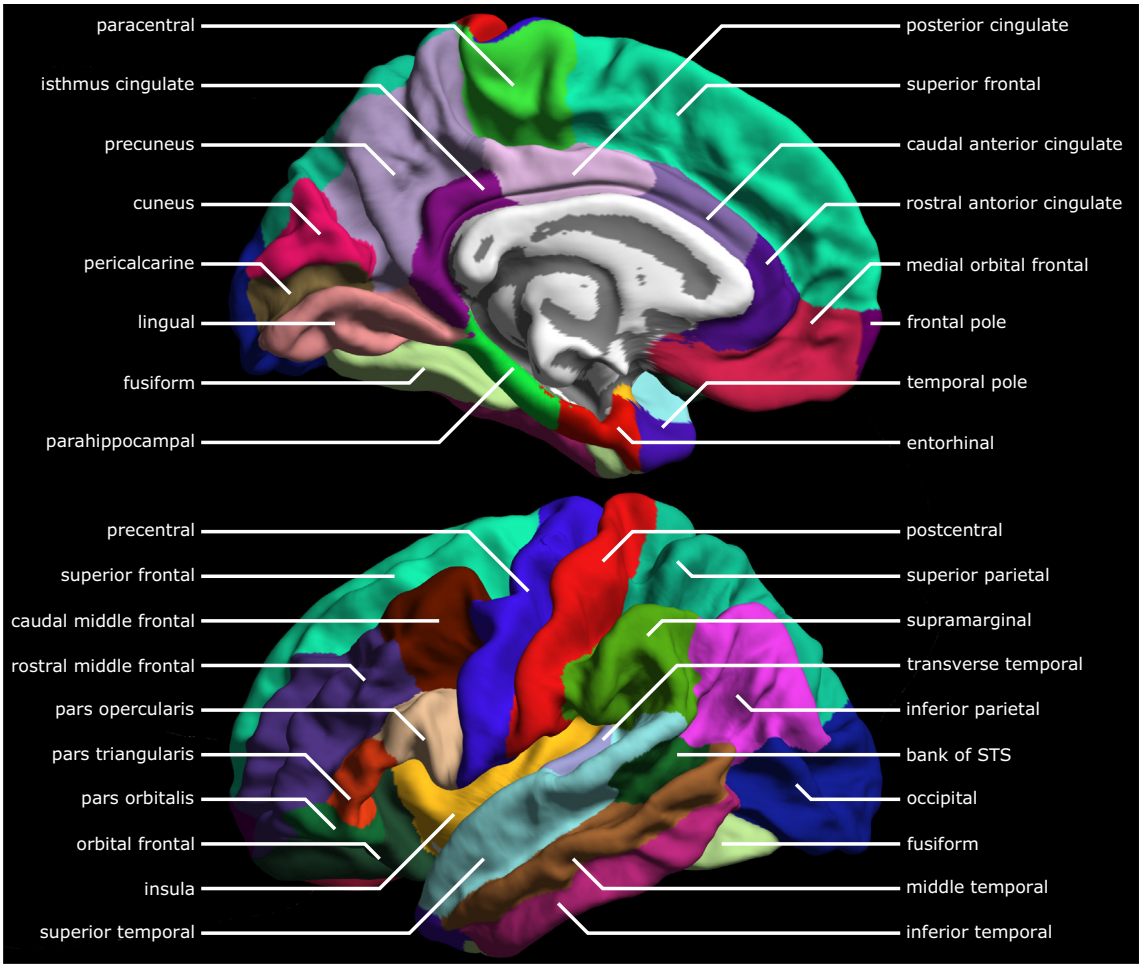

Fig. 2. Cortical regions from the Desikan–Killiany [81] atlas presented on the central surface of the template mesh-brain via the Computational Anatomy Toolbox (CAT12) [17,82].

post-RT (LD: late delayed). They compared cortical thickness between these groups in both vertex-wise and ROI-wise analyses. The latter was done by dividing the brain into 148 ROIs according to the Destrieux brain atlas. Comparing the pre-RT group to the post-RT-ED groups revealed one vertex cluster of thinner cortex located in the left precentral gyrus of the treated patients. However, when comparing the cortical thickness of the pre-RT to the post-RT-LD, they found a thicker cortex in the latter group in 5 vertex clusters and 22 ROIs, spread across all cerebral lobes and both hemispheres. The cortex in these ROIs showed a relative thickness difference between 4.4% and 12.8%. The dose and location of radiation were not taken into account in these analyses, so it is not certain whether or not the areas showing cortical differences were subjected to irradiation. Although age and gender were included as covariates in the ROI-wise analysis, pre-existing cortical differences between the two patient groups can be the explanation for some or all found differences. Additionally, patients were treated with different radiation techniques (2D-CRT or IMRT), adding to the inhomogeneity of the study population.

The three remaining cross-sectional studies all described a paediatric population who received both RT and chemotherapy. Two studies by Tamnes et al. and Liu et al. compared survivors of childhood malignancies to healthy controls, and found 1 and 5 brain regions with a significantly thinner cortex, respectively [43,44]. However, the former study only had 18 patients treated with RT in their 130-patient study population, and the latter included 9 patients only, all treated with both RT and chemotherapy. Nieman et al. found a thicker cortex in the frontal, occipital and temporal lobes in their >7 year-old group [45]. Finally, Correa et al. performed cross-sectional analysis in addition to their longitudinal one, but found no significant differences [40].

