



## Cognitive effects of low dose of ionizing radiation – Lessons learned and research gaps from epidemiological and biological studies

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### ABSTRACT

The last decades have seen increased concern about the possible effects of low to moderate doses of ionizing radiation (IR) exposure on cognitive function.

An interdisciplinary group of experts (biologists, epidemiologists, dosimetrists and clinicians) in this field gathered together in the framework of the European MELODI workshop on non-cancer effects of IR to summarise the state of knowledge on the topic and elaborate research recommendations for future studies in this area.

Overall, there is evidence of cognitive effects from low IR doses both from biology and epidemiology, though a better characterization of effects and understanding of mechanisms is needed.

There is a need to better describe the specific cognitive function or diseases that may be affected by radiation exposure. Such cognitive deficit characterization should consider the human life span, as effects might differ with age at exposure and at outcome assessment.

Measurements of biomarkers, including imaging, will likely help our understanding on the mechanism of cognitive-related radiation induced deficit. The identification of loci of individual genetic susceptibility and the study of gene expression may help identify individuals at higher risk.

The mechanisms behind the radiation induced cognitive effects are not clear and are likely to involve several biological pathways and different cell types.

**Abbreviations:** ADHD, attention deficit and hyperactivity disorder; AHS, Adult Health Study; BPRS-18, Brief Psychiatric Rating Scale; CASI, Cognitive Abilities Screening Instrument; CBVD, cerebrovascular disease; CT, Computer Tomography; FACT-Cog, Functional Assessment of Cancer Therapy - Cognitive function issues; GHQ-28, General Health Questionnaire; ICRP, International Commission for Radiological Protection; IR, Ionizing Radiation; MELODI, Multidisciplinary European Low Dose Initiative; MMSE, Mini-mental State Examination; MRI, Magnetic Resonance Imaging; NCQ, Neurocognitive Questionnaire; RAVLT, Rey Auditory Verbal Learning Test; RP, Radiation Protection; SD, Standard Deviation; SGZ, SubGranular zone; SRA, Strategic Research Agenda; SR, Systematic Review; SVZ, Sub-Ventricular Zone.

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Well conducted research in large epidemiological cohorts and experimental studies in appropriate animal models are needed to improve the understanding of radiation-induced cognitive effects. Results may then be translated into recommendations for clinical radiation oncology and imaging decision making processes.

## 1. Introduction

Cognition is a set of functions which ensure the ability to think, learn, reason, image and remember (Forns et al., 2012). These functions develop during the *in-utero* period and continue maturing until young adulthood (Cognitive Development) (Casey et al., 2005), while at older ages they start to decline (Cognitive Decline) (Raz et al., 2005). Specific clinical diseases of the neurodevelopment (i.e. Attention Deficit Hyperactivity Disorders, ADHD) and of aging (Parkinson, Alzheimer, dementia) may also be associated with cognitive dysfunction, as cognitive impairment may present as a symptom of these diseases or as a consequence of medication or of social isolation and associated depression. Cognition is a major determinant of an individual's quality of life, independence, and social functioning. Better knowledge of factors that affect cognition throughout life, particularly in the most vulnerable periods of human life (fetal life, childhood, adolescence, and old age) is therefore of major public health importance.

It is well known that environmental (including IR) and genetic factors may play a role in, and determine the trajectory of, both cognitive development (Júlvez et al., 2016) and decline (Gunnarsson and Bodin, 2019; Tanner et al., 2014). Specific neurodevelopmental disorders (including ADHD) and disorders of aging (such as Alzheimer's disease and dementia spectrum disorders) are known to be influenced by environmental and/or genetic factors (Aghaei et al., 2019; McKenzie et al., 2017; Power et al., 2016). Additionally, health and psychological status, including psychiatric disorders such as schizophrenia and depression, and use of specific medication can also influence cognitive function (Cheung et al., 2017; Park and Kwon, 2008; Vuotto et al., 2017).

IR at moderate to high doses (of the order of hundreds and thousands of mGy) is a well-known risk factor for cancer, and results of recent studies support the existence of an excess cancer risk even at low doses of radiation (below 100 Gy, for comparison, an average person in the world receives about 2–3 mGy per year, i.e. of the order of 100 mGy over a lifetime) (Hauptmann et al., 2020). There has been considerable interest in the potential non-cancer effects of low (<0.1 Gy) to moderate (0.1–0.5 Gy) doses of IR in the Radiation Protection (RP) community in recent decades, and, in particular on cognitive and neurodevelopmental effects, since the publication of the results of the Swedish Haemangioma study, in which low IR doses were associated with a decline in cognitive function (Hall et al., 2004). Research in this area is still scarce, however, though it is well known that high doses of IR can induce a cognitive deficit (Armstrong et al., 2010; Chen et al., 2015). Current RP recommendations, in the International Commission for Radiological Protection (ICRP) 118 report, are based on a deterministic threshold for cognitive effects of 1–2 Gy in adults and 0.1–0.2 Gy in children (ICRP, 2012).

In Europe, the Multidisciplinary European Low dose Initiative (MELODI) platform, was set-up in 2010 to coordinate, promote and implement European research on the risks associated with low dose exposure to IR. An integral part of its activities is to review the state of the art and developing and periodically update a Strategic Research Agenda (SRA), as well as a list of short-medium term priorities (MELODI, 2019). These have been an important basis for setting research priorities for European Commission and national RP research funding programs in Europe. An important priority set-out in the current MELODI SRA is research, both epidemiological and mechanistic, on the effects of low to moderate doses of IR on cognition (Bouffler et al., 2019). Indeed, assessing whether low and moderate doses of IR have an effect on cognition is important in terms of both public health and RP as these are the levels of doses received by the vast majority of people from

environment, occupational and medical sources (other than radiotherapy).

The current paper is part of a special issue arising from the international workshop organized by MELODI on non-cancer effects of low doses of IR (Sitges, Spain, 10–12 April 2019). It aims to summarize the state of the art to identify research gaps in our current understanding of cognitive effects at low to moderate doses of IR and sets-out recommendations for future research. This represents the combined work of epidemiologists, biologists, clinicians, and dosimetrists with expertise in this area.

## 2. Materials and methods

The workshop, information about which was broadly disseminated in Europe and around the world in the RP research community, brought together experts in clinical, epidemiological and biological/mechanistic research on the effects of IR on cognition to review the current literature and discuss limitations and research gaps. Speakers (EP, FB, KO, DB, MAB, AN) were invited, based on their recent work and specific expertise on the topic, to present current knowledge on the effects of low doses on cognitive function from the clinical, epidemiological and biological.

These findings were discussed in the workshop, and a working group, including the speakers and participants with relevant expertise (SP, FdV, LR, ITC) and the chairpersons of the session (MAB and EC) met on the last day of the meeting to discuss the evidence, with particular focus on the results presented the day before, the research gaps and to set-out recommendations for future research. The current paper does not intend to provide a systematic and comprehensive summary of the literature available, instead it aims to summarize the results of the workshop, updated with results of research published since then.

## 3. Results

### 3.1. Effects of low to moderate doses of IR on cognitive development and decline – current state of knowledge

#### 3.1.1. Clinical perspective on cognitive effects in patients

Clinicians constantly weigh benefits and risks when considering any treatment, intervention, or diagnostic test. The negative effects of IR on cognition have been known for some time (Ron et al., 1982), with effects associated with exposure to high doses of radiation from radiotherapy (of the order of several Gy to 10 s of Gy). In the mid-2000s, the paper by Hall and collaborators raised the possibility that even low doses of IR could affect cognitive function raising concern among radiologists, pediatricians and RP professionals (Hall et al., 2004). This led in particular to optimization of Computed Tomography (CT) doses in children (Lee et al., 2016) and to the increased use of Magnetic Resonance Imaging (MRI) as an alternative diagnostic modality. Concerns also exist about MRI, however, due to potential cognitive risks from anesthesia, especially in case of repeated procedures (Rappaport et al., 2015; Wilder et al., 2009), free gadolinium deposition in children (Stanescu et al., 2020).

Newer CT techniques, CT Angiography and CT Head Perfusion, have added a growing urgency to quantify the risk of IR, since these new modalities deliver higher radiation doses than conventional diagnostic procedures and based on the reports of radiation induced damage from these examinations (Imanishi et al., 2005; Wintermark and Lev, 2010). Some patients might receive high cumulative doses through the use of repeated CT, CT Angiography and CT Perfusions. Indeed, it has been



recently estimated that in 35 high income countries (total population 1.2 billion), 2.5 million patients (i.e. about 2 subjects per 1000 receive a cumulate dose over 0.1 Gy over a 5 year period (Rehani and Hauptmann, 2020). Though there are increasing efforts to reduce radiation dose from diagnostic examinations (Gottumukkala et al., 2019), additional research on radiation health effects, including non-cancer effects, is needed to better inform optimization and clinical decision.

### 3.1.2. The state of the art in epidemiology

**3.1.2.1. Cognitive effects after the Chernobyl accident.** Studies of Ukrainian *clean-up workers* (average dose around 100 mGy), demonstrated an increased incidence of cognitive dysfunctions, though the nature of effects and the possible association with radiation dose, especially at low doses, remain unclear (Loganovsky et al., 2008; Bazyka et al., 2018).

A study to evaluate possible effects of low-dose IR on human cognitive function in adulthood was conducted within the CEREBRAD project (CEREBRAD, 2015) among 326 Ukrainian clean-up workers, 290 of which had doses under 500 mSv (Bazyka et al., 2015). An age-matched group of 44 other workers, with doses lower than 20 mSv, was used as internal control. The study included neurocognitive function assessment (memory, attention, language, executive and visuo-spatial functions) and neurophysiologic investigation. Telomere length and expression of genes regulating telomere function were measured to study the role of radiation aging.

Results of the neurocognitive and psychological tests (General Health Questionnaire (GHQ-28), the Brief Psychiatric Rating Scale (BPRS-18), Rey Auditory Verbal Learning Test (RAVLT), Zung scores, and Mini-mental State Examination (MMSE)) indicate a higher prevalence of cognitive and psychological deficit in those workers with doses above 100 mSv, particularly among those with doses above 500 mGy.

Telomere length was reduced in clean-up workers over the age of 50 (6.1%), with the greatest reduction among those aged 70 years or more (11.7%). Telomere length was also statistically significantly reduced when comparing those with cognitive disorders (presence of a diagnosis of cerebrovascular diseases (CBVD) or MMSE score lower than 28) to the healthy subjects by all IR dose category. The degree of cognitive deficit (MMSE scale) was negatively correlated with telomere length and age, however not statistically significant. Regarding expression of genes regulating telomere length, high *TERF2* expression combined with low expression of *TERT* was found 25–30 years after exposure. Statistically significant correlation between gene expression levels and radiation doses were also reported. Workers with mild cognitive deficit (MMSE < 28) and/or a medical diagnosis of CBVD (ICD-10 I69.0–I69.8) showed up-regulation of *CDKN2A*, *CLSTN2*, *CSF2*, *IFNG*, *ILB*, *TERF1*, *TERT*, *VEGFA* genes. Overall, this study suggests that cognitive deficit in humans, 25–30 years post-irradiation, might be influenced by dose, as well as by age at exposure and gene regulation of telomere function in the 100–500 mGy range (Bazyka et al., 2015, 2013).

To describe the functional brain changes associated with cognitive dysfunction, evoked bioelectrical brain activity was measured in clean-up workers (Kogan and Chesalin, 1989). In workers exposed to doses less than 1 Gy and not diagnosed with acute radiation syndrome, alterations of brain electrical activity, especially in the Wernicke area, were observed 10–15 years after exposure in the low dose range, with evidence of a threshold at 0.05 Gy and most prominent changes at doses over 0.3–0.5 Gy. Compared with the general population, higher rates of depression and alcohol abuse (24%) were registered in cleanup workers (Loganovsky et al., 2008). This was not associated with alterations of brain electrical activity, however; thus, these factors are unlikely to confound the association between radiation dose and alterations of brain electrical activity. These findings may support the hypothesis of cortico-limbic dysfunction related to hippocampal neurogenesis impairment as a mechanism of radiation induced cognitive dysfunction (Loganovsky and Kuts, 2017, 2016; Loganovsky et al., 2018).

Increased rates of CBVD were also seen 7–21 years after exposure in a cohort of 42,982 *evacuees from the Chernobyl zone*, with the highest rates between 12 and 21 years after exposure (Buzunov and Kapustynska, 2018). Though external doses and doses from long-lived radionuclides among these subjects are low, thyroid doses from <sup>131</sup>I are much higher. <sup>131</sup>I thyroid dose estimates were available for 957 subjects, who were divided into 4 dose groups (276 subjects with less than 0.3 Gy; 208 between 0.31 and 0.75 Gy; 325 with between 0.76 and 2.0 Gy; and 138 above 2). A statistically significant increase in occurrence of CBVD was associated with thyroid dose from <sup>131</sup>I in the range 0.31–0.75 Gy when compared with the lowest dose group. For other dose groups, no increase in CBVD occurrence was reported and no statistically significant trend was observed (Buzunov and Kapustynska 2018). More evidence is needed on the association between thyroid dose and the development of cognitive deficiency in radiation-exposed individuals.

**3.1.2.2. Cognitive decline among atomic bomb survivors.** Survivors of the atomic bombing (A-bomb) in Hiroshima and Nagasaki exposed *in utero*, especially between 8 and 15 weeks of gestation, with doses of several hundred mGy or higher experienced higher rates of intellectual disability (Otake and Schull, 1998). Investigations are underway, since the early 1990s, to assess if exposure to radiation after birth might also result in the development of cognitive dysfunction or dementia in adulthood or older age.

Between 1992 and 1998, a cross-sectional study was conducted on 3100 subjects selected from the Adult Health Study (AHS) in Hiroshima and Nagasaki, aged 13 years or older at the time of the bombings – 60 or older at the time of the study (Yamada et al., 2002). The association between radiation dose and dementia was studied among the Hiroshima survivors in a cross-sectional study (Yamada et al., 1999) and a longitudinal follow-up carried out from 1992 to 2011 (2300 subjects) (Yamada et al., 2016).

Cognitive function was measured quantitatively using a short form of the Cognitive Abilities Screening Instrument (CASI) screening test (Teng et al., 1994). CASI has a high sensitivity (almost 100%) and specificity (about 90%) to detect dementia (Larson et al., 1998; Yamada et al., 1999). Dementia, including Alzheimer disease, vascular dementia, and others, was based on diagnosis by a panel of neurologists (Yamada et al., 1999).

