Chapter 2

Aims, design and outline of the thesis

AIM OF THE STUDY

The present study is conducted to detect the neurocognitive sequelae of current therapy for childhood cancer. The more frequent childhood cancers are studied: acute lymphoblastic leukemia (ALL) and brain tumors, as well as kidney tumors (Wilms tumor) as example of non-central nervous system (CNS) solid tumors. As the detrimental effects of cranial irradiation on neurocognitive development in children have been established, and there are efforts to reduce cranial irradiation in the treatment of children with cancer as much as possible, our main focus is on the effects of other CNS-directed treatment modalities. In children with ALL, the effects of CNS-directed chemotherapy are studied. In children with brain tumors the outcome after neurosurgery only is investigated. Children with Wilms tumors, who receive non-CNS directed treatment, are studied as a cancer comparison group.

Our main research questions are:

- What are the neurocognitive effects of CNS- directed chemotherapy in children with ALL as opposed to systemic, non CNS-directed, chemotherapy in children with a Wilms tumor?
- What is the relationship between intensity of CNS-directed chemotherapy and neurocognitive function?
- Can risk factors be identified for neurocognitive dysfunction in children after chemotherapy?
- How is behavioral and educational outcome in survivors of childhood cancer, and is there a relationship with neurocognitive function?
- What is the neurocognitive outcome in children after a cerebellar tumor, treated by neurosurgical resection, without additional radio- or chemotherapy?

STUDY POPULATION

Childhood cancer survivors were studied between the age of 4.5 and 18 years. Children were studied once, at a minimum of 1 year after end of treatment. A group of children with ALL, treated with CNS-directed chemotherapy, was included.

In order to enable identification of the effects of CNS-directed chemotherapy specifically, another group of pediatric cancer patients, diagnosed at a similar age and with a good prognosis, treated with non-CNS chemotherapy, were included: children with a Wilms tumor, treated with systemic, non-CNS directed chemotherapy. For a healthy control group, siblings were included, controlling in part for the emotional distress associated with the diagnosis of cancer in the family. Also age-matched schoolchildren were recruited, among them schoolmates of the children with ALL or a Wilms tumor. A group of children treated surgically for a

cerebellar tumor were compared to healthy controls, selected randomly from an age and sex matched sub-sample of the larger control group, mentioned above.

METHODS

Participants were individually administered a selection of neuropsychological tests from the Amsterdam Neuropsychological Tasks (ANT) program, designed to measure the various aspects of attention and information processing.[1] The tasks employed in our studies are described in the appendix.

Parents of the survivors were interviewed to obtain information on development of the child and on current neurological symptoms. Clinical neurological examination was performed. Behavioral functioning and school performance were assessed using parent and teacher questionnaires, the Child Behavior Checklist (CBCL) parent report, the Conners' Teacher Rating Scale (CTRS) and a School Performance Index (SPI).

OUTLINE OF THE THESIS

Chapter 3 focuses on attentional function in children after chemotherapy, and on the role of CNS-directed chemotherapy in children with ALL. Standard- and intensified ALL treatment are differentiated to assess the role of treatment intensity.

Chapter 4 deals with visuomotor ability in survivors of ALL. The long-term effects of chemotherapy on various levels of visuomotor control are analyzed.

In ***Chapter 5*** behavioral and educational functioning are evaluated in survivors of childhood acute lymphoblastic leukemia (ALL) or a Wilms tumor, in relationship to neurocognitive function.

In ***Chapter 6***, executive functioning in children after a cerebellar tumor treated by neurosurgical resection only is described.

Chapter 7 consists of a review of the literature concerning the neurocognitive effects of chemotherapy in children with ALL.

Chapter 8 is the summary and general discussion, where our findings are discussed in relation to our research questions. We will also deal with remaining research questions and discuss clinical implications and directions for future research in the area of neurocognitive outcome in children with cancer.

Chapter 9 is the Dutch summary.