Cortical volume

Of the papers on cortical volume changes after radiotherapy, three had a longitudinal design, ten were cross-sectional, and one did both.

Longitudinal studies

The best level of evidence, according to our assessment tool, was found in the paper by Simó et al. They studied the changes in grey matter volume in 22 small cell lung cancer (SCLC) patients receiving prophylactic cranial irradiation [46]. They found a significant volume reduction in the bilateral insular cortex, right parahippocampal gyrus and superior and temporal middle gyrus three months post-radiation. These longitudinal changes were not found in either healthy controls or non-small cell lung cancer (NSCLC) patients who did not undergo radiation therapy. This difference is unlikely to be caused by systemic therapy, as both SCLC and NSCLC groups received comparable chemotherapy regimens. Additionally, they performed neuropsychological tests on these three groups, and found that the SCLC patients performed worse in several domains, including verbal fluency and processing speed.

No attempts were made to correlate these cognitive deficits to radiation dose or cortical volume reduction. In a previous study by the same research group, similar grey matter (GM) changes were observed 1 month after starting platinum-based chemotherapy, before cranial irradiation was started [47]. As the SCLC patients who received cranial irradiation also underwent this chemotherapy regimen, the authors suggest the GM change is most likely the result of chemotherapy. However, as stated above, no longitudinal changes were observed in the NSCLC patients, who underwent chemotherapy only. Furthermore, group by time analysis of cortical volumes between the two groups found significant differences in GM volume change in several brain areas.

In a study by Petr et al., the effects of radiotherapy on brain matter volumes of the healthy hemisphere were compared between patients receiving photon and proton therapy for glioblastoma [48]. In the photon group, which included 41 patients, a loss of total GM volume was seen after 3 and 6 months. Furthermore, they found that GM volume loss increased with mean radiation dose, with areas receiving >10 Gy showing more volume loss when compared to those receiving <10 Gy (−2.4% and −1.6%, respectively). Further stratification of dose revealed highest volume loss in the regions that received 30–60 Gy, namely −3.1%. In multivariate linear regression mean received dose had a significant effect on GM volume of 0.9%/10 Gy. Prust et al. also found a loss of GM volume after chemoradiation for glioblastoma [49]. This study only included 8 patients who were eligible for image analysis, and data at last follow-up (35 weeks) was available for only 3 participants. Also note that these last two studies measured GM volume as a whole, which not only includes cerebral cortex, but also the thalamus and basal ganglia.

The final longitudinal study, by Gommlich et al., found no significant change in 14 glioblastoma patients who received radiation therapy [50].

Cross-sectional studies

Of the cross-sectional studies, three had an adult study population, all treated with radiation therapy for nasopharyngeal carcinoma (NPC). Lv et al. found a smaller cortical volume in several areas in the temporal and frontal lobes in treated NPC patients compared to pre-treatment patients [51]. They also found a negative correlation between the mean dose to the temporal lobes and cortical volume of select areas therein. Similarly, Leng et al. found numerous areas of smaller volume in all follow-up groups (<6 months, 6–12 months and >12 months after RT) [52]. Hu et al. found a smaller volume of the right paracentral lobule in patients treated in the last 6 months compared to pre-treatment controls [53]. However, in their delayed reaction group (7–24 months) they observed a bigger volume of this area compared to the early treatment group.

Edelmann et al. found a smaller GM volume of the parietal and temporal lobes in acute lymphoblastic leukaemia (ALL) survivors who received cranial RT in childhood compared to those who underwent chemotherapy only [54]. Follin et al. and Zeller et al. both found smaller total GM volume and total cortical volume, respectively, in ALL patients compared to healthy controls. [55,56] However, when correcting for total intracranial volume, Follin et al.'s result lost significance. Zeller et al. used the same study population as Tamnes et al. which, as mentioned above, only had a small fraction of RT patients in their patient group. When analysing the effect of treatment variables on GM volume, they found no significant correlation. They also subjected the participants to neuropsychological testing, and found a correlation between cortical GM volume and processing speed as well as executive function. This correlation lost its significance when corrected for multiple comparisons.

Finally, Nieman et al., Porto et al., Reddick et al. and Riggs et al. found no significant differences in their RT population compared to controls [45,57–59].

Discussion

In this systematic review we set out to find all available evidence regarding the effects of radiation therapy on cortical thickness and volume. From 1915 manuscripts we included 21 studies, of which 7 studied cortical thickness, 13 studied cortical or grey matter volume after RT, and 1 studied both.

Fifteen papers seemed to show at least some degree of cortical change, with Karunamuni et al. and Seibert et al. providing the most reliable evidence as scored by our checklist (Tables 1 and 4). They correlated longitudinal cortical change to radiation dose, and found that cortical thickness decreases with every additional Gy delivered to healthy brain tissue in select brain regions. Furthermore, Karunamuni et al. found a threshold of 34.6 Gy above which cortical thinning increases. Similarly, Petr et al. found an increase in GM volume loss with higher total doses of RT. These findings are in line with cortical atrophy and other gross morphological changes seen in the cortex in older imaging studies [13–16] and studies of pre-natal radiation exposure in animals [32–34].

