CHAPTER 8

Summary & General Discussion
Summary

Objective
Pediatric lymphoid malignancies are types of cancer such as acute lymphoblastic leukemia (ALL) and lymphoma. Their incidences peak around the age of 2-5 years. Prophylaxis to prevent relapses in the central nervous system used to consist of both intrathecal chemotherapy (CT) and cranial radiation therapy (CRT). The neurotoxic side-effects of prophylactic CRT became apparent around the 1980s, after which it was largely abolished and replaced with chemotherapy such as high-dose methotrexate and intensification of the intrathecal CT. Although regarded less neurotoxic, CT can cause late effects as well. As survival rates have increased from 50% in the 1970s to almost 90% nowadays, these neurocognitive late effects, and their effect on quality of life, have gained considerable importance. In order to better understand long-term survivors’ current needs, late effects and their underlying mechanisms need to be studied. Additionally, late effects of current treatments need to be anticipated. Although not standardly used in treatment for ALL anymore, CRT is still applied in some cases of relapsed ALL, e.g., where total body irradiation is used in the conditioning regimen before allogeneic stem cell transplantation, and, usually in higher doses, in the treatment of some brain tumors.

Late effects in middle adulthood have been sparsely described so far. Most studies regarding late effects have focused on the first 10–15 years after treatment. This thesis however, describes late effects in CRT-treated survivors ca. 25 years after treatment, and in CT-treated survivors approximately 20 years after treatment. These survivors, treated according to the last protocols using CRT, and the first protocols containing CT only, represent one of the first cohorts of considerable size that reached middle adulthood. In this stage of life, other types of problems than those seen in childhood and adolescence may emerge. Currently, concerns are
being raised about the development of neurocognitive deficits in the aging brain. This thesis describes late effects of treatment on brain function, using assessment of executive functions and sensitive neuroimaging methods.

**Methods**

Executive function and its neural substrate were assessed in 50 survivors of childhood lymphoid malignancies treated with CRT (average age at assessment (AaA) 31.1 ± 4.9 years, age at diagnosis (AaD) 5.6 ± 3.8 years), 58 survivors treated with CT only (AaA 26.8 ± 4.9 years, AaD 5.2 ± 3.4 years), and 58 controls (AaA 26.3 ± 5.8 years) who were siblings, partners, or friends of the survivors. These controls were preferred because of the likelihood of having similar socioeconomic status to controls. Also, survivors were probably more inclined to participate in the study because they could undergo the assessments and travel to the hospital together with a familiar person.

Executive function was evaluated with subtests of the Amsterdam Neuropsychological Tasks (ANT) program assessing speed and accuracy of information processing, working memory, executive control of visuomotor performance, inhibition, and cognitive flexibility. Resting state eyes-closed magnetoencephalography (MEG) recordings were obtained and used to calculate relative spectral power in the δ, θ, α1, α2, β and γ frequency bands, indicating intrinsic brain activity defined by the organization of neural circuitry and the properties of the neurons. Differences in Fractional Anisotropy (FA) - a diffusion tensor imaging (DTI) measure describing white matter (WM) microstructure - were analysed using whole brain voxel-based analysis. Questionnaires were completed on physical health (RAND-36), mood states (POMS), fatigue (MFI-20), and cognitive failures (CFQ). Differences between both treatment groups and controls were
assessed, and neuropsychological task performance was correlated with spectral power outcomes, fractional anisotropy, and self-report scores

**Results**

The CRT-treated survivors showed significantly decreased response speed, irrespective of the task at hand. Furthermore, we found deficits in working memory capacity, inhibition, cognitive flexibility, executive visuomotor control, and sustained attention (Chapter 2). Female survivors performed worse than male survivors and controls on executive visuomotor control. More specifically, 41% of female CT-treated survivors and 50% of female CRT-treated survivors scored in the abnormal range (>1.5 SD) on executive visuomotor control, versus 14% of male CT-treated survivors, 15% of male CRT-treated survivors, 4% of male controls, and 6% of female controls (Chapter 2 & 3).

