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# Pediatric Brain Tumor Survivors after Radiotherapy

*Long-Term Neurocognitive Outcomes, Oculomotor  
Function, and Arousal*

HELENA SÖDERSTRÖM



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### **Abstract**

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Pediatric brain tumor survivors (PBTS) are at increased risk of long-term neurocognitive late effects, particularly following radiotherapy (RT), with processing speed being one of the domains most commonly impaired. The developing brain is particularly vulnerable to RT, and long-term neuropsychological follow-up is therefore recommended. Most studies addressing this topic have primarily focused on prescribed dose, planning target volume (PTV), and whole-brain radiotherapy (WBRT) dose, whereas the association between mean radiation dose to organs at risk (OAR) and neurocognitive outcomes remains insufficiently explored. Although neurocognitive functioning is routinely assessed through standardized neuropsychological testing, eye-tracking measures—including eye movements and pupillometry—may serve as sensitive complementary indicators of attention, processing speed, arousal, and executive functioning.

This thesis investigated neurocognitive outcomes in relation to different RT dose measures, including PTV dose and mean RT dose to established and potential new OAR, using both neuropsychological assessment and eye-tracking metrics. Additional clinical risk factors were also explored. Both retrospective and prospective studies of PBTS treated with RT between 2003-2015 were included. Neurocognitive function was assessed before, after, and 8–20 years post-RT. Long-term outcomes were related to RT dose parameters, and eye-tracking and fatigue were compared with age-matched controls.

Neurocognitive impairments were present prior to RT and became more prevalent with increasing time after treatment. Higher PTV dose was associated with lower working memory performance. Higher mean RT doses to several established and potential new OAR were associated with lower intelligence quotient and processing speed, as well as impaired oculomotor performance, altered pupil responses, and higher fatigue. WBRT and larger tumor size were also linked to poorer outcomes.

In conclusion, the findings from this thesis show that PBTS are at elevated risk of long-term neurocognitive, oculomotor, and arousal-related difficulties following RT. Mean RT dose to OAR provides valuable information on radiation-related impairment beyond PTV dose. These findings underscore the need of structured neuropsychological follow-up. They further demonstrate the value of mean RT dose metrics and eye-tracking measures in evaluating radiation-related neurocognitive outcomes and guiding targeted treatment and rehabilitation strategies.

*Keywords:* Pediatric brain tumor, radiotherapy, organs at risk, mean dose, neurocognition, processing speed, fatigue, eye-tracking, pupillometry

*Helena Söderström, Clinical and translational research in pediatric oncology, Uppsala University, Sweden.*

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*To my family and friends.  
To the children and families who inspire this work.*

Errata: Revisions to the abstract were completed after the thesis had been sent for printing; therefore the abstract in this version differs slightly from the printed version.

# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I. Söderström, H., Brocki, K., Kleberg, J. L., Martinsson, U., & Ljungman, G. (2022). Neurocognitive functions before and after radiotherapy in pediatric brain tumor survivors. *Pediatric Neurology*, 133, 21–29. <https://doi.org/10.1016/j.pediatrneurol.2022.05.006>
- II. Söderström, H., Walfridsson, A., Martinsson, U., Isacson, U., Brocki, K., Kleberg, J. L., & Ljungman, G. (2023). Neurocognition and mean radiotherapy dose to vulnerable brain structures: new organs at risk? *Radiation Oncology (London, England)*, 18(1), 132–132. <https://doi.org/10.1186/s13014-023-02324-2>
- III. Söderström, H., Brocki, H., Martinsson, U., Isacson., Ljungman, G., † Kleberg, J.L.† (2025). Value of Eye Metrics as Biomarkers for Neurocognitive Function in Pediatric Brain Tumor Survivors? Submitted.
- IV. Söderström, H., Brocki, H., Martinsson, U., Isacson., Kleberg, J.L., † Ljungman, G.† (2025). Altered Arousal Regulation, Fatigue, and Processing Speed Impairments in Long-Term Survivors of Childhood Brain Tumor Radiotherapy. Manuscript.