The exact biological process that leads to this visible loss of cortical thickness and volume remains unknown. There is evidence that, as part of a complex inflammatory reaction, phagocytosis of healthy and damaged neurons occurs after radiation through activated microglia [60]. This atrophy of neural cells is likely to be a contributor to the diminished cortex, along with the loss of glial cells [61]. Another histopathological change often seen in the cortex after radiation therapy is vascular damage [1,62], a potential consequence of which is demyelination of the cortex. Demyelination is a known effect of vascular damage in WM [1,2], and although myelin is most abundant in WM, the cortex also contains myelinated axons [11]. Loss of myelination in the cortex could lead to a decrease in cortical volume, and thereby also affect thickness. Demyelination, as well as glial atrophy, has already been observed in radiation damage in mice and rats [63]. Several of our selected papers examined additional outcomes that reflect these structural changes, like those by Petr et al., who looked at grey matter perfusion and Edelman et al., who performed diffusion tensor imaging (DTI).

In contrast, Lin et al. found select regions of a thicker cortex in their late delayed (7–18 months post-RT) patient group compared to the pre-RT group. This difference could simply be explained due to pre-existent differences between the two patient groups, but an effect of RT is also possible. The authors suggest that the thicker cortex post-RT could be caused by astrogliosis, which is a known long-term effect of brain irradiation [60].

Another hypothesis for changes in cortical morphology we would like to pose, and which we have not seen discussed before, has to do with the border between GM and WM. As radiation leads to demyelination and myelin is the main component of WM, we hypothesise that the boundary between white and grey matter could become less defined. As the WM contains more myelin than GM, loss of demyelination could affect the WM more than the cortex, which might cause the perceived GM/WM border to shift towards the white matter. The method of cortical thickness estimation starts with segmentation into WM and GM, so when the border shifts, results of cortical measurement change accordingly. As the changes are mostly measured on sub-millimetre level, even the smallest shifts in the GM/WM border can lead to significant changes in perceived morphology. Supportive of this hypothesis is the fact that demyelinated WM appears hypointense on T1

weighted MRI [64], which is the same imaging sequence that is used for cortical morphology measurements.

Even the papers that scored highest in our assessment tool did not meet all our criteria for a methodologically sound paper. In fact, none of the found papers used the statistical methods which would meet the requirements of modern neuroimaging standards: multiple comparison correction, nonparametric statistical inference and controlling for possible confounding factors. For instance, analysing the change in cortical thickness on a voxel-wise or vertex-wise basis means that for each patient more than 100,000 data points are used for analysis. For each of these data points a statistical test is performed, and using the usual 0.05 threshold for *p*-values results in 5% of the 100,000 tests giving a false positive result, even if the null hypothesis is really true. The resulting 5000 false positive voxels are large enough to interpret as a meaningful finding, while they are actually a mere consequence of the testing setup. In other words, when not correcting for these multiple comparisons, this may lead to a false significance of the observed effect of radiation on the cerebral cortex. Examples of multiple comparison corrections are the false discovery rate (FDR) [65] or the control of the voxel-level family-wise error rate (FWE) [66]. Other studies used the Desikan–Killiany or Destrieux brain atlases, which are comprised of 34 and 74 brain areas respectively. This vast difference in data quantity means the power of the study can increase based on the method used, while keeping the same number of patients. This problem can be overcome with adequate statistical methods, but these have been largely unused in the studies we found. And even when the significance of an observed change is legitimate, it remains unclear which effect size has any meaningful consequences. A change of several micrometres may be significant, but its effect on cognitive symptoms may be negligible. So the question remains how clinically relevant these results are.

Aside from these statistical objections, the way cases were selected and reported was also found lacking in fifteen papers according to our assessment tool. Using a non-consecutive or non-random patient sample is accompanied by the risk of selection bias. This might be a particularly important factor in papers that use a retrospective cohort and are unclear in their method of patient selection.

The biggest limitation to this systematic review is the great inhomogeneity between the selected papers, in both study design and quality. No two papers had similar study designs, patient population and follow-up time. Other major differences are sample size (ranging from 9 to 130), RT type and dose, and type of controls in the cross-sectional studies. These differences make comparing papers difficult, and an attempt at meta-analysis unjustifiable.

There are several additional methodological issues with the selected studies. Eight papers discussed cortical changes after treatment during childhood, with follow-up times varying between 3 months and 34 years. During normal brain maturation and development, changes are seen in the thickness of the cerebral cortex. Whether the cortex decreases from birth or undergoes a period of thickening before it reduces is still an on-going debate, in which no consensus had been reached [67]. Either way, the effect of this normal biological process cannot be easily separated from the effect of radiation therapy, which also means the results of these studies cannot be reliably interpreted, and certainly cannot be extrapolated to an adult population.

