CHAPTER 1

General Introduction
**Lymphoid malignancies in childhood**

Pediatric lymphoid malignancies are types of cancer such as acute lymphoblastic leukemia (ALL) and lymphoma. ALL is an acute type of blood cancer (leukemia) characterized by the overproduction and accumulation of cancerous, immature white blood cells, called lymphoblasts. It causes symptoms such as anemia, fever, unexplained bruising, and general weakness and fatigue. The symptoms result from a lack of normal blood cells (red blood cells, leukocytes, and platelets), which are crowded out by malignant white blood cells. ALL is the most common type of childhood malignancy. In the Netherlands, in 2013, ALL accounted for 21% of cancers occurring in childhood and adolescence. The incidence peaks around the age of 2-5 years. Lymphoblastic lymphoma refers to a group of blood cell tumors that develop from lymphatic cells and cause symptoms often similar to ALL. Lymphoblastic lymphoma accounted for about 5% of childhood cancers in the Netherlands. These types of cancer are deadly if not treated. ALL and specific types of lymphoma require similar treatment. The first stage is to induce remission by rapidly killing the malignant cells using a combination of chemotherapeutic agents such as prednisolone or dexamethasone, vincristine, and asparaginase. Then follows a stage of consolidation/intensification aimed at further reducing the cancerous cells and at the same time avoiding the production of new cancer cells. After that, a period of maintenance therapy follows, in which any residual malignant cells are killed which would cause relapse if not eradicated. The remission induction and consolidation stages include a form of central nervous system (CNS) prophylaxis, targeted at dormant cancer cells in the meninges, which can be achieved via cranial or craniospinal irradiation and/or intrathecal chemotherapy, mostly including prednisolone, cytarabine and/or methotrexate.
Late effects of treatment

Treatment for pediatric lymphoblastic malignancies has taken a tremendous flight over the last decades. Survival chances have increased from 50% in the 1970s to almost 90% in the beginning of the 21st century.4,5 With the increase in the number of survivors, long-term quality of life has become an issue of increasing importance.6 Late effects of treatment, both psychological and medical, can jeopardize the quality of life. Much of the literature on late effects has been restricted to the first ten years of survival.7,8 But now the first sizable cohorts to survive pediatric lymphoblastic malignancies for over 20 years are emerging, meaning that late effects of treatment can be studied in middle adulthood for the first time.9 As this stage of life imposes different challenges on people than childhood and adolescence, new types of problems are expected to emerge, related to e.g. independent living, fertility, and employment. Besides the various medical and psychosocial late effects of childhood cancer treatment, cognitive late effects can occur due to the CNS-directed prophylactic therapy. These effects on the brain have been studied in the first decade after treatment, but hardly after 20-25 years. The current study is one of the first to assess this neurotoxicity this long after treatment.

In the Netherlands, the Dutch Childhood Oncology Group (DCOG), or Stichting Kinderoncologie Nederland (SKION) in Dutch, formerly known as the Dutch Childhood Leukemia Study Group (DCLSG), develops and evaluates treatment protocols. Cranial radiotherapy (CRT) as CNS-prophylaxis was part of the standard treatment protocols for ALL until 1984. Around that time, the detrimental effects of CRT on healthy brain tissue became evident, and alternative treatments consisting of chemotherapy (CT) only were developed, achieving similar or even better chances of survival.10,11 Chemotherapeutic agents such as methotrexate (MTX), were considered relatively safe at that time, but over the years reports
accumulated that CT could cause cognitive late effects too. E.g. Raymond-Speden et al. (2000) reported that not only irradiated survivors, but also survivors treated with CT only demonstrated lower levels of intellectual and academic functioning than healthy controls. Furthermore, Espy et al. (2001) reported a deterioration of visuomotor integration after CT. Brain imaging demonstrated several cases of acute neurotoxicity (encephalopathy) after CT, but recovery from the structural damage shortly after the acute stage was often observed, and the consequences on the long term remained unclear. Reddick et al. (2005) reported that more courses and higher doses of MTX were associated with more acute cases of leukoencephalopathy. But 1.5 years after completion of the therapy, many changes had resolved. However, the long-term effects on neurocognitive functioning remained unclear.