In the cross-sectional study, the CASI score, in both sexes, decreased with age, especially older ages, and increased with longer education. IR exposure had no effects on CASI scores after adjusting for sex, city, age, and education history (Yamada et al., 2002).

The prevalence of dementia was not associated with IR exposure, in the cross-sectional Hiroshima study (Yamada et al., 1999). In the longitudinal study, among 2044 dementia-free subjects at the initial survey (1992–1996), 195 subjects developed dementia, including 123 Alzheimer disease and 34 vascular dementia cases, by 2003. No association between radiation dose and dementia was observed (Yamada et al., 2009).

An additional analysis, among 1844 dementia-free survivors aged 13–33 years at the time of bombing in Hiroshima, shows that the CASI-short form score declined more steeply with age among those who developed dementia (N = 313), though this decline appeared not to be associated with radiation dose (Yamada et al., 2016). Overall, these studies suggest no effect of exposure after 13 years of age on cognitive decline.

A cognitive follow up of subjects involved in the AHS study aged 0–13 years at the bombing has also been conducted. Neurocognitive function was measured with a self-reported measurement, the NCQ, and an objective measurement, the CASI score. A baseline analysis of the data showed that older age and less education is associated with more subjective neurocognitive complaints (Yamada et al., 2019). Analyses of radiation risks are underway and were not yet available at the time of this review.

**3.1.2.3. Systematic review (SR) of the neurodevelopmental effect of IR exposure.** Epidemiological studies of neurodevelopmental effects following low to moderate IR doses received during fetal life, childhood and adolescence were systematically reviewed (Pasqual et al., 2020).

The SR identified 26 epidemiological studies, including large cohorts: the A-bomb survivors study (Otake and Schull, 1998), the Israeli tinea capitis cohort (Ron et al., 1982), the two Swedish hemangioma cohorts (Blomstrand et al., 2014; Hall et al., 2004). It also included studies of effects of IR received: a) in medical settings, both for radiotherapy and diagnosis (Krull et al., 2018; Nordenskjöld et al., 2015; Salonen et al., 2018; Zeltzer et al., 2008); b) from fallout from the Chernobyl nuclear power plant accident (Almond et al., 2009; Bar Joseph et al., 2004; Bazyka et al., 2015; Heiervang et al., 2010; Igumnov and Drozdovitch, 2000; Lie et al., 2017; Loganovskaja and Loganovsky, 1999; Nyagu et al., 1998; Taormina et al., 2008); and c) from other environmental contamination (Black et al., 2013).

The strength of the evidence for an association between IR exposure and each aspect of cognitive neurodevelopment (general cognition, memory, attention, executive function, language and visual-spatial abilities) was evaluated using qualitative synthesis methods (Popay et al., 2006; The Cochrane Collaboration, 2011).

The most informative studies were those of the A-bomb survivors, tinea capitis and haemangioma cohorts, studies with a large sample size and very low chance of bias or confounding. Little information could be obtained from other medical exposures studies or from studies of populations exposed to Chernobyl fall-out *in utero* or childhood as these studies generally had low statistical power, potential for confounding (e.g. maternal stress in subjects evacuated from contaminated territories), limited or no dose estimation, and low outcome specificity (i.e. use of school achievement as proxy of cognitive measure).

The SR concluded that current evidence for an effect of low to moderate doses on general cognition (IQ) and language abilities is *limited*, meaning that “A causal interpretation of the positive association observed in the body of evidence [...] is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence” (IARC, 2019). For the other cognition domains (memory, attention, executive function, visual-spatial abilities) the evidence was *inadequate* (IARC, 2019) due to the small sample size of studies on which findings were based. There was also inadequate epidemiological evidence for heterogeneity of effect between exposure *in utero*/early life as compared with exposure later in life, due to the scarcity of studies evaluating this question.

#### 3.1.2.4. Other ongoing epidemiological studies

**3.1.2.4.1. Ongoing studies of cognitive development.** Cohort studies of *Childhood Cancer Survivors* (Tikellis et al., 2018; Winther et al., 2015) can potentially provide important information about neurodevelopment following low to moderate doses of IR from radiotherapy outside the brain and head. Most existing cohorts include subjects that are still relatively young, a large proportion of whom undergo annual check-ups, an important opportunity for cognitive testing. It is well known that brain tumor survivors are at risk of cognitive deficit (Mulhern et al., 2004) and cranial radiotherapy is a recognized risk factor for such cognitive impairment (Armstrong et al., 2010; Krull et al., 2018; Robinson et al., 2010). Whether cognitive effect in CCS may also exist at lower doses, such as doses received from scatter radiation when the target organ for radiotherapy is far from the brain, is under debate. Recent report reported cognitive effects in Hodgkin lymphoma survivors having undergone mantle radiotherapy (Krull et al., 2018). However, these effects appear to be mediated by cardio-vascular damage (due to high doses to the heart and major vessels close to the radiotherapy field) rather than the lower doses of scatter radiation in different brain structures. A small-scale study, COGNITO, is currently ongoing in the two largest pediatric oncology units in Barcelona, Spain, using standardized computer evaluation of general cognition, memory, executive

function and attention domains used in other epidemiological studies in young people (Rivas et al., 2019). This study provides a model for a future European/international collaboration to study the cognitive effects of low to moderate doses from scatter radiation to the brain, showing that cognitive evaluation using a standardized computer battery can be integrated in the standard follow up of cancer patients. The possible impact of low to moderate doses on cognitive effect is a topic of increasing interest due to the emerging use of proton therapy. Studies on the cognitive effect of proton therapy are ongoing (Dutz et al., 2020; Kahalley et al., 2019).

The *French Haemangioma Cohort* (Dondon et al., 2004) includes individual treated for skin haemangioma before 1973, below the age of 15 years (the majority below 1 year of age). Doses received by the brain lobes, hypophysis and thyroid have been estimated (Shamsaldin et al., 2000), with dose to the brain being below 1 Gy on average. In the framework of CEREBRAD (CEREBRAD, 2015), neurocognitive tests were performed on 105 patients from this cohort. The following tests were used: i) General cognitive decline (MMSE, Montreal Cognitive Assessment); ii) Memory (RAVLT); iii) psychometric tests (Zung Self-rating Depression Scale, BPRS, Hospital Anxiety and Depression scale); iv) Self-reported cognitive fatigability (FACT-Cog); v) Quality of Life (Short Form 36). Analyses are underway to evaluate the relation between the score for each test and the dose received by different brain structures. The interpretation is challenging because of multiple testing issues in a relatively small sample size.

**3.1.2.4.2. Ongoing studies on cognitive decline.** Studies of the A-bomb survivors are continuing, as indicated above, as are studies of Chernobyl clean-up workers. A recent study, among Mayak workers suggests a possible dose-related increased risk of Parkinson’s disease (Azizova et al., 2019). A study of cognitive effects in the cohort of British nuclear testing veterans is also ongoing, to evaluate the effect of psychological stress related to knowledge of radiation exposure on cognitive decline (Collett et al., 2020b, 2020a).

The aging of the population in these large-scale epidemiological studies offers an important opportunity to study possible cognitive effects of low to moderate IR doses in old age.

#### 3.1.3. The state of the art in experimental studies

**3.1.3.1. Results from the CEREBRAD project.** The CEREBRAD project (CEREBRAD, 2015) provided extensive experimental data on radiation induced cognitive effects, as well as epidemiological data mentioned in 3.1.2.

In a set of experiments, mice were exposed pre- and post-natally to X-ray doses ranging between 0 and 1 Gy, with behaviour tested at 12 weeks of age (Verreet et al., 2015). Behavioural defects were observed at doses above 0.5 Gy for both prenatal and postnatal exposures and increased linearly with dose. Lower prenatal doses (0.1 Gy) resulted in subtle changes in prefrontal-cortex function and in social behaviour (Verreet et al., 2015)

In the same experiments, 3D T2-weighted MRI was used to measure the volumes of the whole brain and of specific brain structures in mice. A reduced head size (microcephaly) phenotype was seen at doses of 0.33 Gy and above (Verreet et al., 2016, 2015), consistent with the literature from animal experiments (Inouye et al., 1995; Jensh et al., 1995; Reyners et al., 1992), and in line with observation from the atomic bomb survivors study (Otake and Schull, 1998; Otake et al., 1991). No difference in relative volumes of particular brain structures could be observed for doses below 0.5 Gy (Verreet et al., 2015). Microcephaly is associated with a reduction in brain volume and often associated with intellectual and/or motor disabilities; it can be induced by any condition that affects brain growth, e.g. progenitor cell proliferation, cell differentiation, cell death (von der Hagen et al., 2014).

Additional experiments were conducted combining exposure to IR and environmental toxicants (paraquat, nicotine, PBDE...). Results



showed a shift in the threshold for behavioral effects to doses below 100 mGy (Buratovic et al., 2018, 2014). This may indicate that the threshold depends not only on radiation dose but also on other co-factors.

**3.1.3.2. Low dose radiation and the developing brain: Not only a question of dose.** The developmental stage of the brain at the time of irradiation (both in the prenatal and postnatal periods) plays an important role in determining radiation-related cognitive changes. Specific biological effects have been observed at different brain developmental stages in animal models, suggesting that the biological mechanism may differ depending on the timing of exposure.

Neural progenitors are highly radiation-sensitive, as they are highly sensitive to radiation-induced apoptosis at doses of the order of 10 mGy in the murine embryonic brain (Saha et al., 2014). Apoptosis is one of the main mechanisms of IR-induced neurodevelopmental dysfunction (Etienne et al., 2012; Nowak et al., 2006; Verreet et al., 2016) and of impairment of brain structures development (Hoshino et al., 1991; Hoshino and Kameyama, 1988; Nowak et al., 2006). Neural progenitors are characterized by specific DNA damage responses distinguishing them from other somatic cells (Mokrani et al., 2020; Roque et al., 2012). The deleterious effects of IR increase with the proportion of actively proliferating neural progenitors which are more prone to cell cycle arrest, apoptosis, or premature differentiation. This proportion varies across not only the neurodevelopmental stage but also across brain structures, thus the effect of radiation may also depend on the cerebral area exposed.

IR can also alter the function and fate of neural progenitors by inducing premature neurogenesis (Eom et al., 2016; Wagle and Song, 2020), thus reducing the pool of proliferating precursors (Krieger et al., 2019; Lancaster et al., 2013). For prenatal exposure, it has been observed that, in the irradiated (with X-ray/Gamma doses of 0.5–1.0 Gy at embryonic day 11 or 13) embryonic neocortex at 24 h after exposure, apoptosis is restricted to differentiated, non-proliferating cells, possibly contradicting the assumption that neural progenitors are the most radiosensitive. However, it cannot be excluded that the observed apoptosis in the differentiated cells may result from a previous damage in the progenitor cells (Nowak et al., 2006; Roque et al., 2012).

For perinatal exposure (postnatal day 10), defects in adult neurogenesis and axonogenesis are observed several months after exposure (Casciati et al., 2016; Kempf et al., 2014). Indeed, radiation can impair adult neurogenesis by inhibiting cell division and production of new neurons in these crucial regions, with long-term consequences on learning and memory (Casciati et al., 2016; Daynac et al., 2013; Kempf et al., 2014; Mizumatsu et al., 2003; Pineda et al., 2013). The mechanism of radiation induced cognitive effects also involves increased neuroinflammation and alteration of synaptic plasticity. Indeed, at the molecular level, the persistent effects on cognitive behavior from perinatal exposure of mice to doses as low as 0.5 Gy, was associated with alterations in Rac1-Cofilin pathway and increased neuroinflammation (Casciati et al., 2016; Kempf et al., 2014). During postnatal hippocampus development, some long-term alterations (increased apoptosis, alterations in neurogenesis, mitochondrial homeostasis, and expression of proteins involved in synaptic plasticity) have also been observed, at doses of 0.1 Gy (Casciati et al., 2016).

Regarding possible genetic susceptibility factors which may modify radiation induced cognitive deficit, genes involved in neurogenesis or in DNA damage response may be implicated (Etienne et al., 2012). There are large polymorphisms in DNA repair genes in humans that could influence individual DNA repair capacity (Cornetta et al., 2006; Mumbrékar et al., 2016; Travis et al., 2006). Transgenic mice with a low deficiency in DNA repair capacity are more prone to develop radiation-induced neurocognitive disorders than wild-type animals (Béry, personal communication). Such mouse models may help understand the pathogenesis of radiation-induced cognitive effects and the search of non-invasive biomarkers using, for example, anatomical and diffusion

MRI (CEREBRAD, 2015; Pérès et al., 2018; Mouton et al., under review).

**3.1.3.3. Elucidating the mechanisms of radiation induced cognitive impairments using animal models.** Animal models suggest that cognitive decline is a consequence of damages in multiple neural cell types due to alterations in the vasculature, in glial and neuronal cells function, a decreased hippocampal neurogenesis, and increased neuroinflammation (Hladik and Tapio, 2016). Indeed, the dynamic interaction between multiple cell types (i.e., neurons, microglia and astrocytes) is involved in the complexity of the pathogenesis of radiation-induced cognitive impairment (Casciati et al., 2016; Kempf et al., 2014).

Irradiation can cause apoptosis, necrosis, inflammation and impaired neuronal migration in mice. Apoptotic response may be influenced by the developmental stage at radiation exposure (see 3.1.3.2), and the irradiation parameters (dose-rate or energy of the beam) (Verreet et al., 2016). Apoptosis may be also the mechanism involved in the radiation-induced microcephaly in mice (Quintens et al., 2015; Yasuda et al., 2006) and in the reduction of cortical thickness hampering correct brain layering (Etienne et al., 2012). However, the underlying causes for radiation-induced microcephaly are not fully understood, as differences in experimental conditions (radiation dose, exposure time points, and definition of cellular layers) hamper comparison across existing animal model studies, although unpublished data from SCK-CEN indicates that apoptosis and premature differentiation are highly involved.

Radiation induced cognitive dysfunction in adults may also be related to the ageing process, such as senescence, which is known to be influenced by radiation (López-Otín et al., 2013; Murga et al., 2009; Suman et al., 2013). Indeed, experiments in mice models have shown that premature aging is related to accumulation of DNA damage during the embryonic period (Murga et al., 2009), suggesting that ageing is influenced, to some extent, by embryonic distress, such as caused by irradiation (Fernandez-Capetillo, 2010).

Adult brain irradiation also induces apoptosis of neural progenitors in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus in animal models, as well as neuroinflammation that persistently inhibits hippocampal neurogenesis (Monje et al., 2003; Yang et al., 2017). The later may be responsible for impairment in learning, memory, and spatial information processing (Gondi et al., 2010; Monje et al., 2003).