More than half of the included studies did not measure differences in cerebral cortex between pre- and post-RT scans of the same patients, but instead applied a cross-sectional design. They compared the cortical thickness or volume of RT patients with either healthy controls or non-RT patients. Most of these controls were age- and gender matched, eliminating the influence these two factors have on the cerebral cortex [25,68]. However, other factors such as handedness, genetics, pregnancy and even socio-economic status have also been related to differences in the cerebral cortex [69–72]. The precise biological processes underlying these differences are not known, but the effect of sex and pregnancy suggests a hormonal component [72]. As these factors are usually not taken into account when using matched controls, pre-existent differences between patients may explain some or all of the results found in the cross-sectional papers. In a study measuring the cortical thickness in 30 healthy patients, a mean standard deviation of 0.54 mm was found [9]. This means that, with an average thickness of 2.7 mm, the cortex can be expected to differ by more than 20% in around one third of cases. The interpersonal difference in cortical thickness is even greater in the association areas, namely the prefrontal and temporal cortices [9].

Another important factor in these studies is the administration of chemotherapy. This treatment has also been linked to changes in the cerebral cortex [73,74]. As mentioned before, not all papers incorporated this confounding factor in their analyses, which may influence the reliability of their results. Furthermore, some studies had a "treated" and an "untreated" group, whereby only a fraction of patients in the treated group received RT, and most received only chemotherapy. This means that no conclusion about the effect of radiation therapy can be drawn.

Finally, also publication bias by 'file drawer effect' might play a role in studies on the effect of RT [75]. As it is not customary to publish a research protocol, or to otherwise make it known this effect is being studied, we do not know how many studies have not been reported due to inconclusive or negative results. It is possible more research groups did similar tests, but found no difference before and after RT, and therefore did not publish their findings. We urge future researchers performing a high-quality study and finding a negative result to still publish their findings, because absence of a relation between RT and cortical damage is also valuable knowledge to have. We are unable to create a funnel plot to test for publication bias, for the same reasons a meta-analysis could not be performed.

All these limitations, especially the great inhomogeneity and consequential unjustifiability of meta-analysis, mean that we cannot reliably claim that RT does indeed affect the thickness or volume of the cerebral cortex based on evidence that is currently available. Similarly, we are unable to point to cortical regions that are especially susceptible to radiation damage.

Suggestions for future research are clear: there is a need for larger studies, with sound methodology. Ideally, studies should also try to correlate radiation dose, longitudinal cortical change and cognitive deficits within the same patient group. The recommendation of this review is to test this association, which may lead to the identification of cortical areas especially vulnerable to radiation-induced cognitive decline. If such areas do indeed exist, we may avoid them during radiation therapy, the same way we now are able to do for the hippocampus [76]. Identification of these areas at risk is especially useful for newer, more precise radiation therapy techniques like the MR-Linac, which combines a 1.5 T MRI scanner with a linear accelerator [77]. With this combination, it becomes possible to correct for patient movements, and to adapt treatment planning to morphological changes in the patient's brain. There are already several studies that have evaluated the techniques and feasibility of cortical sparing, which show a significant dose reduction in the cortex, while maintaining adequate target coverage [78–80]. Should a clear indication arise that radiotherapy delivered to certain cortical regions causes cognitive decline, a decision needs to be made whether to favour sparing of the hippocampus, or sparing of the cerebral cortex. A controlled trial comparing the effect of cortical sparing versus hippocampal sparing on cognitive outcome may provide an answer to this question.

Conclusion

Thinning of the cerebral cortex is associated with cognitive decline. Thickness and volume of the cerebral cortex can be easily measured from T1 MRIs that are acquired as part of the normal clinical routine. There seems to be a relation between radiation therapy and changes in cortical thickness and volume. Furthermore, higher doses may lead to more thinning and sharper cognitive decline. However, despite the amount of studies found, the present studies are too inhomogeneous and lacking in quality to safely make this conclusion or make suggestions for changes in clinical practice. Therefore, we recommend that multiple larger, longitudinal studies need to be performed that address the methodological problems stated in this review, in order to identify vulnerable cortical areas. If such areas do indeed exist, we may avoid them during radiation therapy, the same way we now are able to do for the hippocampus. Newest radiotherapy planning software and linear accelerator hardware would enable precise sparing of these cortical structures. With this, we can treat brain tumours optimally while preserving quality of life of our patients after radiotherapy.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.02.013.