† These authors share senior authorship

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# Abbreviations

CNS	Central nervous system
FSIQ	Full-scale IQ
Gy	Gray
IICP	Increased intracranial pressure
IMPT	Intensity-modulated proton therapy
IMRT	Intensity-modulated radiation therapy
IQ	Intelligence quotient
LC-NE	Locus-coeruleus norepinephrine
NPA	Neuropsychological assessment
OAR	Organs at risk
PBTS	Pediatric brain tumor survivors
PBRT	Partial-brain RT
MFS	PedsQL Multidimensional Fatigue Scale
PRI	Perceptual reasoning index
PSI	Processing speed index
PTV	Planning target volume
RT	Radiotherapy
$r_s$	Spearman's rank correlation coefficient
SD	Standard deviation
SS	Standardized scores
VRI	Verbal reasoning index
VMAT	Volumetric-modulated arc therapy
WBRT	Whole-brain RT
WMI	Working memory index



# Introduction

The number of pediatric brain tumor survivors (PBTS) has increased due to improved treatment protocols and multimodal treatments. However, PBTS remain at elevated risk for neurocognitive impairments resulting from both the tumor and its treatment effects. The developing brain is particularly vulnerable to radiotherapy (RT), due to ongoing white and gray matter maturation and network development<sup>(1-4)</sup>. RT is effective for tumor control, but can induce neurocognitive late effects that progress with time. The immature central nervous system (CNS) is particularly vulnerable to RT-induced injury. White matter lesions can affect neurocognitive networks and may alter the anatomy of visual and oculomotor pathways<sup>(2,5,6)</sup>. Despite advances in RT techniques and improved dose conformity PBTS frequently exhibit impairments in attention, processing speed, memory and executive function, and cancer-related fatigue<sup>(2-4,7)</sup>. Systematic neuropsychological assessment (NPA) before and after RT is essential to identify pre-morbid level, potential risk factors, monitoring treatment-related effects and guiding rehabilitation<sup>(8,9)</sup>. Long-term follow up is strongly recommended due to the elevated risk of late complications and progressive neurocognitive decline<sup>(2,10,11)</sup>. Processing speed impairments are one of the most common late effects, regardless of RT modality, mainly due to white matter loss<sup>(2)</sup>. Reducing RT doses to organs at risk (OAR) is a key strategy to mitigate RT-induced injury to the developing brain. Modern RT techniques permit more conformal dose delivery and greater sparing of healthy tissue<sup>(12-14)</sup>. However, associations between mean RT dose distributions to OAR and long-term neurocognitive outcomes remain insufficiently investigated, particularly for structures involved in neurocognitive, visual, and oculomotor networks such as the cerebellum, pons, and optic nerves<sup>(15,16)</sup>. Eye movements and pupillometry, measured with an eye-tracker, may serve as potentially sensitive biomarkers of core neurocognitive impairments, including attention, arousal regulation, processing speed and executive function<sup>(17)</sup>. Integrating detailed RT dosimetry, NPA and eye-tracking may improve understanding of how RT dose to OAR relate to neurocognitive late effects and support future dose-sparing strategies and targeted rehabilitation.

The focus of this thesis is to improve understanding of neurocognitive late effects after RT in PBTS by examining how RT dose to established and potential new OAR relates to neurocognitive outcomes. To address this, neurocognitive outcomes were first characterized broadly, and then examined in specific domains through investigating associations with OAR, with particular emphasis on processing speed. A multimodal approach was applied, integrating RT dosimetry, clinical factors, standardized NPA and eye-tracking methods to capture subtle core process that complement conventional NPA.

## Neurocognition before and after radiotherapy

Systematic NPA before and after RT at multiple time points is recommended to identify vulnerabilities, monitor treatment-related effects and support rehabilitation (<sup>9,18,19</sup>). Neurocognitive impairments are common in PBTS and often involve multiple domains, such as attention, processing speed, perceptual and visuomotor function, memory, learning, and executive function, as well as global intelligence (IQ) (<sup>2-4,10</sup>).