The CT-treated group reported more mental fatigue than controls, whereas the CRT-treated group reported significantly worse scores on physical functioning, role limitations due to physical health, energy, general health, physical fatigue, mental fatigue, and achieved a lower educational level (Chapter 4). Worse executive visuomotor control and smaller visuospatial sequential working memory capacity were generally associated with worse physical functioning, more role limitations due to physical health, and more physical and mental fatigue. In female survivors together, a remarkably strong correlation was found between executive visuomotor performance and role limitations attributed to physical health, but not in male survivors or controls. No associations were found between EF deficits measured with the ANT, and cognitive failures reported on the CFQ (Chapter 5).

MEG showed that, in CRT-treated survivors, relative θ power was increased (statistical trend) and α2 power was significantly decreased. Executive visuomotor
control was significantly associated with the deviating regional θ and α2 powers. Furthermore, a significant association between decreased regional α2 power and less attentional fluctuations, i.e. more stable sustained attention, was found for CRT-treated survivors as well as controls. CT-treated survivors displayed a power spectrum similar to controls, except for a significantly increased level of left frontal α2 power. The CT-treated group did not show the correlation between α2 power and more stable sustained attention that was visible in controls and CRT-treated survivors. The increase in left frontal α2 power did not correlate with other neuropsychological outcomes either, which were in the normal range except for executive visuomotor control. Possibly, the increased α2 power represents compensatory activity (Chapter 6).

In CRT-treated survivors, older age was associated with worse performance on executive visuomotor control and inhibition. CRT-treated survivors demonstrated significantly decreased FA compared to controls in frontal, parietal, and temporal WM tracts. Trends for lower FA were seen in the CT-treated survivors. Decreases in FA correlated significantly with neuropsychological dysfunction, especially in executive visuomotor control. In contrast to the CT group and controls, the CRT group showed a steep decline of FA with age at assessment. Cranial irradiation at a younger age and higher dosage of CRT were associated with worse outcome of WM integrity (Chapter 7).

Conclusions
CRT-treated survivors showed significantly worse cognitive scores than controls and reported lower QoL in multiple domains. The neuropsychological deficiencies currently present, combined with the tendency towards global slowing of brain oscillatory activity, and the tentatively decreasing quality of WM with increasing
age, suggest that the irradiated brain is aging faster, and CRT-treated survivors could be at increased risk for early-onset dementia.

No signs of accelerated aging of the brain were found in CT-treated survivors, and late neurocognitive effects seemed mild in this group. Although WM quality was slightly decreased, no association with increasing age was seen, and the MEG power spectrum did not show signs of aging either. The CT-treated survivors only showed a deficiency in executive visuomotor control, but this deficit was highly prevalent in women. The deficit seemed to reduce efficiency in daily functioning, in female CT-treated and CRT treated survivors. Both groups also reported heightened levels of mental fatigue.

The ANT task Pursuit, measuring executive visuomotor control, turned out to be a sensitive measure for compromised executive function. It also correlated with θ and α2 power, white matter integrity, and self-reports of role limitations. Furthermore, it demonstrated the effect of accelerated aging in CRT-treated survivors. Especially in female survivors, a clinically significant deficiency in executive visuomotor control was highly prevalent, and associated with role limitations in daily life. Future research should explore the suitability, in terms of specificity and sensitivity, of tasks that measure executive visuomotor control as quick, cheap, and easy to administer screening instruments for executive function deficits and decline in long-term survivors. It is important to identify long-term survivors with potential executive function deficits, so they can be referred for more extensive neuropsychological assessment. Survivors are aided by acknowledgment of late neurocognitive effects, because accurate diagnostics are a prerequisite to determine suitable interventions, but also to understand and accept limitations that cannot be remediated.
**General Discussion**

The assessment with the Amsterdam Neuropsychological Tasks program (ANT) demonstrated that our group of 50 long-term survivors treated with CRT besides intrathecal chemotherapy performed significantly worse than controls on general response speed, visuospatial and sequential working memory capacity, sustained attention, inhibition, and cognitive flexibility. Additionally, women showed a salient deficit in executive visuomotor control, not observed in men. Of female survivors, 50% performed worse than 1.5 SD below average on this function. Normally, men and women do not perform differently on the ANT tasks.