References

[1] Makale MT, McDonald CR, Hattangadi-Gluth JA, Kesari S. Mechanisms of radiotherapy-associated cognitive disability in patients with brain tumours. Nat Rev Neurol 2017;13:52–64. https://doi.org/10.1038/nrneurol.2016.185.
[2] Greene-Schloesser D, Robbins ME. Radiation-induced cognitive impairment-from bench to bedside. Neuro Oncol 2012;14:iv37–44. https://doi.org/10.1093/neuonc/nos196.
[3] Lee YW, Cho HJ, Lee WH, Sonntag WE. Whole brain radiation-induced cognitive impairment: pathophysiological mechanisms and therapeutic targets. Biomol Ther (Seoul) 2012;20:357–70. https://doi.org/10.4062/biomolther.2012.20.4.357.
[4] Yin C, Li S, Zhao W, Feng J. Brain imaging of mild cognitive impairment and Alzheimer's disease. Neural Regen Res 2013;8:435–44. https://doi.org/10.3969/j.issn.1673-5374.2013.05.007.
[5] Pääkkö E, Harila-Saari A, Vanionpää L, Himanen S, Pyhtinen J, Lanning M. White matter changes on MRI during treatment in children with acute lymphoblastic leukemia: correlation with neuropsychological findings. Med Pediatr Oncol 2000;35:456–61. https://doi.org/10.1002/1096-911X(20001101)35:5<456::AID-MPO3>3.0.CO;2-1.
[6] Fujii O, Tsujino K, Soejima T, Yoden E, Ichimiya Y, Sugimura K. White matter changes on magnetic resonance imaging following whole-brain radiotherapy for brain metastases. Radiat Med 2006;24:345–50. https://doi.org/10.1007/s11604-006-0039-9.
[7] Gondi V, Hermann BP, Mehta MP, Tome WA. Hippocampal dosimetry predicts neurocognitive function impairment after fractionated stereotactic radiotherapy for benign or low-grade adult brain tumors. Int J Radiat Oncol Biol Phys 2013;83:e487–93. https://doi.org/10.1016/j.ijrobp.2011.10.021.
[8] Gondi V, Tomé WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. Radiother Oncol 2010;97:370–6. https://doi.org/10.1016/j.radonc.2010.09.013.
[9] Fischl B, Dale AM. Measuring the thickness of the human cerebral cortex from magnetic resonance images. Proc Natl Acad Sci USA 2000;97:11050–5. https://doi.org/10.1073/pnas.200033797.
[10] Kandel ER, Schwartz JH, editors. Principles of neural science. New York: McGraw-Hill; 2013.
[11] Mancall EL, Brock DG, editors. Gray's clinical neuroanatomy. Philadelphia: Elsevier Saunders; 2010.
[12] Bosma I, Douw L, Bartolomei F, Heimans JJ, van Dijk BW, Postma TJ, et al. Synchronized brain activity and neurocognitive function in patients with low-grade glioma: a magnetoencephalography study. Neuro Oncol 2008;10:734–44. https://doi.org/10.1215/15228517-2008-034.
[13] Valk PE, Dillon WP. Radiation injury of the brain. AJNR Am J Neuroradiol 1991;12:45–62.
[14] Postma TJ, Klein M, Verstappen CCP, Bromberg JEC, Swennen M, Langendijk JA, et al. Radiotherapy-induced cerebral abnormalities in patients with low-grade glioma. Neurology 2002;59:121–3.
[15] Rabin BM, Meyer JR, Berlin JW, Marymount MH, Palka PS, Russell EJ, et al. Radiation-induced changes in the central nervous system and head and neck. Radiographics 1996;16:1055–72. https://doi.org/10.1148/radiographics.16.5.8888390.
[16] Harder H, Holtel H, Bromberg JEC, Poortmans P, Haaxma-Reiche H, Kluin-Nelemans HC, et al. Cognitive status and quality of life after treatment for primary CNS lymphoma. Neurology 2004;62:544–7.
[17] Dahnke R, Yotter RA, Gaser C. Cortical thickness and central surface estimation. Neuroimage 2013;65:336–48. https://doi.org/10.1016/j.neuroimage.2012.09.050.
[18] Kriegeskorte N, Goebel R. An efficient algorithm for topologically correct segmentation of the cortical sheet in anatomical MR volumes. Neuroimage 2001;14:329–46. https://doi.org/10.1006/nimg.2001.0831.
[19] Ashburner J, Friston KJ. Voxel-based morphometry—the methods. Neuroimage 2000;11:805–21. https://doi.org/10.1006/nimg.2000.0582.
