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.