Higher doses of CRT were associated with worse executive visuomotor control. Younger age at diagnosis and older age at assessment were significantly associated with lower response speed, and poorer inhibition and executive visuomotor control. Notably, half of the female survivors already performed in the abnormal range at the time of our assessment, in particular on executive visuomotor control, and this deficit rate may rise, possibly accompanied by an increasing impact on the quality of daily life. Declining executive control, as well as the potential deterioration of inhibition, may influence behavioral and emotional self-regulation. For example, disinhibition could become a noticeable symptom. This, in turn, could have an impact on the demand on (neuro)psychological health care. It is unclear however, how below average performance on executive visuomotor control influences daily life. Selectively in the group of *female* survivors of our study, worse executive visuomotor control was significantly associated with more role limitations due to physical health. Presumably, deficiencies in executive visuomotor control result in reduced efficiency in daily activities, like being able to spend less time on necessary tasks, accomplishing less than desired, and having to invest more effort, attributed by these women to limitations due to physical health. This association has also been reported in multiple sclerosis patients.\(^1\) As this is the first
study to report the association in cancer survivors, and uses a different paradigm, future research should attempt to replicate this finding. Confirmation of this result would provide valuable information for female survivors reporting these symptoms, and could facilitate acceptance of experienced limitations. In research, it could be a starting point for the development of effective interventions aimed at improvement of quality of life.

**Accelerated aging**

Our assessments with MEG and DTI revealed that survivors treated with CRT showed signs compatible with accelerated aging of the brain. The DTI study demonstrated a steep decline of white matter integrity with increasing age, not present in controls or CT-treated survivors in the same range of age. However, a similar pattern of decline is observed in healthy people in an older age range. The DTI results also revealed that decreased white matter integrity was mainly localized in brain areas which are also affected in Alzheimer’s disease. The MEG power spectrum displayed similarities with that of Alzheimer patients. The increase in $\theta$ and decrease in $\alpha_2$ indicated a tendency towards global slowing of brain oscillatory activity. These same indicators have been found in other types of neurological disorders, but also in the general population of older age. The pattern is thought to reflect aging in the form of vascular or fibrillary degeneration.\(^2\) Together with the declining executive control in CRT-treated survivors, this strongly suggests a pattern of accelerated aging of the brain. As the risk of developing dementia in the general population rises to 40% in 80-year old people, CRT-treated survivor might reach this risk level earlier in life, translating into a higher risk of early-onset dementia.

Both white matter integrity and deviating power in the alpha and theta bands were significantly associated with executive visuomotor control. This suggests that deficiencies in executive visuomotor control might be caused by decreasing
integrity of white matter. White matter is formed by glial cells (oligodendrocytes) forming myelin sheets around axons. Decreased white matter integrity compromises speed and effectivity of neuronal signal transport through axons. The electrical currents that transport information between neurons create a magnetic field that would scramble the electrical signals in neighboring axons if they are not sufficiently isolated by myelin. Other glial cells (astrocytes) serve to clean up debris and nourish neurons by receiving glucose from capillary blood and breaking it down to lactate, which is more easily metabolized by neurons. The astrocytes also have a protective role for oligodendrocytes, so if the first are compromised, this could also lead to decreased integrity of the myelin formed by oligodendrocytes.  

Glial cells are capable of mitosis (cell division and replication), while mature neurons do not proliferate any more after birth. Mitosis is very sensitive to radiation exposure. Kudo et al. prepared glial cells and neurons from the fetal rat brain in vitro and exposed them to radiation. Glial cells and neurons were both radiosensitive at seven days in vitro. After 21 days in vitro however, the glial cells were radiosensitive, but neurons were not anymore, indicating that neurons become radioreistant with maturation, while proliferating glial cells remain radiosensitive. The radiation causes DNA damage, resulting in an inability to grow or divide, and eventually in death. This is precisely the principle behind cancer treatment: the cancer cells will not grow or divide anymore.