[20] Ashburner J, Friston KJ. Unified segmentation. Neuroimage 2005;26:839–51. https://doi.org/10.1016/j.neuroimage.2005.02.018.
[21] Van Essen DC, Drury HA, Dickson J, Harwell J, Hanlon D, Anderson CH. An integrated software suite for surface-based analyses of cerebral cortex. J Am Med Inform Assoc 2001;8:443–59.
[22] June SK, Singh V, Jun KL, Lerch J, Ad-Dab'bagh, Y,, MacDonald, D,, et al. Automated 3-D extraction and evaluation of the inner and outer cortical surfaces using a Laplacian map and partial volume effect classification. Neuroimage 2005;27:210–21. https://doi.org/10.1016/j.neuroimage.2005.03.036.
[23] MacDonald D, Kabani N, Avis D, Evans AC. Automated 3-D extraction of inner and outer surfaces of cerebral cortex from MRI. Neuroimage 2000;12:340–56. https://doi.org/10.1006/nimg.1999.0534.
[24] Dahnke R, Gaser C. Surface and shape analysis, 2018, p. 51–73. doi: 10.1007/978-1-4939-7647-8_4.
[25] Salat DH. Thinning of the cerebral cortex in aging. Cereb Cortex 2004;14:721–30. https://doi.org/10.1093/cercor/bhh032.
[26] Du A-T, Schuff N, Kramer JH, Rosen HJ, Gorno-Tempini ML, Rankin K, et al. Different regional patterns of cortical thinning in Alzheimer's disease and frontotemporal dementia. Brain 2007;130:1159–66. https://doi.org/10.1093/brain/awm016.
[27] Pereira JB, Ibarretxe-Bilbao N, Marti M-J, Compta Y, Junqué C, Bargallo N, et al. Assessment of cortical degeneration in patients with Parkinson's disease by voxel-based morphometry, cortical folding, and cortical thickness. Hum Brain Mapp 2012;33:2521–34. https://doi.org/10.1002/hbm.21378.
[28] Lim HK, Jung WS, Ahn KJ, Won WY, Hahn C, Lee SY, et al. Regional cortical thickness and subcortical volume changes are associated with cognitive impairments in the drug-naive patients with late-onset depression. Neuropsychopharmacology 2012;37:838–49. https://doi.org/10.1038/npp.2011.264.
[29] Peterson BS, Warner V, Bansal R, Zhu H, Hao X, Liu J, et al. Cortical thinning in persons at increased familial risk for major depression. Proc Natl Acad Sci USA 2009;106:6273–8. https://doi.org/10.1073/pnas.0805311106.
[30] Seo SW, Im K, Lee J-M, Kim Y-H, Kim ST, Kim SY, et al. Cortical thickness in single- versus multiple-domain amnestic mild cognitive impairment. Neuroimage 2007;36:289–97. https://doi.org/10.1016/j.neuroimage.2007.02.042.
[31] Garcia-Diaz AI, Segura B, Baggio HC, Uribe C, Campabadal A, Abos A, et al. Cortical thinning correlates of changes in visuospatial and visuoperceptual performance in Parkinson's disease: a 4-year follow-up. Parkinsonism Relat Disord 2018;46:62–8. https://doi.org/10.1016/j.parkreldis.2017.11.003.
[32] Gazdzinski LM, Cormier K, Lu FG, Lerch JP, Wong CS, Nieman BJ, et al. Radiation-induced alterations in mouse brain development characterized by magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2012;84:e631–8. https://doi.org/10.1016/j.ijrobp.2012.06.053.
[33] Selemon LD, Ceritoglu C, Ratnanather JT, Wang L, Harms MP, Aldridge K, et al. Distinct abnormalities of the primate prefrontal cortex caused by ionizing radiation in early or midgestation. J Comp Neurol 2013;521:1040–53. https://doi.org/10.1002/cne.23217.
[34] Aldridge K, Wang L, Harms MP, Moffitt AJ, Cole KK, Csernansky JG, et al. A longitudinal analysis of regional brain volumes in macaques exposed to X-irradiation in early gestation. PLoS One 2012;7:. https://doi.org/10.1371/journal.pone.0043109e43109.
[35] Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, et al. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage 2010;53:1135–46. https://doi.org/10.1016/j.neuroimage.2009.12.028.
[36] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:. https://doi.org/10.1371/journal.pmed.1000097e1000097.