Cognitive impairment may be the result of multifactorial processes at the hippocampus level: indeed, both alteration of the neuronal cell population and of microenvironments (i.e. microglia hyperactivation) may play a role. It has been shown that both exposure to IR and traumatic brain injury are associated with dysregulation of the chemokine receptor-2 (CCR2), which is involved in microglia activation (Allen et al., 2013). Microglia depletion and CCR2 inhibition have been clearly shown in different studies to improve cognition and are considered as such a plausible strategy to prevent cognitive decline following radiation therapy (Acharya et al., 2016; Parihar et al., 2016). In addition, mice behavior can be significantly affected by radiation-induced persistent inhibition of neurogenesis in the subventricular zone (SVZ) of the anterior lateral ventricles (Feierstein et al., 2010; Lazarini et al., 2009; Tada et al., 1999). However, quiescent neural stem cells of SVZ are highly radiation-resistant and can restore neurogenesis thereafter (Daynac et al., 2013). Therefore, inhibition of neurogenesis in the SVZ, is due to radiation-induced changes in the microenvironment of the neurogenic niches, such as an increase of vascular-derived TGF- $\beta$ , that impairs the activation and/or proliferation of the neural stem cells (Morizur et al., 2018; Pineda et al., 2013).

Disruption of neural network formation and improper synaptic communication, due to disturbed dendritic organization following *in utero* irradiation, may be a crucial mechanism of IR induced cognitive dysfunction. Irradiation leads to alterations in dendritic morphology and mature neurons physiology. A dose-dependent reduction in dendritic complexity has been observed in hippocampal neurons in mice (Parihar and Limoli, 2013). These alterations affect neuronal connectivity, and

**Table 1**

Current state of knowledge concerning radiation-induced cognitive effects across the life course, by exposure time and dose range.

Exposure time	IR Dose range	Cognitive function over life		Cognitive decline > 70 years of age
		Neurodevelopment Prenatal – 30 years of age	Adult life 30–70 age	
Prenatal	Low to Moderate	Epidemiological and biological evidence suggesting prenatal IR dose, even in the low dose range, affects the normal neurodevelopment.	The extent to which prenatal IR exposure affects cognition later in life has not been adequately studied	
Infancy- Early childhood	Low to Moderate	Exposure during infancy may have an effect on neurodevelopment, however, of small magnitude.	There is little information to date on the extent to which IR exposure in infancy and early childhood affects cognition later in life	
	High	It is well known, especially from Childhood cancer survivors studies, that IR at high doses induces cognitive deficit during neurodevelopment	Reports from long term childhood cancer survivor's cohort studies are emerging, with the progressive aging of these cohorts. Studies in childhood cancer survivors suggest?? that exposure to high dose IR early in life may accelerate aging, including an accelerated decline of cognitive functions. However, this research is still in an early phase.	
Childhood/ adolescence	Low to Moderate	It is less known the effect of exposure on late childhood/ adolescence on neurodevelopment	The effect of exposure on adult and late life cognition is not well studied. The study of A-bomb survivors exposed during adolescence suggests no effect on cognitive decline at older ages.	
	High	It is well known, especially from Childhood cancer survivors studies, that IR at high doses induce cognitive deficit	Reports from long term childhood cancer survivor's cohort studies are emerging, with the progressive aging of these cohorts. Studies in childhood cancer survivors suggest that exposure to high dose IR happening early in life may accelerate aging, including an accelerated decline of cognitive functions. However, this research is still in an early phase.	
Adult life	Low to Moderate	Not applicable	The effect of exposure during adult life on cognitive function is unclear.	
	High	Not applicable	The study of Chernobyl clean-up workers suggests a decrease in cognitive function in the low to moderate dose range, while	

Low to moderate range is defined here as below 0.1–0.5 Gy; For high dose we meant much higher dose (cranial radiotherapy range)

post-irradiation impairment of long-term potential has been reported in mice (Wu et al., 2012).

Transcriptomic and proteomic analyses have shown modulation of genes and proteins six months after exposure to radiation, in mice (Kempf et al., 2015; Quintens et al., 2015) and indicate possible contribution of epigenetic events in the processing of the late cognitive effects, requiring thus future investigations.

For internal contamination, the transport mechanism of inhaled or ingested radioactive elements to the brain may play an important role in the mechanisms of radiation-induced cognitive effects. After inhalation of uranium particles, a direct transport of elemental uranium (particulate and solubilized) through the olfactory nerve bundles has been observed in rats (Ibanez et al., 2019). This entry route might be responsible for neurogenesis and neuroinflammation alterations. Chronic ingestion of uranium, via drinking water, during brain development has also been shown to alter cell proliferation and cell death, resulting in mice behavioral consequences in adulthood (Dinocourt et al., 2017).

### 3.2. Intersection of clinical, epidemiological and experimental perspectives

Table 1 summarizes and briefly defines the current state of knowledge about radiation induced cognitive effects over life, by specific exposure period and dose-range.

Table 2 shows a map of current knowledge concerning IR-induced

cognitive effects, by a series of key questions explored so far. For each of the questions, we briefly provide the current epidemiological (E) and biological (B) knowledge, taking into account the amount and quality of the available data (legend of Table 2). We also specify how such knowledge has been translated into clinical practice (C). The meaning of the colors and shapes is explained in the legend of Table 2.

## 4. Discussion

Overall, there is evidence of cognitive effects from low IR doses both from biology and epidemiology, though a better characterization of effects in term of outcome definition, exposure time vulnerability, and mechanism and susceptibility factors is needed.

### 4.1. Research gaps

#### 4.1.1. Clinical perspective

Exposure in the medical setting deserves particular attention and results should inform clinicians in addressing decisions, both in diagnostic and therapeutic procedures. Medical IR exposure in children and adults is different, thus, specific age-related risk assessment is needed to generate precise clinical recommendations. There is a need to better characterize the effect on the postnatal developing brain. Indeed, the development of the brain continues until young adulthood, and cognitive effects of exposure to radiation may vary during the course of life (infancy, early childhood, adolescence and young adulthood). Data on

**Table 2**  
Map of the current state of art across research disciplines. (See below-mentioned references for further information.)

Research question	Current knowledge in brief
<b>Outcome characterization</b>	
Is there a specific cognitive function affected by IR at low (below 100 mGy) to moderate (100- 500 mGy) IR dose?	<ul style="list-style-type: none"> <li>●B No clear conclusion concerning specific cognitive function.</li> <li>●E <u>Neurodevelopment</u>: there is limited evidence for an effect on general cognition and language: the evidence for other domains is inadequate. <u>Cognitive decline</u>: There is a limited number of studies addressing cognitive decline in the elderly.</li> <li>▲C Identifying the functions most at risk would help design specific follow-up guidelines for neuropsychological rehabilitation, if needed.</li> </ul>
Is there evidence of increased risk of a particular clinical cognitive disease?	<ul style="list-style-type: none"> <li>●B Rodent models of neurodegenerative diseases may be used to answer this specific question.</li> <li>●E Neurodevelopment: Few studies on spectrum of cognitive diseases or mental health disorders (Sadetzki et al., 2011). Cognitive decline: Evidence of increased risk of Parkinson disease in Mayak workers (Azizova et al., 2019); no evidence of dementia in A-bomb survivors; evidence of increased cerebrovascular pathology in Chernobyl clean-up workers; evidence of an association between residential radon exposure and Alzheimer disease based on an ecological study (Lehrer et al., 2017).</li> <li>▲C Cognitive diseases are clinically relevant and deserve particular attention.</li> </ul>
What is the magnitude of effects?	<ul style="list-style-type: none"> <li>●B There is evidence that the magnitude of effects depends on the time at exposure in relation to brain maturation, the effect being greater for prenatal irradiation.</li> <li>●E For functional neurodevelopmental outcomes, the changes are small (0.15-0.2 IQ points for 100 mGy (Blomstrand et al., 2014; Hall et al., 2004; Otake et al., 1991). However, there is still a need to understand the variation of this magnitude with dose and exposure time.</li> <li>▲C There is a need to evaluate the impact of the cognitive changes on social functioning and quality of life outcomes.</li> </ul>
Are there any non-invasive biomarkers of radiation-induced cognitive deficit?	<ul style="list-style-type: none"> <li>●B Some initial studies indicate some MRI features may be biomarkers of radiation-induced cognitive deficit.</li> <li>●E No low-dose epidemiology study has used MRI (just an old case report study on A-bomb survivors (Schull et al., 1991))</li> <li>▲C Studies planning the use of MRI in children should take into account the possible risk of cognitive effects due to anesthesia; thus, the use of MRI biomarkers of radiation-induced effect may be limited.</li> </ul>

**Table 2 (continued)**

<b>Characterization of vulnerable period of exposure</b>	
Is there any prenatal period in which the developing brain is more at risk of radiation induced cognitive effect, even at low dose?	●B The prenatal period is a vulnerable period of exposure, and current evidence suggests that vulnerability is high between 11 and 15 embryonic days in experimental animals.
	●E A-bomb survivors study suggest the most vulnerable <i>in utero</i> period to be 8-26 week gestation (Otake et al., 1991).
	▲C Protection of pregnant women and their children is already in place because of the teratogenic effects of radiation during the whole pregnancy period.
Does exposure during postnatal brain maturation (birth to young adulthood) affect neurodevelopment?	●B Rodent models of radiation-induced brain injury show that young age at irradiation is a risk factor for neurodevelopmental deficit. However, the effects of low dose radiation on proliferating neural progenitors in the postnatal brain (SVZ, SGZ, cerebellum) are still poorly documented.
	●E The SR shows limited to inadequate epidemiological evidence across the domains of neurodevelopment for postnatal exposure.
	▲C Clinical decision is well informed of the effects of high dose (cranial radiotherapy) but less for low to moderate dose procedure, in particular CT scanning, although radiation exposure should be kept as low as reasonably possible.
Does exposure during adolescence-young adulthood cause cognitive deficit in old age?	●B <i>In vivo</i> experiments are needed to determine whether adolescence-young adult low-dose exposure is a risk factor for age-related cognitive deficit.
	●E The A-bomb study on adolescent- adult exposure show no evidence of radiation-related cognitive deficit in persons over 60 (Yamada et al., 2016).
	▲C There is a need for long-term follow-up of young patients to better inform clinicians
Does occupational exposure cause cognitive deficit in old age?	●B Understanding of neurobiological mechanisms underlying aging-related and radiation-induced cognitive changes is limited. <i>In vivo</i> experiments may elucidate the interactions between aging-related and radiation-induced cognitive dysfunctions.
	●E There is evidence of an effect on brain function in both Chernobyl clean-up workers and Mayak workers. The study of Chernobyl clean-up workers study suggests cognitive deficit is dependent on dose, age at exposure and telomere length gene regulation.
<b>Dose-response characterization</b>	
Existence of threshold and of dose response	●B In animal models, overall, a threshold of around 0.3 Gy for behavioral changes has been detected.
	●E There is a need for improved dosimetry, but so far a threshold has not been identified.

(continued on next page)



Table 2 (continued)

	▲C	May be important from the clinical perspective, though radiation protection practice is currently based on non-threshold models to prevent cancer.
<b>Genetic susceptibility</b>		
Is there evidence of genetic susceptibility to radiation-induced cognitive changes?	●B	Genetic susceptibility may be linked to genes involved in neurogenesis or to DNA damage response.
	●E	No study available
	▲C	If so, knowledge of genetic susceptibility would help individual risk assessment and personalized medicine in clinical practice
<b>Understanding of the mechanism</b>		
Is there a particular brain cell type that is more sensitive to IR?	●B	Multiple cells types are involved, though radiation is more deleterious when neural progenitors proliferate actively. There is also a need for more research on the role of microglia and inflammatory response.
Is there any specific brain structure that is more sensitive to IR?	●B	Areas that seem most affected are the SGZ of the hippocampus (apoptosis, long-term inhibition of neurogenesis), and SVZ of the lateral ventricle (apoptosis, long-term inhibition of neurogenesis), and the prefrontal cortex.
	●E	In Chernobyl liquidators cognitive damage may be due to a cortico-limbic dysfunction related to deficit in hippocampal neurogenesis (Bazyka et al., 2015). In the haemangioma cohort study (Blomstrand et al., 2014) cognitive deficit appears to correlate more with dose to the hippocampus.
Is there any specific brain damage mechanism that might explain a radiation-induced cognitive deficit?	●B	Results from animal models indicate that radiation-related cognitive dysfunction might be caused by multiple different mechanisms.
	●E	There is evidence that radiation may cause vascular damage (Bazyka et al., 2018; El-Fayech et al., 2017).
	▲C	Understanding the mechanism is relevant to implementing neuroprotective treatments or adequate clinical follow-up.
Is there any other organ of interest that could be responsible of a consequent cognitive related deficit?	●B	No studies available.
	●E	There is evidence from Chernobyl clean-up workers that thyroid radiation exposure may be involved in subsequent radiation related cognitive dysfunction. Radiation dose to the circle of Willis was associated with CBVD risk in Childhood Cancer Survivors (El-Fayech et al., 2017)
●	GREEN: The question has been explored in a large amount of data from a large or a number of different well-conducted studies; interpretation across studies is possible and results across the studies are coherent	
●	YELLOW: The question has been explored in a number of different well-conducted studies, but an overall interpretation of those studies isn't yet possible because of discrepancy in methods or inconsistency in results	
●	RED: The question has been explored in a single well-conducted study and is an interesting point for future research	
●	Lack of studies	
<b>Legend</b> (Note: The color of "*" or "▲" must be interpreted as expert judgment.)		
▲	Knowledge is already applied in clinical decision practice	
▲	Answer to the question is likely to influence clinical practice	

medical exposure (the Swedish haemangioma cohorts) seem to indicate that exposure during infancy may influence cognitive function measured in early adulthood (Hall et al., 2004), while no effect on cognitive function, as measured in the elderly, was found in the A-bomb survivors study of subjects exposed during adolescence and early adulthood (Yamada et al., 2016). A better characterization of the risk at doses in the ranges of a single CT Head examination (30–50 mGy) and after repeated examinations would likely inform clinical practice. Risk characterization should follow the continuous progress in imaging and therapeutic techniques.

4.1.2. Epidemiological studies

From an epidemiological point of view, there is a need to: i) identify, describe and quantify the magnitude of radiation-induced impairment in the different cognitive function domains; ii) estimate the radiation-associated risk for specific cognitive diseases of neurodevelopment (including autism spectrum disorders, attention-deficit/hyperactivity, learning and intellectual disabilities) and cognitive decline (Parkinson, Dementia, Alzheimer). Epidemiological studies should frame appropriately the research questions within the life span of individuals, as cognitive function changes with aging. There is also a need to characterize the possible effect modification of age at exposure. Additionally, in the study of long-term effects, the role of brain plasticity in possible reversing some of these effects is also of interest. Thus, to better characterize cognitive radiation induced effect in epidemiological studies, priority should be given to prospective studies, in which repeated measurement is feasible.