Another cell type that most probably endures the effects of cancer treatment is the progenitor cell. Progenitor cells are capable of differentiating into various kinds of other cell types, including glial cells and neurons. However, they cannot, contrary to stem cells, divide and reproduce indefinitely. Each time they divide, the ends of the chromosomes (telomeres) shrink a bit. After dozens of divisions, when the telomere decrease has reached a certain length, cells will go into senescence characterized by the inability to divide, often followed by apoptosis. Stem cells
counteract this effect by using proteins capable of repairing the chromosome ends, but progenitor cells do not have these proteins. Cell senescence can be evoked by free radicals, UV light, radiation, overexpression of oncogenes and chemotherapeutic drugs, all causing DNA damage. Reduction in progenitor cells and shortening of telomeres are also seen in normal aging. Apparently, this process is accelerated or induced prematurely by the exposure to radiation. Animal studies suggest that proliferative activity of neuronal cell precursors of the dentate gyrus of the hippocampus is highest shortly after birth, and declines steadily during aging. The higher proliferation rate at younger age is probably the reason why radiation at younger age is associated with worse late effects on the brain. It inhibits neurogenesis, an effect that will continue to affect restorative capacity of the brain for life. Postmortem analysis of hippocampal neurogenesis in medulloblastoma survivors 2-23 years after the completion of radiation therapy, revealed a tenfold lower rate of neurogenesis compared with age- and sex-matched controls.

Besides a reduction in the amount of progenitor cells, the chromosomes of the surviving cells become damaged. The genomic instability caused by telomere dysfunction can make these cells more prone to become cancerous. Furthermore, chromosomal instability of irradiated cells will propagate through the offspring of these cells for decades, which explains why the risk of secondary brain tumors long after treatment is substantially elevated in this population. Also other proliferating cell types are affected. Schneider et al. (1993) did a longitudinal study of thyroid cancer after radiation exposure to the head or neck in childhood. They concluded that the effects of radiation must last at least 40 years, because the dose-response relationship they observed remained constant for that long. They reasoned that if the effects of radiation would have ceased, then the latest incidences of thyroid cancers would not show a dose-response relationship
anymore. Veiga et al. (2016) did a follow-up on Schneider’s study and concluded that effects of radiation were still present 50 years after treatment.\textsuperscript{13}

Chemotherapeutic agents are also suspected to induce senescence.\textsuperscript{7,14} Buttiglieri et al. (2011) exposed human stem cells to doxorubicin and observed double stranded DNA breaks and progressive telomere shortening. In our study however, we could not confirm accelerated aging in our CT-treated survivors, but it would be premature to rule it out. A trend for decreased FA was found in our CT-treated group. There was, however, no correlation with increasing age. Yet animal studies have demonstrated CT to be capable of delayed degenerative damage to WM.\textsuperscript{15} The effect might be more subtle, or slower, than the aging effect of CRT, and would perhaps take several decades to show. The development of WM quality should therefore be monitored for several more decades in CT-treated survivors to shed light on this matter.

Progressive decline of memory function has been associated with (radiation induced) inhibition of hippocampal neurogenesis.\textsuperscript{9} Animal studies have demonstrated that exposure to therapeutic doses of irradiation results in increased apoptosis, decreased cell proliferation, and decreased neuronal differentiation in the neurogenic region of the hippocampus.\textsuperscript{16} Whereas working memory deficits have been confirmed in our CRT-treated survivors, their most salient deficit, also present in CT-treated survivors, was in executive visuomotor control. This function is presumably supported by the prefrontal cortex, which has been studied less frequently in this context.\textsuperscript{17} Functioning of the prefrontal cortex seems to be extra vulnerable in comparison with other brain areas. Supposedly, this is because it is dependent on both the integrity of the neurons in the prefrontal cortex and the white matter integrity, challenged by (progressive) glial cell damage, of connective pathways used in functional networks, especially those involved in executive functions. Our DTI study demonstrated the highest correlation between executive
visuomotor control and white matter integrity in a cluster located in the superior longitudinal fasciculus, a major white matter tract subserving fronto-parietal integration and important in functional networks reflecting operational executive functions, but also making a prominent contribution to processing speed.\textsuperscript{18} The prefrontal cortex as well as these long distance white matter tracts are last to myelinate in brain development, so additionally, their axons remain vulnerable longer than in other brain regions. All these effects added together apparently make the functioning of the prefrontal cortex especially vulnerable to CNS-directed cancer treatment.