**The current study**

The first objective of the current study, was to investigate the late neurocognitive effects of both the last DCLSG treatment protocol for ALL containing CRT (ALL-V, 1979-1984) and the first DCLSG treatment protocol consisting of CT only (ALL-VI, 1984-1988), described in Table 1. To increase the number of participants, also Belgian survivors were recruited who were treated with the Riehm protocol, similar to ALL-V, or the European Organization for Research and Treatment of Cancer (EORTC) trial 58831, similar to ALL-VI (see Table 1). To assess whether increased dosages of CT or CRT, such as applied when there is a high risk to relapse, caused more severe late effects, survivors treated with customized protocols based on ALL-V, ALL-VI, the Riehm protocol, EORTC trial 58832, and the BACOP protocol (Bleomycin, Adriamycin, Cyclophosphamide, Oncovin, and Prednisone; only when MTX IT or MTX IV was added) were recruited. High-risk treatment usually involved either high-dose MTX IV, or more gifts of MTX IT, or both. All these protocols were based on the Berlin-Frankfurt-Münster (BFM) protocol design with...
a duration of approximately 2 years. Survivors were recruited from the clinical cohorts of the Academic Medical Center and VU University Medical Center Amsterdam (The Netherlands) and the University Hospitals of Leuven (Belgium). Survivors who were willing to participate were requested to invite a control. Besides assessing the patterns of cognitive late effects of these protocols, this study aimed to investigate the underlying mechanisms in the brain of these late effects. More research was needed into the neural substrate of the cognitive complaints. After CRT, several structural abnormalities in the brain, such as secondary neoplasms and cavernomas, had been reported.\textsuperscript{19,20} However, after CT only, abnormalities detected by conventional imaging (structural MRI) had not consistently been found to correlate with clinical findings and neurocognitive status.\textsuperscript{21,22} Chu et al. (2003) could not establish structural white matter abnormalities, but did find cerebral metabolite changes indicating white matter changes after high-dose MTX.\textsuperscript{21} And WM abnormalities could be associated with poor performance on visuomotor integration, but not with attention or intelligence.\textsuperscript{22} Therefore, the need for more accurate and sensitive neuroimaging methods was felt. This study thereto used diffusion tensor imaging (DTI) to investigate white matter (WM) integrity, and magnetoencephalography (MEG) as a measure of brain activity.

**Cognitive sequelae**

CRT has been reported to cause (middle to) long-term neurocognitive deficits among survivors, such as lower intelligence, attention deficits, memory deficiency and cognitive slowing.\textsuperscript{23-26} From the literature on the potential adverse consequences of CT, it could be concluded that CT was not such a benign form of treatment, although its effects were observed to be more subtle than those after CRT.\textsuperscript{14,26,27} For example, Copeland reported a decline in visuomotor skills, but outcomes remained within the normal range.\textsuperscript{28}
**Table 1.** Standard-risk protocols for treatment of acute lymphoblastic leukemia between 1979 and