4.1.3. Experimental studies

Experimental studies should better explore the age- and dose-dependent cognitive deficits at low to moderate IR doses. Priority should be given to the characterization of brain effects in children and adolescence and to age-related neurodegenerative diseases. Indeed, the possible link between prenatal radiation exposure and neuro-senescence has not yet been well described.

Research has shown that the underlying mechanisms acting at low doses (below 0.1 Gy) are not identical to those at high doses. Thus, further research should focus on understanding mechanisms at low to moderate doses. The contribution of "out-of-target" radiation exposure to the risk of brain-related detrimental effects and the effects of protracted low doses on brain development are also largely unknown. Additionally, the contribution of neuroinflammation in cognitive decline deserves more attention in children and adults.

Biology can contribute to identify biomarkers (imaging and biological) of susceptibility and of radiation-induced cognitive impairment. Genetic analysis may contribute to investigate possible susceptibility and elucidate genetic and epigenetic mechanisms of radiation-induced cognitive impairment. Nevertheless, access to human samples remain very limited for biologists, and it may not be possible to completely extrapolate results from controlled animal studies to humans. Future epidemiological studies should collect biological samples in living human subjects as well as tissue samples in post-mortem in autopsies, where relevant.

4.2. Methodological issues and recommendations

4.2.1. Recommendations for epidemiological studies

4.2.1.1. Outcome assessment in epidemiological studies. Cognitive development and decline are challenging to address in epidemiological studies, and different strategies may be implemented.

In the case of a functional neurodevelopmental outcome, lessons can be learned from a birth cohorts studies, which recommend the use of computerized tests to reduce inter-observer variability and facilitate collection of repeated measures of cognitive development (Forns et al.,



2012; Júlvez et al., 2016). Study protocols should ideally include measurement of a number of specific cognitive functions, in addition to a general measure of IQ, which, in a computerized test, can be measured using tests similar to the Raven's Progressive Matrices. In IR studies, priority should be given to processing speed, executive functions, attention and memory, as those are the areas that seem most affected in high dose studies (Krull et al., 2018; Ullrich and Embry, 2012).

Computerized tests need to be administered by trained personnel, thus they imply effort and cost to be implemented. They can be applied in large-scale epidemiological studies that have an active follow-up in place, for example among cancer survivors. Online applications are being developed for some tests (Feenstra et al., 2018) allowing self-administration and reducing costs, though study participants should be motivated and able to understand instructions autonomously.

Self-reported measures of cognitive function, such as the NCQ test used in the A-bomb survivors study (Yamada et al., 2019), can be considered, as they can inform on the subjective burden of the perceived cognitive impairment, which influences quality of life, and are thus of particular interest for clinicians.

Tests used in the screening of cognitive decline and dementia in the elderly, such as the MMSE and the MoCa (Montreal Cognition Assessment), are also of interest and they have been implemented in CEREBRAD project (CEREBRAD, 2015). These tests should be administered by trained personnel and are design as screening instruments; thus they do not give a precise measure of a specific cognitive function. They could be used, however, in epidemiological studies to identify subjects with a clinical form of dementia (mild or severe).

Where available, functional cognitive indicators in population-based registries would be useful for record linkage in large cohort studies.

Regarding *clinical outcomes*, in some countries, health registries may provide a useful basis for data collection, though the presence and quality of such registries should be checked. In addition, the continuous evolution of clinical criteria for some of the disorders of interest may challenge the identification and interpretation of results.

Measures of the social impact of cognitive deficit (such as socioeconomic variables, educational achievement, and quality of life) are needed to plan appropriate public health actions. Expertise from social scientists would be of major benefit to evaluate the impact of possible radiation induced subtle changes in cognitive function on education and social functioning and discuss possible interventions.

**4.2.1.2. Age at outcome assessment and age at exposure.** An important issue for the interpretation of results of epidemiological studies is the age at which the outcome is assessed. Indeed, cognitive function increases and matures during fetal, childhood and adolescent life and starts to decline in old age. In addition, there are age-specific diseases of neurodevelopment and of neurocognitive decline.

Current evidence, especially from experimental studies, suggests that age at exposure is also an important effect modifier.

Thus, epidemiological studies should formulate their questions, plan the study protocol and interpret the results carefully considering both the timing of exposure and of outcome measurement across the lifespan of the population.

**4.2.1.3. Populations of interest.** In epidemiology, cohort studies in which there is the potential for repeated assessments are the ideal model for the study of cognitive effects of low IR doses.

There is a need both for cohorts of persons exposed *in utero* and at young ages to assess impact of exposure on cognitive development, and for cohorts of adults with sufficiently long follow-up to assess impact on cognitive decline.

The cohort of the A-bomb survivors, aging cohorts of patients treated for benign diseases (tinea capitis, haemangioma) and cohorts of workers with sufficiently high doses – such as the Mayak worker cohort – can contribute substantially to the assessment of impact on cognitive

decline, if repeated assessments can be performed. In addition, assessment of specific neurodegenerative diseases may also be considered.

For cognitive development, cohorts of pediatric patients who undergo long-term follow-up, in particular childhood cancer survivors, are ideal populations for study.

Record linkage studies, such as the international studies of nuclear industry workers – including INWORKS (Hamra et al., 2015), and studies of patients who underwent CT in childhood or adolescence, for example EPI-CT (Bernier et al., 2018), are not suitable for the study of cognitive effects in the absence of valid population based registries of the outcomes of interest.

**4.2.1.4. Biological sample collection.** Collection of biological samples in epidemiological studies evaluating cognitive effects could help to advance the understanding of the mechanisms behind such effects and identify susceptible populations.

A first possible strategy to perform such analyses is to use stored biological materials. Some established cohorts may have collected and stored biological samples, which could eventually be analyzed together with cognitive tests results. Indeed, collection of biological samples from Chernobyl clean-up workers has been performed in several multinational studies, and in Ukraine the total number of blood and saliva samples for RNA/DNA analysis exceeds 1000 (Bazyka et al., 2017; Ojha et al., 2018). Thus, an inventory of stored materials is needed when designing study protocols.

In cohorts of patients undergoing active follow-up (such as cancer survivors), prospective collection of biological materials may also be feasible. The possibility of collecting imaging biomarkers (through structural and functional MRIs) is also of interest to study brain volumes, white and grey brain matter status, and other imaging anomalies, though there is potential for confounding as discussed above.

Multidisciplinary approaches, including collection of biological samples and imaging biomarkers together with comprehensive cognitive function assessment and precise dosimetry to different brain structures, is already being implemented in high dose radiation epidemiological studies (Durand et al., 2015).

**4.2.1.5. Doses and dosimetry.** Estimating effects in the low-dose range requires very large populations to detect cognitive effects, which are likely to be very small (e.g. variation of a few IQ points).

To ensure adequate statistical power, epidemiological studies should include subjects with a wide range of doses and with a sufficient proportion of subjects with doses in the range of 100 mGy or more. If categorical analysis is planned, choice of categorical cut points should span the breadth of the dose distribution.

Based on these considerations, general population-based studies, including case-control studies, are generally unlikely to be informative in this field, though case-control studies nested within cohorts of exposed persons may be useful if doses can be reconstructed precisely and accurately.

As different brain anatomical structures are responsible of the correct functioning of different domains of cognition, individual estimates of dose (and all associated uncertainties) should be derived for the brain as a whole and for the relevant brain anatomical structures. Alternative target organs, such as the thyroid and major vessels, should also be considered to elucidate possible alternative mechanisms of radiation induced cognitive decline.

**4.2.1.6. Confounders and co-exposures.** Epidemiological studies need to collect information on possible confounding factors, which depend on the context in which radiation exposure occurred.

For example, if exposure happens in the context of a major environmental disaster, stress should be taken into account as it is well known that stress may influence cognitive function, especially when exposure occurs during foetal life (maternal stress) (Graignic-Philippe

et al., 2014; Van den Bergh et al., 2017). Indeed, interpretation of studies on evacuees from areas contaminated by fall-out from the Chernobyl accident, are subject to bias due to confounding by factors such as stress, which is likely to be greater in evacuees than in residents of areas where they resettled.

In medical cohorts, presence of specific chronic diseases, which may lead to higher medical IR exposure, might also influence cognition (Armstrong, 2006; Crump et al., 2013; Taras and Potts-Datema, 2005). In the case of cancer survivors, several confounding variables should be considered. First, details of cancer treatment (including surgery and chemotherapy) should be collected. Indeed, it is known that some chemotherapeutic agents induce neurotoxicity (Hodgson et al., 2013; Myers et al., 2008), such as cisplatin, which can cross the blood-brain barrier. Additionally, cancer survivors are at increased risk of CBVDs (Morris et al., 2009; El-Fayech et al., 2017) and ototoxicity, which can cause cognitive impairment (Nielsen et al., 2016), and these may confound or act as mediators of radiation-induced cognitive deficit. Long-term medical consequences of therapy may influence school attendance and cancer survivors may suffer psychological consequences, which can potentially affect cognition (Willard et al., 2017).

The effect of co-exposure might be relevant for occupational cohorts in which also some lifestyle factors (smoking and alcohol) might play an important role. Potential neuroprotective factors, such as positive lifestyle factors, may also be identified.

The issue of co-exposure can also be elucidated in animal experiments, as done in CEREBRAD. Future co-exposure research needs to focus on combining more than two agents/stressors to reflect real life. This research should cover nutrition and dietary factors and their combined contribution with radiation.

Additionally, in the case of internal radiation contamination, analyses should take into account results of experimental studies to disentangle the radiological from the chemical toxicity effects of specific radionuclides (Gagnaire et al., 2011).

#### 4.2.2. Recommendations for experimental studies

**4.2.2.1. The importance of animal models in elucidating radiation induced cognitive deficit.** Appropriate animal models are critically required to decipher the complex pathogenic mechanisms of the IR-induced cognitive impairment (Dos Santos et al., 2018). Animal models may characterize the effect of low dose radiation (single versus protracted/fractionated doses) on neural stem, progenitor cells, and their micro-environment, in the short- and long-term and for different window of exposure. Indeed, they may help to: i) explore age- and dose-dependent neurogenesis impairment and cognitive deficits at low to moderate doses; ii) elucidate the interactions between aging-related and radiation-induced cognitive changes; iii) identify genetic susceptibility factors in radiation-induced cognitive dysfunction at low doses; iv) elucidate genetic and epigenetic mechanisms of radiation-induced neurogenesis impairment.

Assessing neurogenesis in humans is challenging. The main body of evidence comes from studies in human brains postmortem, using immunohistochemistry as cell proliferation markers. However, there are technical limitations in studying postmortem brain tissues and these require methodological standardization of the maximum premortem agonal period, the maximum time elapsed from death to tissue fixation, fixation times etc. (Nogueira et al., 2018). Animal models offer the opportunity to elucidate the pathophysiology of radiation-induced cognitive decline and its molecular mechanisms (Pazzaglia et al., 2020).

**4.2.2.2. Need for harmonization of study protocols in animal experiments.** Behavioral tests are considered the best available strategy to uncover brain function in animal experiments. Extremely sensitive behavioral test batteries are now available and are necessary to uncover possible low-dose consequences (MELODI, 2019).

Harmonization of study protocols, in terms of behavioral tests adopted, radiation dose and dose-rate will help to compare results between laboratories. Indeed, discrepancies exist between studies and no consistent conclusions can be drawn at present regarding the gestational age at which irradiation induces modifying effects on rodent behavior.

**4.2.2.3. Specific biological mechanisms that need further clarification.** As described above, the effects of radiation at high doses are different from those at low doses. Effects of high doses of IR includes apoptosis, defect in cell proliferation and migration, and alterations of blood brain barrier permeability. At low to moderate doses, aberrant neuronal communication after prenatal/perinatal irradiation, impairment of the synaptogenesis, and inhibitory neuron development at early time-points after irradiation need to be further explored. Additionally, future studies should especially target childhood and adolescence to study the effects of IR on postnatal brain maturation, in particular changes in neurotransmitters availability and synaptic plasticity. Indeed the formation of the dendritic tree and the synaptic connections, which is usually completed in early adulthood, may be impaired by co-exposure to low dose ionizing radiation and ketamine (Hladik et al., 2019). We strongly recommend further similar research on radiation induced changes in dendritic structures.

Research should also focus on the role of the imbalance of inflammatory response during brain maturation, which may be a trigger of late cognitive impairment when associated with cytokines overexpression and dysregulation (Sochocka et al., 2017).

Animal models in CEREBRAD showed that blood brain barrier permeability correlated strongly with age at exposure and radiation dose and further investigations are required to fully understand the underlying mechanisms and the possible role on radiation induced cognitive dysfunction.

Defective cortical development and disturbed hippocampal neurogenesis have been associated with decreased thickness of the prefrontal cortex in the long-term. More experiments are required to investigate frontal and prefrontal cognitive functions related to the prefrontal cortex in irradiated animals.

Recent results from the SEPARATE project (SEPARATE, 2014) suggests the existence of out-of-target radiation responses in the hippocampus *in vivo*. Indeed, partial-body irradiated mice display changes in non-coding RNAs and proteins and defects in neurogenesis similar to those induced by whole-body irradiation (Pazzaglia et al., in preparation). Thus, further mechanistic investigations on the contribution of “out-of-target” effects are needed. The direct effects of IR on the postnatal brain need to be disentangled from the abscopal effect linked to whole body exposures.

#### 4.2.3. Modelling

It is premature for a modelling of risk assessment that integrates mechanistic studies and epidemiology as epidemiological and biological studies are still not conclusive at present.

However, with a better understanding of mechanisms, development of dedicated mathematical models would be useful to analyse both new and available epidemiological and animal data on radiation-induced cognitive impairment.

## 5. Conclusions

The presentations and discussions at the workshop indicate, both from the epidemiological and experimental perspectives, a possible effect of low doses of IR on cognitive development and decline.

Particular research gaps include: i) better characterization of the cognitive deficit across the human life span; ii) understanding of the effect modification of age at exposure and at cognitive assessment; iii) understanding of the effect of co-exposures, in particular in the medical setting. Addressing such gaps will likely better inform clinicians in the



decision-making process thus improving radiation protection of patients undergoing diagnostic and therapeutic procedures.