**Genetic risk factors**

A question of high clinical relevance is whether vulnerability to (late) effects of treatment can be predicted by genetic factors. One of them seems to be female gender, as confirmed by the current study. Recent research by Meeske et al. (2015) demonstrated that female ALL patients had greater risk for developing both acute and long-term treatment-related toxicities.\textsuperscript{19} They reported that female patients had a 1.5 times higher chance of developing any grade 3 (severe) or 4 (unacceptable) toxicities during treatment than male patients, among which nervous system toxicities (OR = 1.6). Furthermore, females were 2.8 times more likely to die of high-risk treatment-related causes such as infection.

Another genetic risk factor might be the Apolipoprotein E-epsilon 4 (APOE ε 4) genotype.\textsuperscript{20} The protein encoded by APOE ε 4 plays a role in the breakdown (catabolism) of triglyceride-rich lipoprotein constituents.\textsuperscript{21} A complex interaction of these lipoproteins with their receptors forms the basis for the metabolic regulation of cholesterol, for example. Carrying this allele has been associated with higher risk for adverse cognitive effects of cancer therapy.\textsuperscript{22} Ahles et al. (2003) discovered that a group of long-term survivors of breast cancer and lymphoma treated with standard-dose chemotherapy and carrying the APOE ε 4 allele demonstrated
significantly lower scores on psychomotor functioning, spatial ability, and visual memory than survivors not carrying the allele. The APOE ε 4 allele has also been associated with accelerated telomere shortening, indicating accelerated cell aging. It is also known as the largest genetic risk factor for late-onset Alzheimer's disease. Lyall et al. (2014) suggested a mediating role of white matter tract integrity in several significant associations between APOE and cognitive aging. Moreover, there seems to be an interaction between carrying the APOE Ε 4 allele and female gender, not only regarding increased risk of developing age-related cognitive decline and Alzheimer's disease, but also regarding susceptibility to radiation induced cognitive impairment. Involvement of the APOE ε 4 allele has been implied in increased susceptibility to chemotherapy as well. Acevedo et al. (2008) described how radiation-induced cognitive impairment in female mice expressing APOE ε 4 involved an important role of testosterone and androgen receptor expression. Jacobs et al. (2013) mentioned that hormone replacement therapy had a modulatory effect on the association between carrying the APOE ε 4 allele and telomere shortening in healthy post-menopausal women. APOE ε 4-carriers who went off their hormone replacement therapy for two years showed telomere shortening comparable with ten years of additional aging, whereas non-carriers did not. These findings suggest important roles of APOE ε 4 and hormones in the frequently described female vulnerability to late effects of cancer treatment. Perhaps the mediating role of hormones and androgen receptor expression can be utilized pharmacologically in future treatment of pediatric lymphoid malignancies to provide girls with a buffer.

**CRT versus CT**

Cognitively, the outcomes after CT are far more favorable than after CRT. While we observed several deficiencies in CRT-treated survivors, in CT-treated survivors cognitive impairment was limited to one domain, and only in female survivors.
Overall, the cognitive profile of the CT-treated group was significantly better than that of the CRT-treated group, indicating that executive function can be spared when CRT is not deployed.

When the CRT-treated and CT-treated survivors were directly compared with each other regarding QoL, the CT-treated survivors only valued their physical functioning and limitations due to physical health significantly higher. The CT-treated group also achieved a significantly higher educational level. On the other scales, their scores fell in between the scores of the CRT-treated survivors and the scores of controls. Similar outcomes were reported by Blaauwbroek et al. (2007), who only found a significantly better general health perceived by CT-treated than CRT-treated survivors. Theoretically, the scores of the CT group on energy/fatigue, general health, and physical fatigue could become significantly different from both controls and CRT-treated survivors in larger samples.

In the CT-treated group, the MEG power spectrum was similar to that of controls. Although detrimental effects of CT on WM and neuropsychological function were not completely absent, they were observed to be mild compared to CRT, while CT is equally effective in terms of survival and recurrence rates after ALL. This warrants a recommendation to only apply CRT as a last resort.