[37] Knoll T, Omar MI, Maclennan S, Hernández V, Canfield S, Yuan Y, et al. Key steps in conducting systematic reviews for underpinning clinical practice guidelines: methodology of the european association of urology. Eur Urol 2018;73:290–300. https://doi.org/10.1016/j.eururo.2017.08.016.
[38] Karunamuni R, Bartsch H, White NS, Moiseenko V, Carmona R, Marshall DC, et al. Dose-dependent cortical thinning after partial brain irradiation in high-grade glioma. Int J Radiat Oncol Biol Phys 2016;94:297–304. https://doi.org/10.1016/j.ijrobp.2015.10.026.
[39] Seibert TM, Karunamuni R, Kaifi S, Burkeen J, Connor M, Krishnan AP, et al. Cerebral cortex regions selectively vulnerable to radiation dose-dependent atrophy. Int J Radiat Oncol Biol Phys 2017;97:910–8. https://doi.org/10.1016/j.ijrobp.2017.01.005.
[40] Correa DD, Root JC, Baser R, Moore D, Peck KK, Lis E, et al. A prospective evaluation of changes in brain structure and cognitive functions in adult stem cell transplant recipients. Brain Imaging Behav 2013;7:478–90. https://doi.org/10.1007/s11682-013-9221-8.
[41] Kundu P, Li MD, Durkee BY, Hiniker SM, Bush K, von Eyben R, et al. Chemoradiation impairs normal developmental cortical thinning in medulloblastoma. J Neurooncol 2017;133:429–34. https://doi.org/10.1007/s11060-017-2453-5.
[42] Lin J, Lv X, Niu M, Liu L, Chen J, Xie F, et al. Radiation-induced abnormal cortical thickness in patients with nasopharyngeal carcinoma after radiotherapy. NeuroImage Clin 2017;14:610–21. https://doi.org/10.1016/j.nicl.2017.02.025.
[43] Tamnes CK, Zeller B, Amlien IK, Kanellopoulos A, Andersson S, Due-Tønnessen P, et al. Cortical surface area and thickness in adult survivors of pediatric acute lymphoblastic leukemia. Pediatr Blood Cancer 2015;62:1027–34. https://doi.org/10.1002/pbc.25386.
[44] Liu AK, Marcus KJ, Fischl B, Grant PE, Poussaint TY, Rivkin MJ, et al. Changes in cerebral cortex of children treated for medulloblastoma. Int J Radiat Oncol Biol Phys 2007;68:992–8. https://doi.org/10.1016/j.ijrobp.2007.01.034.
[45] Nieman BJ, Elizabeth De Guzman A, Gazdzinski LM, Lerch JP, Mallar Chakravarty M, Pipitone J, et al. White and gray matter abnormalities after cranial radiation in children and mice. Int J Radiat Oncol Biol Phys 2015;93:882–91. https://doi.org/10.1016/j.ijrobp.2015.07.2293.
[46] Simo M, Vaquero L, Ripolles P, Gurtubay-Antolin A, Jove J, Navarro A, et al. Longitudinal brain changes associated with prophylactic cranial irradiation in lung cancer. J Thorac Oncol 2016;11:475–86. https://doi.org/10.1016/j.jtho.2015.12.110.
[47] Simó M, Root JC, Vaquero L, Ripollés P, Jové J, Ahles T, et al. Cognitive and brain structural changes in a lung cancer population. J Thorac Oncol 2015;10:38–45. https://doi.org/10.1097/JTO.0000000000000345.
[48] Petr J, Platzek I, Hofheinz F, Mutsaerts HJMM, Asllani I, van Osch MJP, et al. Photon vs. proton radiochemotherapy: effects on brain tissue volume and perfusion. Radiother Oncol 2018;128:121–7. https://doi.org/10.1016/j.radonc.2017.11.033.
[49] Prust MJ, Jafari-Khouzani K, Kalpathy-Cramer J, Polaskova P, Batchelor TT, Gerstner ER, et al. Standard chemoradiation for glioblastoma results in progressive brain volume loss. Neurology 2015;85:683–91. https://doi.org/10.1212/WNL.0000000000001861.
[50] Gommlich A, Raschke F, Wahl H, Troost EGC. Retrospective assessment of MRI-based volumetric changes of normal tissues in glioma patients following radio (chemo)therapy. Clin Transl Radiat Oncol 2018;8:17–21. https://doi.org/10.1016/j.ctro.2017.11.008.
[51] Lv X-F, Zheng X-L, Zhang W-D, Liu L-Z, Zhang Y-M, Chen M-Y, et al. Radiation-induced changes in normal-appearing gray matter in patients with nasopharyngeal carcinoma: a magnetic resonance imaging voxel-based morphometry study. Neuroradiology 2014;56:423–30. https://doi.org/10.1007/s00234-014-1338-y.
[52] Leng X, Fang P, Lin H, An J, Tan X, Zhang C, et al. Structural MRI research in patients with nasopharyngeal carcinoma following radiotherapy: a DTI and VBM study. Oncol Lett 2017;14:6091–6. https://doi.org/10.3892/ol.2017.6968.
[53] Hu F, Li T, Wang Z, Zhang S, Wang X, Zhou H, et al. Use of 3D-ASL and VBM to analyze abnormal changes in brain perfusion and gray areas in nasopharyngeal carcinoma patients undergoing radiotherapy. Biomed Res 2017;28:7879–85.
[54] Edelmann MN, Krull KR, Liu W, Glass JO, Ji Q, Ogg RJ, et al. Diffusion tensor imaging and neurocognition in survivors of childhood acute lymphoblastic leukaemia. Brain 2014;137:2973–83. https://doi.org/10.1093/brain/awu230.
[55] Follin C, Erfurth EM, Johansson A, Lätt J, Sundgren PC, Österberg K, et al. Impaired brain metabolism and neurocognitive function in childhood leukemia survivors despite complete hormone supplementation in adulthood. Psychoneuroendocrinology 2016;73:157–65. https://doi.org/10.1016/j.psyneuen.2016.07.222.
[56] Zeller B, Tamnes CK, Kanellopoulos A, Amlien IK, Andersson S, Due-Tonnessen P, et al. Reduced neuroanatomic volumes in long-term survivors of childhood acute lymphoblastic leukemia. J Clin Oncol 2013;31:2078–85. https://doi.org/10.1200/JCO.2012.47.4031.
[57] Porto L, Preibisch C, Hattingen E, Bartels M, Lehrnbecher T, Dewitz R, et al. Voxel-based morphometry and diffusion-tensor MR imaging of the brain in long-term survivors of childhood leukemia. Eur Radiol 2008;18:2691–700. https://doi.org/10.1007/s00330-008-1038-2.