Based on a review of past studies and their limitations, the workshop participants identified specific populations most suitable for the study of cognitive effects. Neurodevelopment may be studied in childhood cancer survivors with low to moderate brain doses and cognitive decline may be addressed in atomic bomb survivors, aging cohorts treated for benign diseases (tinea capitis, haemangioma) and in workers with relatively high doses, such as Mayak workers or Chernobyl liquidators.

Regarding experimental studies, rodents are extensively used to model neurodegenerative disease, and they have also played a pivotal role in the mechanistic understanding of radiation-induced cognitive dysfunctions. Notwithstanding the importance of these models in elucidating the pathogenic pathways in radiation-induced brain effects, the translational validity of the gained knowledge to humans should be further investigated.

Finally, modeling may play an important role in bridging the information from epidemiology and mechanistic studies for a better risk assessment.

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### CRediT authorship contribution statement

**E. Pasqual:** Conceptualization, Data curation, Project administration, Methodology, Writing original draft, Writing (Review and editing). **F. Boussin:** Data curation, Writing original draft (section 3.1.3), Writing (review and editing). **D. Bazyka:** Data curation, Writing original draft (section 3.1.2.1), Writing (review and editing). **A. Nordenskjöld:** Data curation, Writing original draft (section 3.1.1), Writing (review and editing). **M. Yamada:** Data curation, Writing original draft (section 3.1.2.2), Writing (review and editing). **K. Ozasa:** Data curation, Writing original draft (section 3.1.2.2), Writing (review and editing). **S. Pazzaglia:** Data curation, Writing original draft (section 3.1.3), Writing (review and editing). **L. Roy:** Writing (review and editing). **I. Thierry-Chef:** Project administration, Writing (review and editing). **F. de Vathaire:** Writing (review and editing). **M.A. Benotmane:** Conceptualization, Data curation, Supervision, Methodology, Writing original draft, Writing (Review and editing). **E. Cardis:** Conceptualization, Data curation, Supervision, Methodology, Writing original draft, Writing (Review and editing).

### Declaration of Competing Interest

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

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### References

- Acharya, M.M., Green, K.N., Allen, B.D., Najafi, A.R., Syage, A., Minasyan, H., Le, M.T., Kawashita, T., Giedzinski, E., Parihar, V.K., West, B.L., Baulch, J.E., Limoli, C.L., 2016. Elimination of microglia improves cognitive function following cranial irradiation. *Sci. Rep.* 6, 31545. <https://doi.org/10.1038/srep31545>.
- Aghaei, M., Janjani, H., Yousefian, F., Jamal, A., Yunesian, M., 2019. Association between ambient gaseous and particulate air pollutants and attention deficit hyperactivity disorder (ADHD) in children; a systematic review. *Environ. Res.* 173, 135–156. <https://doi.org/10.1016/j.envres.2019.03.030>.
- Allen, A.R., Eilertson, K., Sharma, S., Schneider, D., Baure, J., Allen, B., Rosi, S., Raber, J., Fike, J.R., 2013. Effects of radiation combined injury on hippocampal function are modulated in mice deficient in chemokine receptor 2 (CCR2). *Radiat. Res.* 180, 78–88. <https://doi.org/10.1667/RR3344.1>.
- Almond, D., Edlund, L., Palme, M., 2009. Chernobyl's Subclinical Legacy: Prenatal Exposure to Radioactive Fallout and School Outcomes in Sweden. *Q. J. Econ.* 124, 1729–1772. <https://doi.org/10.1162/qjec.2009.124.4.1729>.
- Armstrong, F.D., 2006. Neurodevelopment and chronic illness: Mechanisms of disease and treatment. *Ment. Retard. Dev. Disabil. Res. Rev.* 12, 168–173. <https://doi.org/10.1002/mrdd.20114>.
- Armstrong, G.T., Jain, N., Liu, W., Merchant, T.E., Stovall, M., Srivastava, D.K., Gurney, J.G., Packer, R.J., Robison, L.L., Krull, K.R., 2010. Region-specific radiotherapy and neuropsychological outcomes in adult survivors of childhood CNS malignancies. *Neuro-oncology* 12, 1173–1186. <https://doi.org/10.1093/neuonc/noq104>.
- Azizova, T.V., Bannikova, M.V., Grigoryeva, E.S., Rybkina, V.L., Hamada, N., 2019. Occupational exposure to chronic ionizing radiation increases risk of Parkinson's disease incidence in Russian Mayak workers. *Int. J. Epidemiol.* <https://doi.org/10.1093/ije/dyz230>.
- Bar Joseph, N., Reinfeld, D., Tirosh, E., Silman, Z., Rennert, G., 2004. Neurobehavioral and cognitive performances of children exposed to low-dose radiation in the Chernobyl accident: the Israeli Chernobyl Health Effects Study. *Am. J. Epidemiol.* 160, 453–459. <https://doi.org/10.1093/aje/kwh231>.
- Bazyka, D., Prysyzhnyuk, A., Gudzenko, N., Dyagil, I., Belyi, D., Chumak, V., Buzunov, V., 2018. Epidemiology of Late Health Effects in Ukrainian Chernobyl Cleanup Workers. *Health Phys.* 115, 161–169. <https://doi.org/10.1097/HP.0000000000000868>.
- Bazyka, D., Sushko, V., Chumak, A., Buzunov, V., Talko, V., Yanovych, L., 2017. State Institution «National Research Center for Radiation Medicine of the National Academy of Medical Sciences of Ukraine» - research activities and scientific advance in 2016. *Probl. Radiac. Med. Radiobiol.* 22, 15–22.
- Bazyka, D.A., Gudzenko, N.A., Dyagil, I.S., Babkina, N.G., Chumak, V.V., Bakhanova, E.V., Paramonov, V.V., Romanenko, A.Y., 2013. Multiple myeloma among Chernobyl accident clean-up workers - state and perspectives of analytical study. *Probl. Radiac. Med. Radiobiol.* 169–172.
- Bazyka, D.A., Loganovsky, K.M., Ilyenko, I.M., Chumak, S.A., Bomko, M.O., 2015. Gene expression, telomere and cognitive deficit analysis as a function of Chernobyl radiation dose and age: from in utero to adulthood. *Probl. Radiac. Med. Radiobiol.* 20, 283–310.
- Bernier, M.-O., Baysson, H., Pearce, M.S., Moissonnier, M., Cardis, E., Hauptmann, M., Struelens, L., Dabin, J., Johansen, C., Journy, N., Laurier, D., Blettner, M., Le Cornet, L., Pokora, R., Gradowska, P., Meulepas, J.M., Kjaerheim, K., Istad, T., Olerud, H., Sovik, A., Bosch de Basea, M., Thierry-Chef, I., Kajiser, M., Nordenskjöld, A., Berrington de Gonzalez, A., Harbron, R.W., Kesminiene, A., 2018. Cohort Profile: the EPI-CT study: A European pooled epidemiological study to quantify the risk of radiation-induced cancer from paediatric CT. *Int. J. Epidemiol.* <https://doi.org/10.1093/ije/dyy231>.
- Black, S.E., Bütikofer, A., Devereux, P.J., Salvanes, K.G., 2013. This Is Only a Test? Long-Run Impacts of Prenatal Exposure to Radioactive Fallout (Working Paper No. 18987). National Bureau of Economic Research. <https://doi.org/10.3386/w18987>.
- Blomstrand, M., Holmberg, E., Aberg, M.A.I., Lundell, M., Björk-Eriksson, T., Karlsson, P., Blomgren, K., 2014. No clinically relevant effect on cognitive outcomes after low-dose radiation to the infant brain: a population-based cohort study in Sweden. *Acta Oncol.* 53, 1143–1150. <https://doi.org/10.3109/0284186X.2014.899434>.
- Bouffler, S., Auvinen, A., Cardis, E., Durante, M., Jourdain, J.R., Kreuzer, M., Madas, B., 2019. Strategic Research Agenda of the Multidisciplinary European Low Dose Initiative. <http://www.melodi-online.eu/doc/MELODI%20SRA%202019%20%20post-consultation%20draft%20FINAL2.pdf>.
- Buratovic, S., Stenerlöv, B., Fredriksson, A., Sundell-Bergman, S., Viberg, H., Eriksson, P., 2014. Neonatal exposure to a moderate dose of ionizing radiation causes behavioural defects and altered levels of tau protein in mice. *Neurotoxicology* 45, 48–55. <https://doi.org/10.1016/j.neuro.2014.09.002>.
- Buratovic, S., Stenerlöv, B., Sundell-Bergman, S., Fredriksson, A., Viberg, H., Gordh, T., Eriksson, P., 2018. Effects on adult cognitive function after neonatal exposure to clinically relevant doses of ionising radiation and ketamine in mice. *Br. J. Anaesth.* 120, 546–554. <https://doi.org/10.1016/j.bja.2017.11.099>.
- Buzunov, V.O., Kapustynska, O.A., 2018. Epidemiological studies of cerebrovascular disease of the population evacuated from the 306km zone of the chnpp at the age of 18–60 years. analysis of the influence of internal ionizing radiation on the thyroid gland 131I. *Probl. Radiac. Med. Radiobiol.* 23, 96–106. <https://doi.org/10.33145/2304-8336-2018-23-96-106>.