**Methodological considerations**

Our methodology demonstrated that age at diagnosis and age at assessment have independent effects on cognitive outcome in survivors. By using time since diagnosis in studying the effects of aging, the significances of both the aging effect and the effect of age at diagnosis are suppressed. Therefore, the use of age at assessment controlled for age at diagnosis is recommended for studying effects of aging. This is probably a principle applicable to other areas of research as well.
A strength of our research is the use of a control group consisting of siblings, partners and friends, which enabled us to compare raw scores instead of only using normative data. A limitation is that the data are cross-sectional. The progression of cognitive deficits should be studied longitudinally to confirm the notion of premature (accelerated) aging.

**Clinical implications**

Professionals should be aware of the fact that there is an increased, and growing, chance of structural abnormalities in the brain, such as meningiomas, cavernomas, or brain tumors that could be a differential cause of cognitive complaints.\(^{11,32}\) As discussed earlier, the effect of radiation on proliferating cells continues long after treatment, and can be carcinogenic. In our cohort of 135 CRT-treated survivors, 12 survivors were excluded because of structural brain abnormalities, and three meningiomas were encountered during our MRI acquisition (11% in total (see Figure 1, Chapter 3)). Whereas physicians working at late effects clinics are well aware of this increased risk, most (neuro)psychologists are probably not. If, for some reason, a survivor does not turn to the late effects clinic, but to a (neuro)psychologist instead, this clinician should ideally be aware of the increased risks of structural brain abnormalities and accelerated aging. It should be debated whether this topic should be addressed at their education.

Currently, Dutch guidelines for follow-up of long-term childhood cancer survivors do not recommend specific screening for secondary tumors, except for secondary mammacarcinoma, or when there is an indication.\(^{33}\) In the absence of neurological problems, follow-up with neurological assessment is only recommended after radiation of a central nervous system tumor, but not specifically after prophylactic cranial irradiation in treatment of lymphoid malignancies. Secondary tumors caused by cranial irradiation are most likely slowly growing meningiomas, so the risk of a fast-growing malignancy after prophylactic cranial irradiation is probably
smaller than after a primary brain tumor. It is debatable whether screening, with
costly neuroimaging methods, for slowly growing tumors is helping the patient.
Frequently, the meningioma is not causing any neurological or neuropsychological
problems, so treatment is often expectant. However, survivors with
neuropsychological deficits often do not voice cognitive complaints as
demonstrated by this study’s research with the Cognitive Failures Questionnaire.
Therefore, it should be considered to include a neurological assessment in the
periodic follow-up protocol conform the protocol after radiation of a central
nervous system tumor. Screening for indications could help physicians to weigh the
pros and cons of referral for neuroimaging for (and with) each individual patient.

For all childhood cancer survivors, neuropsychological anamnestic follow-up is
recommended. Survivors treated with cranial irradiation are also recommended to
be assessed with the Kaufman – Short Neuropsychological Assessment Procedure
(K-SNAP) every three years until three subsequent assessments are normal.
Considering the possibility of radiation effects not becoming visible until several
decades later, and the possibility of early-onset dementia, this last part of the
guideline is recommended to be revisited. Lifelong periodic neuropsychological
assessment should be considered. Furthermore, instead of comparing K-SNAP
scores to normative data, subsequent test scores of the same person should also
be compared with each other. People can perform within the normal range three
times in a row, but that does not rule out the possibility that the fourth score is
below cut-off, if the first three scores form a declining pattern. A decline in raw
scores can be normal for some cognitive functions, but norm scores, corrected for
normal aging effects, should remain stable. In other words, screening should not
only be for cognitive deficits, but also for cognitive decline. It is however unknown
whether the K-SNAP is sensitive enough to detect this type of cognitive decline.
The Pursuit task of the ANT program turned out to be a sensitive assessment tool
in this respect. A below normal performance on executive visuomotor control
might warrant assessment of other functions requiring executive control, like inhibition. A task like Pursuit takes just a few minutes and could be administered by clinicians from many disciplines. It would therefore be a quick, cheap, and easy screening tool. But first, sensitivity and specificity of such a tool should be researched.