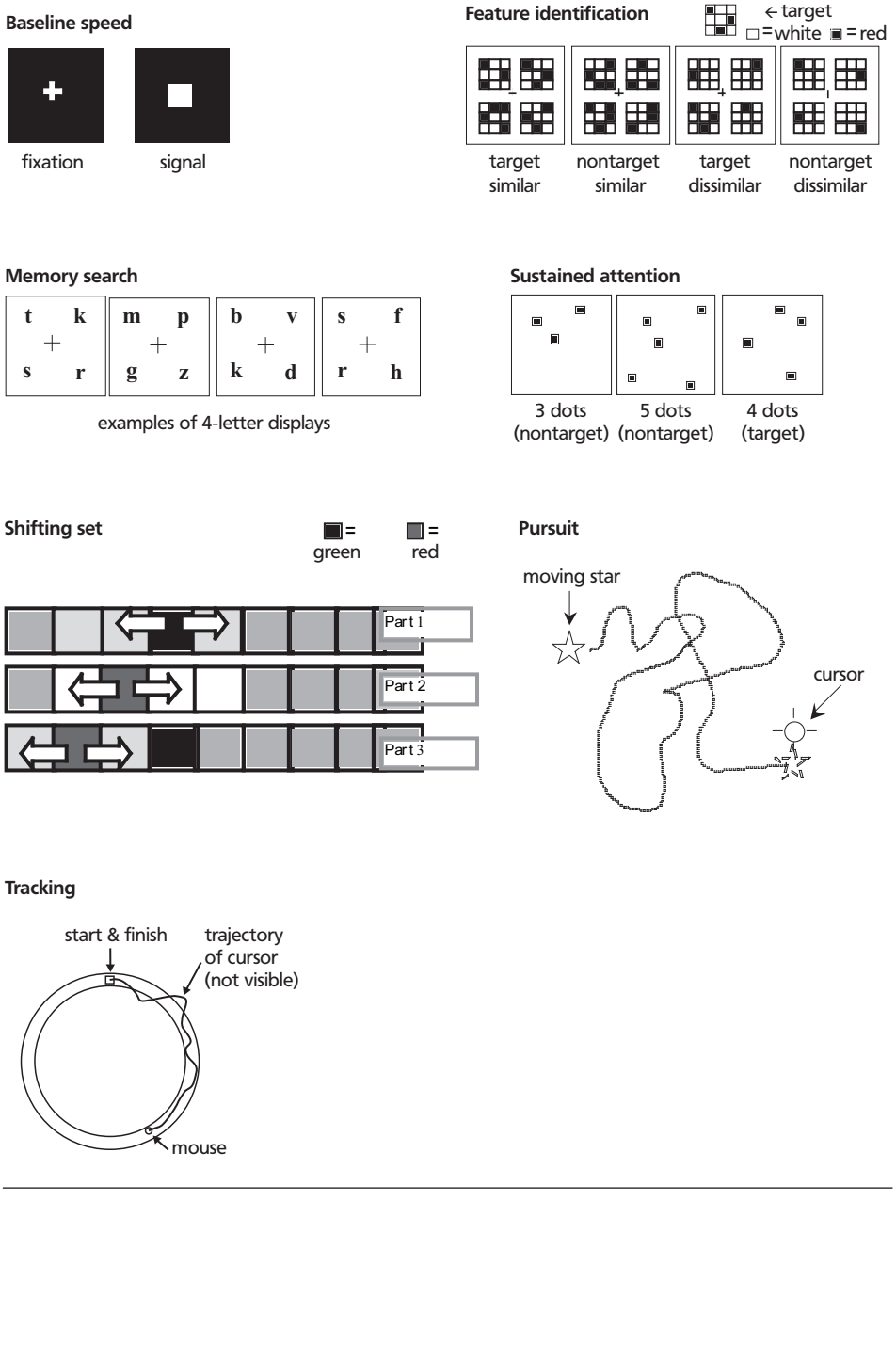
REFERENCE

1. De Sonneville LMJ. Amsterdam Neuropsychological Tasks. 2007. Amsterdam, Boom Test Publishers. www.antprogram.nl

APPENDIX: NEUROPSYCHOLOGICAL TASKS EMPLOYED IN OUR STUDIES (Figure 1)

Baseline speed: measures simple reaction time involving minimal cognitive effort, by requiring to press a mouse-key as quickly as possible when a fixation cross in the center of the computer screen changes into a white square.
Feature identification: assesses efficacy of visuo-spatial processing. The participant is required to detect a specific visuo-spatial matrix pattern (target) that is presented between patterns that are either similar or dissimilar to the target.
Memory search: a divided attention task that assesses working memory capacity. The memory load is increased across 3 task parts by increasing the memory set from 1 to 3 letters, respectively.
Shifting set: assesses attentional flexibility and inhibition, important aspects of executive functioning. A colored square moves randomly to the right and to the left on a horizontal bar that is permanently present on the computer screen. The task consists of 3 parts. Depending on the color of the square, compatible responses (part 1) or incompatible responses (part 2) are required, by pressing the mouse-key on the same side as the direction of movement of the square, or on the mouse-key on the side opposite to the direction of movement of the square, respectively. Part 2 requires inhibition of prepotent responses. During part 3, the color of the moving square varies randomly, requiring attentional flexibility by continuously having to adjust response type (compatible/incompatible).
Sustained attention: a continuous performance test, requiring the subject to discriminate between signals containing test, requiring the subject to discriminate between signals containing 3, 4 or 5 dots, presented in 50 series of 12 signals each. Presentation of a 4 dot signal requires the participant to press one mouse key and presentation of a 3- or 5 dot signal requires pressing the other. Completion time and errors per series are computed as main outcome parameters.
Pursuit: a visuo-motor task that requires the participant to continuously track a target moving randomly on the screen, by moving the computer mouse. As the trajectory of the target is unpredictable, this task demands the concurrent planning and execution of movements. Main outcome parameters are the mean distance to the target and the within-subject standard deviation during time on task.
Tracking: This task measures accuracy and stability of movement along a planned trajectory. The subject is required to move the cursor in between an outer circle and an inner circle presented on the computer screen by moving the computer mouse cursor. Main outcome parameters are the mean distance to the ideal midline between the inner and outer circles and the within-subject standard deviation during time-on-task.

FIGURE 1. Examples of stimuli and signal types of the selected tasks from the Amsterdam Neuropsychological Tasks (ANT) program.



Speed, stability and accuracy of responses are the main outcome measures of the tasks. Stimuli are presented on a computer screen and a response is requested from the participant by pressing a computer mouse key with the right or left index finger or using the computer mouse as a tracking device. General instruction for the reaction time tasks was to respond as fast and as accurately as possible. Prior to the administration of each task, participants received practice trials to ensure that they understood the instructions and executed the tasks accordingly. Total duration of the assessment was around 90 minutes.