- Casciati, A., Dobos, K., Antonelli, F., Benedek, A., Kempf, S.J., Bellés, M., Balogh, A., Tanori, M., Heredia, L., Atkinson, M.J., von Toerne, C., Azimzadeh, O., Saran, A., Sáfrány, G., Benotmane, M.A., Linares-Vidal, M.V., Tapio, S., Lumniczky, K., Pazzaglia, S., 2016. Age-related effects of X-ray irradiation on mouse hippocampus. *Oncotarget* 7, 28040–28058. <https://doi.org/10.18632/oncotarget.8575>.
- Casey, B.J., Tottenham, N., Liston, C., Durston, S., 2005. Imaging the developing brain: what have we learned about cognitive development? *Trends Cogn. Sci. (Regul. Ed.)* 9, 104–110. <https://doi.org/10.1016/j.tics.2005.01.011>.
- CEREBRAD [WWW Document], 2015. URL <https://www.cerebrad-fp7.eu/en/Project-Summary>.
- Chen, J.-H., Yen, Y.-C., Liu, S.-H., Lee, F.-P., Lin, K.-C., Lai, M.-T., Wu, C.-C., Chen, T.-M., Yuan, S.-P., Chang, C.-L., Wu, S.-Y., 2015. Dementia Risk in Irradiated Patients With Head and Neck Cancer. *Medicine (Baltimore)* 94, e1983. <https://doi.org/10.1097/MD.0000000000001983>.
- Cheung, Y.T., Brinkman, T.M., Li, C., Mzayek, Y., Srivastava, D., Ness, K.K., Patel, S.K., Howell, R.M., Oeffinger, K.C., Robison, L.L., Armstrong, G.T., Krull, K.R., 2017. Chronic Health Conditions and Neurocognitive Function in Aging Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study. *J. Natl Cancer Inst.* 110, 411–419. <https://doi.org/10.1093/jnci/djx224>.
- Collett, G., Craenen, K., Young, W., Gilhooly, M., Anderson, R.M., 2020a. The psychological consequences of (perceived) ionizing radiation exposure: a review on its role in radiation-induced cognitive dysfunction. *Int. J. Radiat Biol.* 96, 1104–1118. <https://doi.org/10.1080/09553002.2020.1793017>.
- Collett, G., Martin, W., Rhona, A., 2020b. Exposure Worry, Ageing and Cognitive Functioning: An in-depth study of British Nuclear Test Veterans [WWW Document]. Centre for Health Effects of Radiological and Chemical Agents. URL <https://chr.c4veterans.uk/exposure-worry/> (accessed 5.26.20).
- Cornetta, T., Festa, F., Testa, A., Cozzi, R., 2006. DNA damage repair and genetic polymorphisms: assessment of individual sensitivity and repair capacity. *Int. J. Radiat. Oncol. Biol. Phys.* 66, 537–545. <https://doi.org/10.1016/j.ijrobp.2006.06.037>.
- Crump, C., Rivera, D., London, R., Landau, M., Erlendson, B., Rodriguez, E., 2013. Chronic health conditions and school performance among children and youth. *Ann. Epidemiol.* 23, 179–184. <https://doi.org/10.1016/j.annepidem.2013.01.001>.
- Daynac, M., Chicheportiche, A., Pineda, J.R., Gauthier, L.R., Boussin, F.D., Mouthon, M.-A., 2013. Quiescent neural stem cells exit dormancy upon alteration of GABAAR signaling following radiation damage. *Stem Cell Res.* 11, 516–528. <https://doi.org/10.1016/j.scr.2013.02.008>.
- Dinocourt, C., Culeux, C., Legrand, M., Elie, C., Lestaevel, P., 2017. Chronic Exposure to Uranium from Gestation: Effects on Behavior and Neurogenesis in Adulthood. *Int. J. Environ. Res. Public Health* 14. <https://doi.org/10.3390/ijerph14050536>.
- Dondon, M.-G., de Vathaire, F., Shamsaldin, A., Doyon, F., Diallo, I., Ligot, L., Paoletti, C., Labbé, M., Abbas, M., Chavaudra, J., Avril, M.-F., Fragu, P., Eschwege, F., 2004. Cancer mortality after radiotherapy for a skin hemangioma during childhood. *Radiother. Oncol.* 72, 87–93. <https://doi.org/10.1016/j.radonc.2004.03.011>.
- Dos Santos, M., Kereselidze, D., Gloaguen, C., Benadjaoud, M.A., Tack, K., Lestaevel, P., Durand, C., 2018. Development of whole brain versus targeted dentate gyrus irradiation model to explain low to moderate doses of exposure effects in mice. *Sci. Rep.* 8, 17262. <https://doi.org/10.1038/s41598-018-35579-x>.
- Durand, T., Jacob, S., Lebouil, L., Douzane, H., Lestaevel, P., Rahimian, A., Psimaras, D., Feuvre, L., Leclercq, D., Brochet, B., Tamarat, R., Milliat, F., Benderitter, M., Vayatis, N., Noël, G., Hoang-Xuan, K., Delattre, J.-Y., Ricard, D., Bernier, M.-O., 2015. EpiBrainRad: an epidemiologic study of the neurotoxicity induced by radiotherapy in high grade glioma patients. *BMC Neurol* 15, 261. <https://doi.org/10.1186/s12883-015-0519-6>.
- Dutz, A., Agolli, L., Bütof, R., Valentini, C., Baumann, M., Lühr, A., Löck, S., Krause, M., 2020. Neurocognitive function and quality of life after proton beam therapy for brain tumour patients. *Radiother. Oncol.* 143, 108–116. <https://doi.org/10.1016/j.radonc.2019.12.024>.
- El-Fayech, C., Haddy, N., Alodjji, R.S., Veres, C., Diop, F., Kahlouche, A., Llanas, D., Jackson, A., Rubino, C., Guibout, C., Pacquement, H., Oberlin, O., Thomas-Teinturier, C., Scaramin, P.-Y., Chavaudra, J., Lefkopoulos, D., Giroud, M., Bejot, Y., Bernier, V., Carrie, C., Diallo, I., de Vathaire, F., 2017. Cerebrovascular Diseases in Childhood Cancer Survivors: Role of the Radiation Dose to Willis Circle Arteries. *Int. J. Radiat. Oncol. Biol. Phys.* 97, 278–286. <https://doi.org/10.1016/j.ijrobp.2016.10.015>.
- Eom, H.S., Park, H.R., Jo, S.K., Kim, Y.S., Moon, C., Kim, S.-H., Jung, U., 2016. Ionizing Radiation Induces Altered Neuronal Differentiation by mGluR1 through PI3K-STAT3 Signaling in C17.2 Mouse Neural Stem-Like Cells. *PLoS ONE* 11, e0147538. <https://doi.org/10.1371/journal.pone.0147538>.
- Etienne, O., Roque, T., Haton, C., Boussin, F.D., 2012. Variation of radiation-sensitivity of neural stem and progenitor cell populations within the developing mouse brain. *Int. J. Radiat Biol.* 88, 694–702. <https://doi.org/10.3109/09553002.2012.710927>.
- Feenstra, H.E.M., Murre, J.M.J., Vermeulen, L.E., Kieffer, J.M., Schagen, S.B., 2018. Reliability and validity of a self-administered tool for online neuropsychological testing: The Amsterdam Cognition Scan. *J. Clin. Exp. Neuropsychol.* 40, 253–273. <https://doi.org/10.1080/13803395.2017.1339017>.
- Feierstein, C.E., Lazarini, F., Wagner, S., Gabelle, M.-M., de Chaumont, F., Olivio-Marin, J.-C., Boussin, F.D., Lledo, P.-M., Gheusi, G., 2010. Disruption of Adult Neurogenesis in the Olfactory Bulb Affects Social Interaction but not Maternal Behavior. *Front. Behav. Neurosci.* 4, 176. <https://doi.org/10.3389/fnbeh.2010.00176>.
- Fernandez-Capetillo, O., 2010. Intrauterine programming of ageing. *EMBO Rep.* 11, 32–36. <https://doi.org/10.1038/embor.2009.262>.
- Forns, J., Aranbarri, A., Grellier, J., Julvez, J., Vrijheid, M., Sunyer, J., 2012. A conceptual framework in the study of neuropsychological development in epidemiological studies. *Neuroepidemiology* 38, 203–208. <https://doi.org/10.1159/000337169>.
- Gagnaire, B., Adam-Guillermier, C., Bouron, A., Lestaevel, P., 2011. The effects of radionuclides on animal behavior. *Rev. Environ. Contam. Toxicol.* 210, 35–58. [https://doi.org/10.1007/978-1-4419-7615-4\\_2](https://doi.org/10.1007/978-1-4419-7615-4_2).
- Gondi, V., Tomé, W.A., Mehta, M.P., 2010. Why avoid the hippocampus? A comprehensive review. *Radiother. Oncol.* 97, 370–376. <https://doi.org/10.1016/j.radonc.2010.09.013>.
- Gottumukkala, R.V., Kalra, M.K., Tabari, A., Otrajki, A., Gee, M.S., 2019. Advanced CT Techniques for Decreasing Radiation Dose, Reducing Sedation Requirements, and Optimizing Image Quality in Children. *Radiographics* 39, 709–726. <https://doi.org/10.1148/rg.2019180082>.
- Graignic-Philippe, R., Dayan, J., Chokron, S., Jacquet, A.-Y., Tordjman, S., 2014. Effects of prenatal stress on fetal and child development: A critical literature review. *Neurosci. Biobehav. Rev.* 43, 137–162. <https://doi.org/10.1016/j.neubiorev.2014.03.022>.
- Gunnarsson, L.-G., Bodin, L., 2019. Occupational Exposures and Neurodegenerative Diseases—A Systematic Literature Review and Meta-Analyses. *Int. J. Environ. Res. Public Health* 16. <https://doi.org/10.3390/ijerph16030337>.
- Hall, P., Adami, H.-O., Trichopoulos, D., Pedersen, N.L., Lagiou, P., Ekblom, A., Ingvar, M., Lundell, M., Granath, F., 2004. Effect of low doses of ionizing radiation in infancy on cognitive function in adulthood: Swedish population based cohort study. *BMJ* 328, 19. <https://doi.org/10.1136/bmj.328.7430.19>.
- Hamra, G.B., Richardson, D.B., Cardis, E., Daniels, R.D., Gillies, M., O'Hagan, J.A., Haylock, R., Laurier, D., Leuraud, K., Moissonnier, M., Schubauer-Berigan, M., Thierry-Chef, I., Kesminiene, A., 2015. Cohort Profile: The International Nuclear Workers Study (INWORKS). *Int. J. Epidemiol.* <https://doi.org/10.1093/ije/dyv122>.
- Hauptmann, M., Daniels, R.D., Cardis, E., Cullings, H.M., Kendall, G., Laurier, D., Linet, M.S., Little, M.P., Lubin, J.H., Preston, D.L., Richardson, D.B., Stram, D.O., Thierry-Chef, I., Schubauer-Berigan, M.K., Gilbert, E.S., Berrington de Gonzalez, A., 2020. Epidemiological studies of low-dose ionizing radiation and cancer: Summary bias assessment and meta-analysis. *J. Natl. Cancer Inst. Monogr.* 2020 (56): 188–200. <http://doi.org/10.1093/jncimonographs/igaa010>. PMID: 32657347.
- Heiervang, K.S., Mednick, S., Sundet, K., Rund, B.R., 2010. Effect of low dose ionizing radiation exposure in utero on cognitive function in adolescence. *Scand. J. Psychol.* 51, 210–215. <https://doi.org/10.1111/j.1467-9450.2010.00814.x>.
- Hladik, D., Buratovic, S., Von Toerne, C., Azimzadeh, O., Subedi, P., Philipp, J., Winkler, S., Feuchtinger, A., Samson, E., Hauck, S.M., Stenleröw, B., Eriksson, P., Atkinson, M.J., Tapio, S., 2019. Combined Treatment with Low-Dose Ionizing Radiation and Ketamine Induces Adverse Changes in CA1 Neuronal Structure in Male Murine Hippocampi. *Int. J. Mol. Sci.* 20. <https://doi.org/10.3390/ijms20236103>.
- Hladik, D., Tapio, S., 2016. Effects of ionizing radiation on the mammalian brain. *Mutat. Res.* 770, 219–230. <https://doi.org/10.1016/j.mrrev.2016.08.003>.
- Hodgson, K.D., Hutchinson, A.D., Wilson, C.J., Nettelbeck, T., 2013. A meta-analysis of the effects of chemotherapy on cognition in patients with cancer. *Cancer Treat. Rev.* 39, 297–304. <https://doi.org/10.1016/j.ctrv.2012.11.001>.
- Hoshino, K., Kameyama, Y., 1988. Developmental-stage-dependent radiosensitivity of neural cells in the ventricular zone of telencephalon in mouse and rat fetuses. *Teratology* 37, 257–262. <https://doi.org/10.1002/tera.1420370311>.
- Hoshino, K., Kameyama, Y., Inouye, M., 1991. Split-dose effect of X-irradiation on the induction of cell death in the fetal mouse brain. *J. Radiat. Res.* 32, 23–27. <https://doi.org/10.1269/jrr.32.23>.
- IARC, 2019. Preamble. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans - Amended January 2019. IARC (International Agency for Research on Cancer).
- Ibanez, C., Suhard, D., Elie, C., Ebrahimi, T., Lestaevel, P., Roynette, A., Dhieux-Lestaevel, B., Gensdarmes, F., Tack, K., Tessier, C., 2019. Evaluation of the Nose-to-Brain Transport of Different Physicochemical Forms of Uranium after Exposure via Inhalation of a UO<sub>4</sub> Aerosol in the Rat. *Environ. Health Perspect.* 127, 97010. <https://doi.org/10.1289/EHP4927>.
- ICRP, 2012. ICRP Statement on Tissue Reactions / Early and Late Effects of Radiation in Normal Tissues and Organs – Threshold Doses for Tissue Reactions in a Radiation Protection Context. *Ann. ICRP* 41 (1/2). ICRP Publication 118.
- Igumov, S., Drozdovitch, V., 2000. The intellectual development, mental and behavioural disorders in children from Belarus exposed in utero following the Chernobyl accident. *Eur. Psychiatry* 15, 244–253.
- Imanishi, Y., Fukui, A., Niimi, H., Itoh, D., Nozaki, K., Nakaji, S., Ishizuka, K., Tabata, H., Furuya, Y., Uzura, M., Takahama, H., Hashizume, S., Arima, S., Nakajima, Y., 2005. Radiation-induced temporary hair loss as a radiation damage only occurring in patients who had the combination of MDCT and DSA. *Eur. Radiol.* 15, 41–46. <https://doi.org/10.1007/s00330-004-2459-1>.
- Inouye, M., Yamamura, H., Nakano, A., 1995. Lithium delays the radiation-induced apoptotic process in external granule cells of mouse cerebellum. *J. Radiat. Res.* 36, 203–208. <https://doi.org/10.1269/jrr.36.203>.
- Jensh, R.P., Eisenman, L.M., Brent, R.L., 1995. Postnatal neurophysiologic effects of prenatal X-irradiation. *Int. J. Radiat Biol.* 67, 217–227. <https://doi.org/10.1080/09553009514550271>.
- Júlvez, J., Paus, T., Bellinger, D., Eskenazi, B., Tiemeier, H., Pearce, N., Ritz, B., White, T., Ramchandani, P., Gispert, J.D., Desrivieres, S., Brouwer, R., Boucher, O., Alemany, S., López-Vicente, M., Suades-González, E., Forns, J., Grandjean, P., Sunyer, J., 2016. Environment and Brain Development: Challenges in the Global Context. *Neuroepidemiology* 46, 79–82. <https://doi.org/10.1159/000442256>.