[58] Reddick WE, Mulhern RK, Elkin TD, Glass JO, Merchant TE, Langston JW, et al. A hybrid neural network analysis of subtle brain volume differences in children surviving brain tumors. Magn Reson Imaging 1998;16:413–21. https://doi.org/10.1016/S0730-725X(98)00014-9.
[59] Riggs L, Bouffet E, Laughlin S, Laperriere N, Liu F, Skocic J, et al. Changes to memory structures in children treated for posterior fossa tumors. J Int Neuropsychol Soc 2014;20:168–80. https://doi.org/10.1017/S135561771300129X.
[60] Lumniczky K, Szatmári T, Sáfrány G. Ionizing radiation-induced immune and inflammatory reactions in the brain. Front Immunol 2017;8:517. https://doi.org/10.3389/fimmu.2017.00517.
[61] Fike JR, Cann CE, Turowski K, Higgins RJ, Chan ASL, Phillips TL, et al. Radiation dose response of normal brain. Int J Radiat Oncol 1988;14:63–70. https://doi.org/10.1016/0360-3016(88)90052-1.
[62] Wong CS, Van der Kogel AJ. Mechanisms of radiation injury to the central nervous system: implications for neuroprotection. Mol Interv 2004;4:273–84. https://doi.org/10.1124/mi.4.5.7.
[63] Yang L, Yang J, Li G, Li Y, Wu R, Cheng J, et al. Pathophysiological responses in rat and mouse models of radiation-induced brain injury. Mol Neurobiol 2017;54:1022–32. https://doi.org/10.1007/s12035-015-9628-x.
[64] Tillema J-M, Pirko I. Neuroradiological evaluation of demyelinating disease. Ther Adv Neurol Disord 2013;6:249–68. https://doi.org/10.1177/1756285613478870.
[65] Benjamini Y, Hochberg Y. Controlling the false discovery rate – a practical and powerful approach to multiple testing. vol. 57. 1995. doi: 10.2307/2346101.
[66] Nichols T, Hayasaka S. Controlling the familywise error rate in functional neuroimaging: a comparative review. Stat Methods Med Res 2003;12:419–46. https://doi.org/10.1191/0962280203sm341ra.
[67] Walhovd KB, Fjell AM, Giedd J, Dale AM, Brown TT. Through thick and thin: a need to reconcile contradictory results on trajectories in human cortical development. Cereb Cortex 2016;bhv301. https://doi.org/10.1093/cercor/bhv301.
[68] Good CD, Johnsrude I, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. Neuroimage 2001;14:685–700. https://doi.org/10.1006/nimg.2001.0857.
[69] Hamilton LS, Narr KL, Luders E, Szeszko PR, Thompson PM, Bilder RM, et al. Asymmetries of cortical thickness: effects of handedness, sex, and schizophrenia. NeuroReport 2007;18:1427–31. https://doi.org/10.1097/WNR.0b013e3282e9a5a2.
[70] Fjell AM, Grydeland H, Krogsrud SK, Amlien I, Rohani DA, Ferschmann L, et al. Development and aging of cortical thickness correspond to genetic organization patterns. Proc Natl Acad Sci USA 2015;112:15462–7. https://doi.org/10.1073/pnas.1508831112.
[71] Piccolo LR, Merz EC, He X, Sowell ER, Noble KG. Pediatric imaging, neurocognition GS. Age-related differences in cortical thickness vary by socioeconomic status. PLoS One 2016;11:. https://doi.org/10.1371/journal.pone.0162511e0162511.
[72] Hoekzema E, Barba-Müller E, Pozzobon C, Picado M, Lucco F, García-García D, et al. Pregnancy leads to long-lasting changes in human brain structure. Nat Neurosci 2017;20:287–96. https://doi.org/10.1038/nn.4458.
[73] McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ. Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. Breast Cancer Res Treat 2010;123:819–28. https://doi.org/10.1007/s10549-010-1088-4.
[74] Stouten-Kemperman MM, de Ruiter MB, Koppelmans V, Boogerd W, Reneman L, Schagen SB. Neurotoxicity in breast cancer survivors ≥10 years post-treatment is dependent on treatment type. Brain Imaging Behav 2015;9:275–84. https://doi.org/10.1007/s11682-014-9305-0.
[75] Rosenthal R. The file drawer problem and tolerance for null results. Psychol Bull 1979;86:638–41. https://doi.org/10.1037/0033-2909.86.3.638.
[76] Gondi V, Tolakanahalli R, Mehta MP, Tewatia D, Rowley H, Kuo JS, et al. Hippocampal-sparing whole-brain radiotherapy: a "how-to" technique using helical tomotherapy and linear accelerator-based intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2010;78:1244–52. https://doi.org/10.1016/j.ijrobp.2010.01.039.
[77] Lagendijk JJW, Raaymakers BW, Raaijmakers AJE, Overweg J, Brown KJ, Kerkhof EM, et al. MRI/linac integration. Radiother Oncol 2008;86:25–9. https://doi.org/10.1016/j.radonc.2007.10.034.
[78] Exeli A-K, Kellner D, Exeli L, Steininger P, Wolf F, Sedlmayer F, et al. Cerebral cortex dose sparing for glioblastoma patients: IMRT versus robust treatment planning. Radiat Oncol 2018;13:20. https://doi.org/10.1186/s13014-018-0953-x.
[79] Karunamuni RA, Moore KL, Seibert TM, Li N, White NS, Bartsch H, et al. Radiation sparing of cerebral cortex in brain tumor patients using quantitative neuroimaging. Radiother Oncol 2016;118:29–34. https://doi.org/10.1016/j.radonc.2016.01.003.
[80] Murzin VL, Woods K, Moiseenko V, Karunamuni R, Tringale KR, Seibert TM, et al. 4pi plan optimization for cortical-sparing brain radiotherapy. Radiother Oncol 2018;127:128–35. https://doi.org/10.1016/j.radonc.2018.02.011.
[81] Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, et al. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 2006;31:968–80. https://doi.org/10.1016/J.NEUROIMAGE.2006.01.021.
[82] Gaser C, Dahnke R. CAT – a computational anatomy toolbox for the analysis of structural MRI data. HBM Conf 2012 2012;32:7743.