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<th>ALL V (NL)</th>
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<td><strong>Induction of remission</strong></td>
<td>6 x Vincristine 2 mg/m²/wk IV 14 x L-Asparaginase 200 E/kg/day IV (Group B: + 4 x Rubidomycine 25 mg/m²/wk IV) 28 x Prednisone 40 mg/m²/day OR</td>
<td>5 x Vincristine 1.5 mg/m² IV 21 x L-Asparaginase 5000 E/m² IV 1x Methotrexate 12 mg IT 4 x Daunomycine 30 mg/m² IV 26 x Prednisone 60 mg/m² OR</td>
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<td><strong>CNS Prophylaxis</strong></td>
<td>CRT 2500 Rad 5 x Prednisolone (DAF) 12.5 mg/m² IT 5 x Methotrexate 12.5 mg/m² IT</td>
<td>CRT 1800 Rad 28 x Prednisone 60 mg/m²/day OR 4 x Methotrexate 12 mg IT 16 x Cytarabine 75 mg/m² IV 2 x Cyclophosphamide 500 mg/m² IV 1 x Vincristine 1.5 mg/m² IV 28x 6-Mercaptopurine 60 mg/m²/day OR</td>
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<td><strong>Consolidation</strong></td>
<td>6 x Vincristine 2 mg/m²/wk IV 42x Prednisone 40 mg/m²/day OR</td>
<td>2 x Vincristine 1.5 mg/m² IV 21 x Dexamethasone 10 mg/m² OR 2x Methotrexate 12 mg IT 2 x Adriamycin 30 mg/m² IV 4 x L-Asparaginase 10.000 E/m² IV 8 x Cytarabine 75 mg/m² IV 14 x 6-thioguanine 60 mg/m² OR</td>
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<td><strong>Maintenance</strong></td>
<td>140 x 6-Mercaptopurine 50 mg/m²/day OR 17 x Methotrexate 30 mg/m²/wk OR</td>
<td>2 x Vincristine 1.5 mg/m² IV 28 x Prednisone 60 mg/m² OR (Group B: 4 x M 26 165 mg/m²)</td>
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**Citrovorum Factor**

ALL = acute lymphoblastic leukemia; NL = The Netherlands; BE = Belgium; EORTC = European Organization for DAF = Diadreson-F-Aquosum.
1989 in the Netherlands and Belgium.

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Research and Treatment of Cancer; m² = body surface; wk = week; IV = intravenous; IT = intrathecal; OR = oral;
More recent studies have steered the focus of interest to executive function (EF) deficits as neuropsychological sequelae of treatment with chemotherapy.29-33 Executive functions are defined as the processes necessary for controlling and coordinating independent, purposive, goal-directed behavior, necessary for complex cognitive tasks.34,35 Typical processes associated with EF are set-shifting and set-maintenance (switching between tasks), interference control and inhibition (focusing attention while ignoring distractions, suppressing unwanted responses), integration across space and time (e.g. navigation), planning (setting a goal and defining the steps to achieve it), and working memory (temporary storage capacity for current information). In 1986, Norman and Shallice introduced the Supervisory Attentional System (SAS) model.36,37 This model makes a distinction between routine behavior (thoughts and actions), and behavior in new circumstances, in terms of the degree of supervisory attention (attentional control) it requires. They describe the SAS as an executive monitoring system that is capable of initiating, consolidating, regulating, and inhibiting cognitive, language, motor and emotional processes under non-routine circumstances.38 The system is thought to be necessary for complex cognitive functions such as self-evaluation, planning, organization, problem solving, set-shifting, controlling impulses, attention, and strategic selection of behavior to reach desired goals.35 The SAS is involved in the executive component of working memory.39 The SAS encompasses sustained, selective, alternative, and divided attention.37,40

Working memory can be described as the ability to ‘hold something in mind’. In doing so, working memory provides short, temporary storage of information.41 Moreover, working memory can manipulate the information, e.g. calculating numbers.42 Baddeley (2003) introduced a model of working memory containing four components: the phonological loop, the visuospatial sketchpad, the episodic buffer, and the central executive.43 The phonological loop and the visuospatial sketchpad are two domain specific components that provide temporary storages
for phonological and visual material. The episodic buffer is a central factor in combining these components of working memory, and has an important role in forming a bridge between working memory and long-term memory.\textsuperscript{42} The central executive is thought to control attention and to regulate retrieval from long-term memory, and as such is comparable with the SAS model of Norman and Shallice.\textsuperscript{41}