- Kahalley, L.S., Douglas Ris, M., Mahajan, A., Fatih Okcu, M., Chintagumpala, M., Paulino, A.C., Whitehead, W.E., Minard, C.G., Stancel, H.H., Orobio, J., Xue, J.J., Warren, E.A., Grosshans, D.R., 2019. Prospective, longitudinal comparison of neurocognitive change in pediatric brain tumor patients treated with proton radiotherapy versus surgery only. *Neuro-oncology* 21, 809–818. <https://doi.org/10.1093/neuonc/noz041>.
- Kempf, S.J., Casciati, A., Buratovic, S., Janik, D., von Toerne, C., Ueffing, M., Neff, F., Moertl, S., Stenelöw, B., Saran, A., Atkinson, M.J., Eriksson, P., Pazzaglia, S., Tapio, S., 2014. The cognitive defects of neonatally irradiated mice are accompanied by changed synaptic plasticity, adult neurogenesis and neuroinflammation. *Mol. Neurodegener.* 9, 57. <https://doi.org/10.1186/1750-1326-9-57>.
- Kempf, S.J., Moertl, S., Sepe, S., von Toerne, C., Hauck, S.M., Atkinson, M.J., Mastroberardino, P.G., Tapio, S., 2015. Low-dose ionizing radiation rapidly affects mitochondrial and synaptic signaling pathways in murine hippocampus and cortex. *J. Proteome Res.* 14, 2055–2064. <https://doi.org/10.1021/acs.jproteome.5b00114>.
- Kogan, A., Chesalin, P., 1989. [Auditory and visual evoked potentials changes in different terms of the restitution period of the acute radiation sickness]. Proceedings of the All[union Scientific Conference: The human nervous system alter[ ation upon exposure to ionizing radiation Moscow: Institute for Biophysics, 32.
- Krieger, T.G., Moran, C.M., Frangini, A., Visser, W.E., Schoenmakers, E., Muntoni, F., Clark, C.A., Gadian, D., Chong, W.K., Kuczynski, A., Dattani, M., Lyons, G., Efthymiadou, A., Varga-Khadem, F., Simons, B.D., Chatterjee, K., Livesey, F.J., 2019. Mutations in thyroid hormone receptor  $\alpha 1$  cause premature neurogenesis and progenitor cell depletion in human cortical development. *PNAS* 116, 22754–22763. <https://doi.org/10.1073/pnas.1908762116>.
- Krull, K.R., Hardy, K.K., Kahalley, L.S., Schuitema, L., Kesler, S.R., 2018. Neurocognitive Outcomes and Interventions in Long-Term Survivors of Childhood Cancer. *J. Clin. Oncol.* 36, 2181–2189. <https://doi.org/10.1200/JCO.2017.76.4696>.
- Lancaster, M.A., Renner, M., Martin, C.-A., Wenzel, D., Bicknell, L.S., Hurler, M.E., Homfray, T., Penninger, J.M., Jackson, A.P., Knoblich, J.A., 2013. Cerebral organoids model human brain development and microcephaly. *Nature* 501, 373–379. <https://doi.org/10.1038/nature12517>.
- Larson, E.B., McCurry, S.M., Graves, A.B., Bowen, J.D., Rice, M.M., McCormick, W.C., Zee, N., Homma, A., Imai, Y., White, L., Masaki, K., Petrovitch, H., Ross, W., Yamada, M., Mimori, Y., Sasaki, H., 1998. Standardization of the clinical diagnosis of the dementia syndrome and its subtypes in a cross-national study: the Ni-Hon-Sea experience. *J. Gerontol. A Biol. Sci. Med. Sci.* 53, M313–319. <https://doi.org/10.1093/gerona/53a.4.m313>.
- Lazarini, F., Mouthon, M.-A., Gheusi, G., de Chaumont, F., Olivo-Marin, J.-C., Lamarque, S., Abrous, D.N., Boussin, F.D., Lledo, P.-M., 2009. Cellular and behavioral effects of cranial irradiation of the subventricular zone in adult mice. *PLoS ONE* 4, e7017. <https://doi.org/10.1371/journal.pone.0007017>.
- Lee, C., Pearce, M.S., Salotti, J.A., Harbron, R.W., Little, M.P., McHugh, K., Chapple, C.-L., Berrington de Gonzalez, A., 2016. Reduction in radiation doses from paediatric CT scans in Great Britain. *Br. J. Radiol.* 89, 20150305. <https://doi.org/10.1259/bjr.20150305>.
- Lehrer, S., Rheinstein, P.H., Rosenzweig, K.E., 2017. Association of Radon Background and Total Background Ionizing Radiation with Alzheimer's Disease Deaths in U.S. States. *J. Alzheimers Dis.* 59, 737–741. <https://doi.org/10.3233/JAD-170308>.
- Lie, R.T., Moster, D., Strand, P., Wilcox, A.J., 2017. Prenatal exposure to Chernobyl fallout in Norway: neurological and developmental outcomes in a 25-year follow-up. *Eur. J. Epidemiol.* 32, 1065–1073. <https://doi.org/10.1007/s10654-017-0350-z>.
- Loganovskaja, T.K., Loganovsky, K.N., 1999. EEG, cognitive and psychopathological abnormalities in children irradiated in utero. *Int. J. Psychophysiol.* 34, 213–224.
- Loganovsky, K., Havenaar, J.M., Tintle, N.L., Guey, L.T., Kotov, R., Bromet, E.J., 2008. The mental health of clean-up workers 18 years after the Chernobyl accident. *Psychol. Med.* 38, 481–488. <https://doi.org/10.1017/S0033291707002371>.
- Loganovsky, K., Kuts, K., 2017. Evoked bioelectrical brain activity following exposure to ionizing radiation. *Probl. Radiac. Med. Radiobiol.* 22, 38–68.
- Loganovsky, K.M., Kuts, K.V., 2016. Cognitive evoked potentials P300 after radiation exposure. *Probl. Radiac. Med. Radiobiol.* 21, 264–290.
- Loganovsky, K.N., Bomko, M.O., Abramenko, I.V., Kuts, K.V., Belous, N.I., Masiuk, S.V., Gresko, M.V., Loganovska, T.K., Antypchuk, K.Y., Perchuk, I.V., Kreinis, G.Y., Chumak, S.A., 2018. Neuropsychobiological mechanisms of affective and cognitive disorders in the chornobyl clean-up workers taking into account the specific gene polymorphisms. *Probl. Radiac. Med. Radiobiol.* 23, 373–409. <https://doi.org/10.33145/2304-8336-2018-23-373-409>.
- López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., Kroemer, G., 2013. The hallmarks of aging. *Cell* 153, 1194–1217. <https://doi.org/10.1016/j.cell.2013.05.039>.
- McKenzie, J.A., Spielman, L.J., Pointer, C.B., Lowry, J.R., Bajwa, E., Lee, C.W., Klegeris, A., 2017. Neuroinflammation as a Common Mechanism Associated with the Modifiable Risk Factors for Alzheimer's and Parkinson's Diseases. *Curr Aging Sci* 10, 158–176. <https://doi.org/10.2174/1874609810666170315113244>.
- MELODI [WWW Document], 2019. URL [http://www.melodi-online.eu/m\\_docs\\_statement.html](http://www.melodi-online.eu/m_docs_statement.html) (accessed 9.30.16).
- Mizumatsu, S., Monje, M.L., Morhardt, D.R., Rola, R., Palmer, T.D., Fike, J.R., 2003. Extreme sensitivity of adult neurogenesis to low doses of X-irradiation. *Cancer Res.* 63, 4021–4027.
- Mokrani, S., Granotier-Beckers, C., Etienne, O., Kortulewski, T., Grisolia, C., de Villartay, J.-P., Boussin, F.D., 2020. Higher chromosome stability in embryonic neural stem and progenitor cells than in fibroblasts in response to acute or chronic genotoxic stress. *DNA Repair (Amst.)* 88, 102801. <https://doi.org/10.1016/j.dnarep.2020.102801>.
- Monje, M.L., Toda, H., Palmer, T.D., 2003. Inflammatory blockade restores adult hippocampal neurogenesis. *Science* 302, 1760–1765. <https://doi.org/10.1126/science.1088417>.
- Morizur, L., Chicheportiche, A., Gauthier, L.R., Daynac, M., Boussin, F.D., Mouthon, M.-A., 2018. Distinct Molecular Signatures of Quiescent and Activated Adult Neural Stem Cells Reveal Specific Interactions with Their Microenvironment. *Stem Cell Rep.* 11, 565–577. <https://doi.org/10.1016/j.stemcr.2018.06.005>.
- Morris, B., Partap, S., Yeom, K., Gibbs, I.C., Fisher, P.G., King, A.A., 2009. Cerebrovascular disease in childhood cancer survivors: A Children's Oncology Group Report. *Neurology* 73, 1906–1913. <https://doi.org/10.1212/WNL.0b013e3181c17ea8>.
- Mouton, L., Etienne, Feat-Vetel, J., Barrière, D., Pérès, E., Boumezeur, F., Boussin, F.D., Le Bihan, D., under review. Noninvasive assessment of neurodevelopmental disorders after in utero irradiation in mice: an in vivo anatomical and diffusion MRI study.
- Mulhern, R.K., Merchant, T.E., Gajjar, A., Reddick, W.E., Kun, L.E., 2004. Late neurocognitive sequelae in survivors of brain tumours in childhood. *Lancet Oncol.* 5, 399–408. [https://doi.org/10.1016/S1470-2045\(04\)01507-4](https://doi.org/10.1016/S1470-2045(04)01507-4).
- Mumbreaker, K.D., Goutham, H.V., Vadhiraja, B.M., Bola Sadashiva, S.R., 2016. Polymorphisms in double strand break repair related genes influence radiosensitivity phenotype in lymphocytes from healthy individuals. *DNA Repair (Amst.)* 40, 27–34. <https://doi.org/10.1016/j.dnarep.2016.02.006>.
- Murga, M., Bunting, S., Montaña, M.F., Soria, R., Mulero, F., Cañamero, M., Lee, Y., McKinnon, P.J., Nussenzweig, A., Fernandez-Capetillo, O., 2009. A mouse model of ATR-Seckel shows embryonic replicative stress and accelerated aging. *Nat. Genet.* 41, 891–898. <https://doi.org/10.1038/ng.420>.
- Myers, J.S., Pierce, J., Pazdernik, T., 2008. Neurotoxicology of chemotherapy in relation to cytokine release, the blood-brain barrier, and cognitive impairment. *Oncol. Nurs. Forum* 35, 916–920. <https://doi.org/10.1188/08.ONF.916-920>.
- Niclasen, J., Obel, C., Guldager, C., Pleinert, S., Dammeyer, J., 2016. Associations between childhood hearing loss and behavioural and academic difficulties: A Danish cohort study. *Int. J. Pediatr. Otorhinolaryngol.* 90, 91–98. <https://doi.org/10.1016/j.ijporl.2016.09.002>.
- Nogueira, Adriano Barreto, Nogueira, Ariel Barreto, Veiga, J.C.E., Teixeira, M.J., 2018. Letter: Human Hippocampal Neurogenesis Drops Sharply in Children to Undetectable Levels in Adults. *Neurosurgery* 83, E133–E137. <https://doi.org/10.1093/neuros/nyy252>.
- Nordenskjöld, A.C., Palme, M., Kaijser, M., 2015. X-ray exposure in utero and school performance: a population-based study of X-ray pelvimetry. *Clin. Radiol.* 70, 830–834. <https://doi.org/10.1016/j.crad.2015.04.002>.
- Nowak, E., Etienne, O., Millet, P., Lages, C.S., Mathieu, C., Mouthon, M.-A., Boussin, F. D., 2006. Radiation-induced H2AX phosphorylation and neural precursor apoptosis in the developing brain of mice. *Radiat. Res.* 165, 155–164. <https://doi.org/10.1667/rr3496.1>.
- Nyagu, A.I., Loganovskaja, K.N., Loganovskaja, T.K., 1998. Psychophysiological aftereffects of prenatal irradiation. *Int. J. Psychophysiol.* 30, 303–311.
- Ojha, J., Dyagal, I., Finch, S.C., Reiss, R.F., de Smith, A.J., Gonseth, S., Zhou, M., Hansen, H.M., Sherborne, A.L., Nakamura, J., Bracci, P.M., Gudzenko, N., Hatch, M., Babkina, N., Little, M.P., Chumak, V.V., Walsh, K.M., Bazzyka, D., Wiemels, J.L., Zablotska, L.B., 2018. Genomic characterization of chronic lymphocytic leukemia (CLL) in radiation-exposed Chernobyl cleanup workers. *Environ Health* 17, 43. <https://doi.org/10.1186/s12940-018-0387-9>.
- Otake, M., Schull, W.J., 1998. Radiation-related brain damage and growth retardation among the prenatally exposed atomic bomb survivors. *Int. J. Radiat Biol.* 74, 159–171. <https://doi.org/10.1080/095530098141555>.
- Otake, M., Schull, W.J., Yoshimaru, H., 1991. Brain Damage among the Prenatally Exposed. *J. Radiat. Res.* 32, 249–264. [https://doi.org/10.1269/jrr.32.SUPPLEMENT\\_249](https://doi.org/10.1269/jrr.32.SUPPLEMENT_249).
- Parihar, V.K., Allen, B.D., Caressi, C., Kwok, S., Chu, E., Tran, K.K., Chmielewski, N.N., Giedzinski, E., Acharya, M.M., Britten, R.A., Baulch, J.E., Limoli, C.L., 2016. Cosmic radiation exposure and persistent cognitive dysfunction. *Sci. Rep.* 6, 34774. <https://doi.org/10.1038/srep34774>.
- Parihar, V.K., Limoli, C.L., 2013. Cranial irradiation compromises neuronal architecture in the hippocampus. *PNAS* 110, 12822–12827. <https://doi.org/10.1073/pnas.1307301110>.
- Park, S.-P., Kwon, S.-H., 2008. Cognitive Effects of Antiepileptic Drugs. *J. Clin. Neurol.* 4, 99–106. <https://doi.org/10.3988/jcn.2008.4.3.99>.
- Pasqual, E., Bosch de Basea, M., López-Vicente, M., Thierry-Chef, I., Cardis, E., 2020. Neurodevelopmental effects of low dose ionizing radiation exposure: A systematic review of the epidemiological evidence. *Environ. Int.* 136, 105371. <https://doi.org/10.1016/j.envint.2019.105371>.
- Pazzaglia, S., Antonelli, F., Giardullo, P., Tanno, B., Babini, G., Subedi, P., Azimzadeh, O., Khan, Z., Oleksenko, K., Metzger, F., von Toerne, C., Traynor, D., Medipally, D., Meade, A., Kadhim, M., Lyng, F., Tapio, S., Saran, A., Mancuso, M., in preparation. Out-of-field hippocampus from partial-body irradiated mice displays changes in multi-omics profile and defects in neurogenesis.
- Pazzaglia, S., Briganti, G., Mancuso, M., Saran, A., 2020. Neurocognitive Decline Following Radiotherapy: Mechanisms and Therapeutic Implications. *Cancers (Basel)* 12. <https://doi.org/10.3390/cancers12010146>.
- Pérès, E.A., Etienne, O., Grigis, A., Boumezeur, F., Boussin, F.D., Le Bihan, D., 2018. Longitudinal Study of Irradiation-Induced Brain Microstructural Alterations With S-Index, a Diffusion MRI Biomarker, and MR Spectroscopy. *Int. J. Radiat. Oncol. Biol. Phys.* 102, 1244–1254. <https://doi.org/10.1016/j.ijrobp.2018.01.070>.
- Pineda, J.R., Daynac, M., Chicheportiche, A., Cebrian-Silla, A., Sii Felice, K., Garcia-Verdugo, J.M., Boussin, F.D., Mouthon, M.-A., 2013. Vascular-derived TGF- $\beta$  increases in the stem cell niche and perturbs neurogenesis during aging and