In case of abnormal K-SNAP scores, the current guidelines advise referral to a neuropsychologist for further evaluation. And although many clinicians would already be suspicious about structural abnormalities in the brain and consider additional neurological assessment including neuroimaging, the current guidelines do not specifically recommend neurological screening in case of neuropsychological symptoms. Perhaps this should be revisited too.

Even when medical treatment is not (immediately) necessary and neuropsychological treatment is unavailable, good diagnostics of neuropsychological deficits can be of great value to survivors. Often, sole acknowledgment and explanation of the causes of their symptoms facilitates acceptance and coping.

**Suggestions for future research and development of interventions**

All outcomes of this dissertation are described to need replication by confirmatory studies, ideally using larger samples. The methodology however, has proven to be very helpful in revealing the underlying mechanisms of cognitive late effects in survivors of pediatric cancer survivors. The pattern of accelerated aging that was revealed, warrants longer follow-up of the current cohorts of long-term survivors. It should be studied, for example, if increased rates of (early-onset) dementia will indeed occur. Furthermore it should be investigated whether genetic factors play a (predictive) role in this.
Several researchers have turned to the venue of cognitive remediation in this population of survivors.\textsuperscript{34,35} Several other intervention strategies, educational and pharmacological approaches, have been reviewed by Castellino et al. (2014).\textsuperscript{36} The problem with the cognitive interventions is that effects are small and transfer to daily life is questionable.\textsuperscript{37} A recent review concluded that still very few conclusions can be drawn.\textsuperscript{38} Therefore, more extensive research into the value of cognitive remediation is recommended. According to Olson and Sands (2015), research should focus on which combinations of interventions establish significant results, and which factors moderate a positive change, be it demographic, medical or neuropsychological.\textsuperscript{38} Also, questions remain about when to initiate interventions, and which measures should be used to assess their effects.

An intervention strategy with very promising preliminary findings is physical activity.\textsuperscript{39} Mostly in animal studies, exercise has been demonstrated to attenuate age-related reduction in adult hippocampal neurogenesis, mediated by enhanced expression of a certain protein in the dentate gyrus.\textsuperscript{40} Laitman and John (2005) hypothesize that APOE is involved in the protective effects of exercise and has a regulating role in the neurovascular integrity during aging.\textsuperscript{39} Research in humans by Erickson et al. suggested that hippocampal volume loss in late adulthood could be reversed by aerobic exercise training, which was accompanied by improved memory function.\textsuperscript{41} The increase in volume was accompanied by an increase in mediators of neurogenesis in the dentate gyrus. Similar findings were reported by Brandt et al. (2010)\textsuperscript{42} and Nam et al. (2014).\textsuperscript{40} Colcombe et al. (2004) described that plasticity and resilience in the prefrontal cortex were enhanced by regular moderate aerobic exercise and that executive functions improved, probably by increasing the blood flow to the prefrontal cortex.\textsuperscript{43} A meta-analysis by Groot et al. (2016) confirmed the beneficial effect of aerobic exercise on cognitive function in dementia patients with both Alzheimer’s Disease (AD) diagnoses and non-AD dementia diagnoses.\textsuperscript{44} Guiney and Machado (2013), as well as Colcombe et al.
(2004), reported that also healthy populations, from young to old, benefit from regular aerobic exercise to optimize their executive functions.\textsuperscript{43,45} Several recent studies have indicated that aerobic activity might slow the progression of age-related neural changes, and reduce the risk for cognitive decline.\textsuperscript{46} The meta-analysis of Groot et al. \textsuperscript{44} found that the beneficial effect was independent of the exercise frequency, the average duration of exercise per week of the so called low frequency interventions being $93 \pm 33$ (range 40-120) minutes, versus $183 \pm 185$ (range 40-840) minutes for the high frequency interventions. Future research should explore the minimum thresholds for frequency and intensity of physical exercise necessary to achieve cognitive improvement in long-term cancer survivors.

Also the role of APOE $\varepsilon$ 4 and its interaction with hormones should be further explored. More insights are needed into the effects of taking (contraceptive) hormones, pubertal status during treatment, and menopause in female survivors of childhood cancer. Furthermore, the physiological mechanisms involved in female vulnerability need to be unraveled, which will hopefully lead to new interventions protecting future female patients against the adverse effects of chemotherapy and radiation.
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