Based on previous research involving assessment of executive functions in cancer survivors between one and nine years after treatment by Buizer et al. (2005ab), and Mennes et al. (2005),\textsuperscript{31-33} our instrument of choice was the program used by these authors, i.e. the Amsterdam Neuropsychological Tasks (ANT) program developed by De Sonneville.\textsuperscript{44,45} The ANT program has proven to be helpful in defining neurocognitive deficit profiles in various conditions associated with generally diffuse impact on the brain, such as phenylketonuria,\textsuperscript{46-48} multiple sclerosis,\textsuperscript{49} neurofibromatosis type 1,\textsuperscript{50,51} and attention deficit hyperactivity disorder (ADHD).\textsuperscript{52} ANT measures have also proven to be sensitive to changes in brain function as a result of medical interventions, such as methylphenidate treatment of ADHD,\textsuperscript{53,54} and dietary treatment of phenylketonuria.\textsuperscript{46,55-57} The program provides for highly standardized assessment and automated recording of speed and accuracy of information processing, i.e. the basic processes underlying the execution of complex cognitive processes such as sustained, focused, and divided attention, flexibility, inhibition and impulsivity, visuomotor control, and memory capacity.\textsuperscript{44} Task load associated with specific aspects of information processing and EF is manipulated by the program, to examine whether increased demands on these functions differentiate survivors from controls. In general, a significant interaction between the factors Task Manipulation and Group indicates that the effect of the increased demand on a particular cognitive function is different for each group. For example, an increase in memory load results in a higher increase in number of errors in patients than in controls. In the current study, we focused on complexity of information processing, working memory load,
executive control of visuomotor performance, inhibition, and cognitive flexibility, to bring out a neuropsychological profile with emphasis on executive functions.

The greatest gap in our knowledge regarding treatment-related EF deficits is a lack of understanding of the mechanisms that account for the observed changes. Evidence suggests that direct effects of chemotherapy and radiation on intracranial endothelial cells and brain white matter, as well as immunological mechanisms could be involved in the pathogenesis of central nervous system damage.58,59 A number of studies have focused on treatment-related structural brain damage.21,22,60-63 So far, abnormalities detected by conventional imaging (structural MRI) have not consistently been found to correlate with clinical findings and neurocognitive status.21,22,60,61,63,64

As the quality of EF is dependent on the integrity of functional networks of the brain, it was hypothesized that EF deficits are associated with disruptions of these networks. Brain networks associated with executive control include the anterior cingulate cortex and supplementary motor area, the orbitofrontal cortex, the dorsolateral prefrontal cortex (PFC), the ventrolateral PFC, portions of the basal ganglia and the thalamus.65-67 Brain imaging methods that provide information on connectivity in these networks may be more suitable than conventional imaging techniques to identify brain pathology underlying EF deficits. Magnetoencephalography (MEG) and diffusion tensor imaging (DTI) are such techniques. There is increasing evidence that DTI measures are more sensitive indicators of white matter pathology than conventional MRI measures, and correlate better with cognition, notably with tests of executive functions.68,69 MEG provides the temporal resolution not provided by DTI, by graphing the continuous encephalic electrical activity.
**Diffusion Tensor Imaging (DTI)**

DTI reveals brain connectivity by examining the orientation of myelinated fibers on a microstructural level.\(^{70}\) DTI quantifies the integrity of WM by assessing the restriction of randomly moving water molecules, reflected in the parameter fractional anisotropy (FA). In cerebrospinal fluid, diffusion of water molecules is the same in all directions, indicated by an FA of one. This state is called (full) isotropy. When the diffusion has preference for a certain direction, it is called (fractional) anisotropy. DTI quantifies the degree of directional preference of diffusion for each voxel of brain tissue. Damage to WM microstructures will result in lower FA, due to relatively more diffusion of water perpendicular to the fiber orientation.\(^{71}\) Significant differences in FA between cancer survivors - up to 10 years after treatment - and controls have been reported. In 2003, Khong et al. demonstrated that DTI was more sensitive compared to conventional MRI in detecting treatment-induced WM damage in a population of young medulloblastoma survivors, and that FA correlated with worse school performance.\(^{72,73}\) Deprez et al. (2011) reported significant correlations between FA and measures of attention, psychomotor speed, and self-reported cognitive failures in post-chemotherapy breast cancer survivors.\(^{74}\) De Ruiter et al. (2012), demonstrated CT-induced decreased FA in survivors of breast cancer 9 years post-treatment, which correlated weakly with Flanker test performance.\(^{75}\) These studies demonstrated that DTI had the required sensitivity to detect long-term WM changes induced by cancer treatment, and that these changes were likely to underlie cognitive impairment.