- following irradiation in the adult mouse brain. *EMBO Mol. Med.* 5, 548–562. <https://doi.org/10.1002/emmm.201202197>.
- Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., Britten, N., 2006. Guidance on the Conduct of Narrative Synthesis in Systematic Reviews 92.
- Power, M.C., Adar, S.D., Yanosky, J.D., Weuve, J., 2016. Exposure to air pollution as a potential contributor to cognitive function, cognitive decline, brain imaging, and dementia: A systematic review of epidemiologic research. *Neurotoxicology* 56, 235–253. <https://doi.org/10.1016/j.neuro.2016.06.004>.
- Quintens, R., Verreert, T., Janssen, A., Neefs, M., Leysen, L., Michaux, A., Verslegers, M., Samari, N., Pani, G., Verheyde, J., Baatout, S., Benotmane, M.A., 2015. Identification of novel radiation-induced p53-dependent transcripts extensively regulated during mouse brain development. *Biol Open* 4, 331–344. <https://doi.org/10.1242/bio.20149969>.
- Rappaport, B.A., Suresh, S., Hertz, S., Evers, A.S., Orser, B.A., 2015. Anesthetic neurotoxicity—clinical implications of animal models. *N. Engl. J. Med.* 372, 796–797. <https://doi.org/10.1056/NEJMp1414786>.
- Raz, N., Lindenberger, U., Rodrigue, K.M., Kennedy, K.M., Head, D., Williamson, A., Dahle, C., Gerstorf, D., Acker, J.D., 2005. Regional Brain Changes in Aging Healthy Adults: General Trends, Individual Differences and Modifiers. *Cereb. Cortex* 15, 1676–1689. <https://doi.org/10.1093/cercor/bhi044>.
- Rehani, M.M., Hauptmann, M., 2020. Estimates of the number of patients with high cumulative doses through recurrent CT exams in 35 OECD countries. *Phys. Med.* 76, 173–176. <https://doi.org/10.1016/j.ejpm.2020.07.014>.
- Reyners, H., Gianfelici de Reyners, E., Poortmans, F., Crametz, A., Coffigny, H., Maisin, J. R., 1992. Brain atrophy after foetal exposure to very low doses of ionizing radiation. *Int. J. Radiat Biol.* 62, 619–626. <https://doi.org/10.1080/09553009214552541>.
- Rivas, I., Basagaña, X., Cirach, M., López-Vicente, M., Suades-González, E., Garcia-Esteban, R., Álvarez-Pedrerol, M., Dadvand, P., Sunyer, J., 2019. Association between Early Life Exposure to Air Pollution and Working Memory and Attention. *Environ. Health Perspect.* 127, 57002. <https://doi.org/10.1289/EHP3169>.
- Robinson, K.E., Kutesch, J.F., Champion, J.E., Andreotti, C.F., Hipp, D.W., Bettis, A., Barnwell, A., Compas, B.E., 2010. A quantitative meta-analysis of neurocognitive sequelae in survivors of pediatric brain tumors. *Pediatr. Blood Cancer* 55, 525–531. <https://doi.org/10.1002/pbc.22568>.
- Ron, E., Modan, B., Floro, S., Harkedar, I., Gurewitz, R., 1982. Mental function following scalp irradiation during childhood. *Am. J. Epidemiol.* 116, 149–160. <https://doi.org/10.1093/oxfordjournals.aje.a113389>.
- Roque, T., Haton, C., Etienne, O., Chicheportiche, A., Rousseau, L., Martin, L., Mouthon, M.-A., Boussin, F.D., 2012. Lack of a p21waf1/cip-dependent G1/S checkpoint in neural stem and progenitor cells after DNA damage in vivo. *Stem Cells* 30, 537–547. <https://doi.org/10.1002/stem.1010>.
- Sadetzki, S., Chetrit, A., Mandelzweig, L., Nahon, D., Freedman, L., Susser, E., Gross, R., 2011. Childhood exposure to ionizing radiation to the head and risk of schizophrenia. *Radiat. Res.* 176, 670–677.
- Saha, S., Woodbine, L., Haines, J., Coster, M., Rickett, N., Barazzuol, L., Ainsbury, E., Sienkiewicz, Z., Jeggo, P., 2014. Increased apoptosis and DNA double-strand breaks in the embryonic mouse brain in response to very low-dose X-rays but not 50 Hz magnetic fields. *J. R. Soc. Interface* 11. <https://doi.org/10.1098/rsif.2014.0783>.
- Salonen, E., Nyman, H., Kizling, I., Geijerstam, J.-L.A., Flodmark, O., Aspelin, P., Kaijser, M., 2018. Cognitive function following head CT in childhood: a randomized controlled follow-up trial. *Acta Radiol.* 59, 221–228. <https://doi.org/10.1177/0284185117708471>.
- Schull, W.J., Nishitani, H., Hasuo, K., Kobayashi, T., Goto, I., Otake, M., 1991. Brain abnormalities among the mentally retarded prenatally exposed atomic bomb survivors (RERF report No. RERF TR 13-91). Radiation Effect Research Foundation, Hiroshima, Japan.
- SEPARATE, 2014. SEPARATE EU PROJECT GRANT Agreement 662287.
- Shamsaldin, A., Lundell, M., Diallo, I., Ligot, L., Chavaudra, J., de Vathaire, F., 2000. Estimation of the radiation dose from radiotherapy for skin haemangiomas in childhood: the ICTA software for epidemiology. *Phys. Med. Biol.* 45, 3589–3599. <https://doi.org/10.1088/0031-9155/45/12/306>.
- Sochocka, M., Diniz, B.S., Leszek, J., 2017. Inflammatory Response in the CNS: Friend or Foe? *Mol. Neurobiol.* 54, 8071–8089. <https://doi.org/10.1007/s12035-016-0297-1>.
- Stanescu, A.L., Shaw, D.W., Murata, N., Murata, K., Rutledge, J.C., Maloney, E., Maravilla, K.R., 2020. Brain tissue gadolinium retention in pediatric patients after contrast-enhanced magnetic resonance exams: pathological confirmation. *Pediatr. Radiol.* 50, 388–396. <https://doi.org/10.1007/s00247-019-04535-w>.
- Suman, S., Rodriguez, O.C., Winters, T.A., Fornace, A.J., Albanese, C., Datta, K., 2013. Therapeutic and space radiation exposure of mouse brain causes impaired DNA repair response and premature senescence by chronic oxidant production. *Aging (Albany NY)* 5, 607–622. <https://doi.org/10.18632/aging.100587>.
- Tada, E., Yang, C., Gobbel, G.T., Lamborn, K.R., Fike, J.R., 1999. Long-term impairment of subependymal repopulation following damage by ionizing irradiation. *Exp. Neurol.* 160, 66–77. <https://doi.org/10.1006/exnr.1999.7172>.
- Tanner, C.M., Goldman, S.M., Ross, G.W., Grate, S.J., 2014. The disease intersection of susceptibility and exposure: chemical exposures and neurodegenerative disease risk. *Alzheimers Dement* 10, S213–S225. <https://doi.org/10.1016/j.jalz.2014.04.014>.
- Taormina, D.P., Rozenblatt, S., Guey, L.T., Gluzman, S.F., Carlson, G.A., Havenaar, J.M., Zakhozha, V., Kotov, R., Bromet, E.J., 2008. The Chernobyl accident and cognitive functioning: a follow-up study of infant evacuees at age 19 years. *Psychol. Med.* 38, 489–497. <https://doi.org/10.1017/S0033291707002462>.
- Taras, H., Potts-Datema, W., 2005. Chronic health conditions and student performance at school. *J. Sch. Health* 75, 255–266. <https://doi.org/10.1111/j.1746-1561.2005.00034.x>.
- Teng, E.L., Hasegawa, K., Homma, A., Imai, Y., Larson, E., Graves, A., Sugimoto, K., Yamaguchi, T., Sasaki, H., Chiu, D., 1994. The Cognitive Abilities Screening Instrument (CASI): a practical test for cross-cultural epidemiological studies of dementia. *Int Psychogeriatr* 6, 45–58; discussion 62. <https://doi.org/10.1017/s1041610294001602>.
- The Cochrane Collaboration, 2011. *Cochrane Handbook for Systematic Reviews of Interventions*, Version 5.1.0 [updated March 2011]. ed.
- Tikellis, G., Dwyer, T., Paltiel, O., Phillips, G.S., Lemeshow, S., Golding, J., Northstone, K., Boyd, A., Olsen, S., Ghantous, A., Herceg, Z., Ward, M.H., Häberg, S.E., Magnus, P., Olsen, J., Ström, M., Mahabir, S., Jones, R.R., Ponsonby, A.-L., Clavel, J., Charles, M.A., Trevathan, E., Qian, Z.M., Maule, M.M., Qiu, X., Hong, Y.-C., Brandalise, S., Roman, E., Wake, M., He, J.-R., Linet, M.S., International Childhood Cancer Cohort Consortium, 2018. The International Childhood Cancer Cohort Consortium (I4C): A research platform of prospective cohorts for studying the aetiology of childhood cancers. *Paediatr Perinat Epidemiol* 32, 568–583. <https://doi.org/10.1111/ppe.12519>.
- Travis, L.B., Rabkin, C.S., Brown, L.M., Allan, J.M., Alter, B.P., Ambrosone, C.B., Begg, C. B., Caporaso, N., Chanock, S., DeMichele, A., Figg, W.D., Gospodarowicz, M.K., Hall, E.J., Hisada, M., Inskip, P., Kleinerman, R., Little, J.B., Malkin, D., Ng, A.K., Offit, K., Pui, C.-H., Robison, L.L., Rothman, N., Shields, P.G., Strong, L., Taniguchi, T., Tucker, M.A., Greene, M.A., 2006. Cancer survivorship-genetic susceptibility and second primary cancers: research strategies and recommendations. *J. Natl Cancer Inst.* 98, 15–25. <https://doi.org/10.1093/jnci/dj001>.
- Ullrich, N.J., Embry, L., 2012. Neurocognitive dysfunction in survivors of childhood brain tumors. *Semin Pediatr Neurol* 19, 35–42. <https://doi.org/10.1016/j.spen.2012.02.014>.
- Van den Bergh, B.R.H., van den Heuvel, M.I., Lahti, M., Braeken, M., de Rooij, S.R., Entringer, S., Hoyer, D., Roseboom, T., Räikkönen, K., King, S., Schwab, M., 2017. Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. *Neurosci. Biobehav. Rev.* <https://doi.org/10.1016/j.neubiorev.2017.07.003>.
- Verreert, T., Quintens, R., Van Dam, D., Verslegers, M., Tanori, M., Casciati, A., Neefs, M., Leysen, L., Michaux, A., Janssen, A., D'Agostino, E., Vande Velde, G., Baatout, S., Moons, L., Pazzaglia, S., Saran, A., Himmelreich, U., De Deyn, P.P., Benotmane, M. A., 2015. A multidisciplinary approach unravels early and persistent effects of X-ray exposure at the onset of prenatal neurogenesis. *J Neurodev Disord* 7, 3. <https://doi.org/10.1186/1866-1955-7-3>.
- Verreert, T., Verslegers, M., Quintens, R., Baatout, S., Benotmane, M.A., 2016. Current Evidence for Developmental, Structural, and Functional Brain Defects following Prenatal Radiation Exposure. *Neural Plast.* 2016, 1243527. <https://doi.org/10.1155/2016/1243527>.
- von der Hagen, M., Pivarcsi, M., Liebe, J., von Bernuth, H., Didonato, N., Hennermann, J. B., Bühner, C., Wiczorek, D., Kaindl, A.M., 2014. Diagnostic approach to microcephaly in childhood: a two-center study and review of the literature. *Dev. Med. Child Neurol.* 56, 732–741. <https://doi.org/10.1111/dmcn.12425>.
- Vuotto, S.C., Krull, K.R., Li, C., Oeffinger, K.C., Green, D.M., Patel, S.K., Srivastava, D., Stovall, M., Ness, K.K., Armstrong, G.T., Robison, L.L., Brinkman, T.M., 2017. Impact of chronic disease on emotional distress in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer* 123, 521–528. <https://doi.org/10.1002/ncr.30348>.
- Wagle, R., Song, Y.-H., 2020. Ionizing radiation reduces larval brain size by inducing premature differentiation of *Drosophila* neural stem cells. *Biochem. Biophys. Res. Commun.* 523, 555–560. <https://doi.org/10.1016/j.bbrc.2019.12.047>.
- Wilder, R.T., Flick, R.P., Sprung, J., Katusic, S.K., Barbareis, W.J., Mickelson, C., Gleich, S.J., Schroeder, D.R., Weaver, A.L., Warner, D.O., 2009. Early exposure to anesthesia and learning disabilities in a population-based birth cohort. *Anesthesiology* 110, 796–804. <https://doi.org/10.1097/01.anes.0000344728.34332.5d>.
- Willard, V.W., Klosky, J.L., Li, C., Srivastava, D.K., Brinkman, T.M., Robison, L.L., Hudson, M.M., Phipps, S., 2017. The impact of childhood cancer: Perceptions of adult survivors. *Cancer* 123, 1625–1634. <https://doi.org/10.1002/cncr.30514>.
- Wintermark, M., Lev, M.H., 2010. FDA investigates the safety of brain perfusion CT. *AJNR Am. J. Neuroradiol.* 31, 2–3. <https://doi.org/10.3174/ajnr.A1967>.
- Winther, J.F., Kenborg, L., Byrne, J., Hjorth, L., Kaatsch, P., Kremer, L.C.M., Kuehni, C.E., Auquier, P., Michel, G., de Vathaire, F., Haupt, R., Skinner, R., Madanat-Harjuoja, L. M., Tryggvadottir, L., Wesenberg, F., Reulen, R.C., Grabow, D., Ronckers, C.M., van Dulmen-den Broeder, E., van den Heuvel-Eibrink, M.M., Schindler, M., Berbis, J., Holmqvist, A.S., Gudmundsdottir, T., de Fine Licht, S., Bonnesen, T.G., Asdahl, P.H., Bautz, A., Kristoffersen, A.K., Himmelslev, L., Hasle, H., Olsen, J.H., Hawkins, M.M., 2015. Childhood cancer survivor cohorts in Europe. *Acta Oncol.* 54, 655–668. <https://doi.org/10.3109/0284186X.2015.1008648>.
- Wu, P.H., Coultrap, S., Pinnix, C., Davies, K.D., Taylor, R., Ang, K.K., Browning, M.D., Grosshans, D.R., 2012. Radiation induces acute alterations in neuronal function. *PLoS ONE* 7, e37677. <https://doi.org/10.1371/journal.pone.0037677>.
- Yamada, M., Kasagi, F., Mimori, Y., Miyachi, T., Ohshita, T., Sasaki, H., 2009. Incidence of dementia among atomic-bomb survivors—Radiation Effects Research Foundation Adult Health Study. *J. Neurosci.* 281 (1–2), 11–14. <https://doi.org/10.1016/j.jns.2009.03.003>.
- Yamada, M., Landes, R.D., Hida, A., Ishihara, K., Krull, K.R., 2019. Effects of Demographic Variables on Subjective Neurocognitive Complaints Using the Neurocognitive Questionnaire (NCQ) in an Aged Japanese Population. *Int. J. Environ. Res. Public Health* 16. <https://doi.org/10.3390/ijerph16030421>.
- Yamada, M., Landes, R.D., Mimori, Y., Nagano, Y., Sasaki, H., 2016. Radiation Effects on Cognitive Function Among Atomic Bomb Survivors Exposed at or After Adolescence. *Am. J. Med.* 129, 586–591. <https://doi.org/10.1016/j.amjmed.2015.09.002>.
- Yamada, M., Sasaki, H., Kasagi, F., Akahoshi, M., Mimori, Y., Kodama, K., Fujiwara, S., 2002. Study of cognitive function among the Adult Health Study (AHS) population in



- Hiroshima and Nagasaki. *Radiat. Res.* 158, 236–240. [https://doi.org/10.1667/0033-7587\(2002\)158\[0236:socfat\]2.0.co;2](https://doi.org/10.1667/0033-7587(2002)158[0236:socfat]2.0.co;2).
- Yamada, M., Sasaki, H., Mimori, Y., Kasagi, F., Sudoh, S., Ikeda, J., Hosoda, Y., Nakamura, S., Kodama, K., 1999. Prevalence and risks of dementia in the Japanese population: RERF's adult health study Hiroshima subjects. *Radiation Effects Research Foundation. J. Am. Geriatr. Soc.* 47, 189–195. <https://doi.org/10.1111/j.1532-5415.1999.tb04577.x>.
- Yang, L., Yang, J., Li, G., Li, Y., Wu, R., Cheng, J., Tang, Y., 2017. Pathophysiological Responses in Rat and Mouse Models of Radiation-Induced Brain Injury. *Mol. Neurobiol.* 54, 1022–1032. <https://doi.org/10.1007/s12035-015-9628-x>.
- Yasuda, T., Aoki, K., Matsumoto, A., Maruyama, K., Hyodo-Taguchi, Y., Fushiki, S., Ishikawa, Y., 2006. Radiation-induced brain cell death can be observed in living medaka embryos. *J. Radiat. Res.* 47, 295–303. <https://doi.org/10.1269/jrr.0617>.
- Zeltzer, L.K., Lu, Q., Leisenring, W., Tsao, J.C.I., Recklitis, C., Armstrong, G., Mertens, A. C., Robison, L.L., Ness, K.K., 2008. Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study. *Cancer Epidemiol. Biomarkers Prev.* 17, 435–446. <https://doi.org/10.1158/1055-9965.EPI-07-2541>.