**Magnetoencephalography (MEG)**

Functional neuroimaging methods like MEG have rarely been applied in late effect studies of cancer treatment, although MEG is very suitable to study subtle brain dysfunction. MEG has the unique property of combining high temporal resolution
with good spatial resolution. The MEG signal is quantified in spectral power, which indicates the strength of magnetic induction fields generated by oscillatory neuronal activity, and is decomposed into frequency bands. A power spectrum that displays a shift towards relatively more power in the lower frequency bands is generally considered to be a pathological sign of slowing brain activity and has been associated with deteriorated cognition.\(^{76,77}\) De Haan et al. (2008) showed that relative power analysis discriminated between Alzheimer patients and controls, and that the patients demonstrated local and diffuse abnormalities in oscillatory brain dynamics with some relation to Mini Mental State Examination scores.\(^{76}\) Bosma et al. (2008) reported global slowing of resting state brain activity in a group of low-grade glioma patients compared to healthy controls. Increased theta and alpha band power correlated significantly with impaired executive functioning, working memory, and information processing.\(^{77}\)

**Quality of Life (QoL)**

Since chances of long-term survival of childhood cancer have increased tremendously, QoL has gained considerable importance. Langeveld et al. did a review in 2002 and observed inconsistent findings in two decades of literature on QoL in young adult survivors of childhood cancer.\(^{78}\) However, general findings were that survivors often reported to be in good health and function well psychologically, although denial and/or response shift could not be ruled out. Frequently, survivors complained of job discrimination and difficulty in obtaining health and life insurance. Other general trends were lower rates of marriage and parenthood, and worries about fertility and future health problems of their offspring. Survivors of ALL specifically were found to be at increased risk of educational deficits. The researchers expressed the need for more accurate evaluation of long-term impact of different kinds of treatment. Also, longer follow-up was recommended to assess whether developmental challenges in (young)
adulthood could be met by survivors. Effects on the maturing brain long after treatment were still unclear. Additionally, the needs of long-term survivors needed to be better understood, and survivor subgroups most at risk needed to be identified.

Associations have been reported between EF and the development of academic performance, social functioning, and health. Therefore, it was hypothesized that EF deficits could correlate with health related (HR) QoL in survivors of childhood cancer. Several questionnaires were chosen to assess self-reported functioning and well-being: the Cognitive Failures Questionnaire (CFQ) to assess subjective cognitive functioning, the Multi-dimensional Fatigue Inventory (MFI-20) to assess physical and mental fatigue, the Profile of Mood States (POMS) to assess depression and other mood disturbances, and the (RAND-36) to assess perception of physical health.

Hypotheses & Outline of the Thesis

We expected an EF profile with clear deficiencies in CRT-treated survivors (Chapter 2), and a pattern of mild deficiencies in CT-treated survivors (Chapter 3). Regarding QoL, we expected significantly worse evaluation of health, mood, and fatigue in CRT-treated survivors compared to controls. Furthermore, we expected to see a beneficial effect of the protocol shift to treatment without CRT (Chapter 4). We were also interested to see if the objectively assessed cognitive deficiencies correlated with subjectively reported cognitive failures (Chapter 5). Regarding the MEG data, we expected to find indications of cortical dysfunction, especially in the CRT-treated group (Chapter 6). In both groups, but more so in CRT-treated survivors, white matter integrity was hypothesized to be decreased compared to controls (Chapter 7). In Chapter 8, all outcomes of the study are brought together. An effort is made to draw general conclusions, and to make suggestions for future research.
References


34. Lezak MD, Howieson DB, Loring DW: Neuropsychological Assessment (ed 4th). New York, Oxford University Press, 2004