Baseline NPA before RT is essential, as difficulties may already be present prior to treatment initiation. Establishing a baseline helps distinguish premorbid vulnerabilities from treatment-related decline (<sup>2,4,20</sup>). Long-term follow-up with standardized NPA is essential to detect slow or late-emerging decline and to plan rehabilitation (<sup>8,9,21</sup>). IQ measures are frequently used to assess neurocognitive outcomes in PBTS (<sup>4</sup>). Full-scale IQ is often influenced by processing speed and visuomotor function. Detailed analysis of index and subtest profiles can therefore reveal clinically relevant weaknesses that are not evident from global scores alone (<sup>22</sup>). However, IQ alone do not adequately capture the breadth of neurocognitive sequelae in PBTS, and broader assessment is recommended and often required (<sup>4,23</sup>).

Adult survivors of pediatric brain tumors remain at elevated risk for persistent neurocognitive difficulties, particularly in processing speed, attention, executive functions, and cancer-related fatigue (<sup>2,3,24</sup>). Early CNS abnormalities following cranial RT may drive chronic pathophysiological processes that can contribute to progressive neurocognitive decline, and disabling long-term neurocognitive impairment has been reported in a substantial proportion of adult patients (<sup>2,25</sup>). These findings underscore the need for comprehensive neurocognitive monitoring and targeted rehabilitation extending into adulthood (<sup>2,3,24,25</sup>).

In Sweden and the other Nordic countries, neuropsychological follow-up is part of standard care for pediatric brain tumors. Nationally coordinated structured NPA has been implemented since the early 2000s (<sup>26</sup>) and since 2015, within a common Nordic protocol according to SIOP-Europe recommendations (<sup>23,27,28</sup>). Recent national care rehabilitation program for children and youth and the updated national cancer strategy emphasize structured assessment of rehabilitation needs, long-term follow-up, registry-based data collection, and age-adapted rehabilitation services. These priorities underscore the need for sustained neuropsychological monitoring and targeted support into adulthood (<sup>23,29</sup>).

## Neurocognition and interrelated risk factors

Neurocognitive outcomes in PBTS arise from multifactorial interactions between tumor- and treatment-related effects, developmental neurobiology, co-occurring medical conditions, individual vulnerabilities, and environmental and educational contexts <sup>(2,4)</sup>. Pediatric brain tumors constitute a diagnostically heterogeneous group, each with distinct biological behavior, anatomical location and treatment strategies <sup>(30)</sup>. This heterogeneity contributes to variability in clinical presentation and neurocognitive outcomes. Importantly, neurocognitive function in PBTS reflects not only tumor biology and anatomical location, but also developmental and treatment-related trajectories over time, which interact to influence neurocognitive development <sup>(2,4)</sup>. Evaluating neurocognitive impairment therefore requires considering how such factors may interact both before and after RT. Several factors such as younger age at RT, increased intracranial pressure (IICP), larger tumor size, sex, and more aggressive biology have been associated with poorer neurocognitive function before treatment <sup>(2,4,20)</sup>. Surgery, chemotherapy and shunt placement (ventriculostomy) may further affect brain microstructure and neurocognitive functioning <sup>(2,3,31,32)</sup>. Longer time since treatment has been associated with worse neurocognitive outcomes <sup>(2,33)</sup>. Accordingly, several of these factors were considered in the present thesis when examining neurocognitive outcomes and their associations with RT.

Among these interacting factors, RT is one of the strongest predictors of long-term sequelae in PBTS. Deficits may show delayed emergence and often worsen over time, particularly in processing speed <sup>(2-4)</sup>.

## Radiotherapy and neurocognitive outcomes

Children receiving RT are at high risk of neurocognitive complications. RT can induce neurocognitive decline through RT-induced inflammation and cellular injury. These processes may initiate biological cascades, such as neuroinflammation, white matter injury, inhibited neurogenesis, and altered synaptic plasticity <sup>(10,34)</sup>. Neurocognitive complications are associated with higher RT dose to normal brain tissue, as well as with the dose and volume of the tissue being irradiated <sup>(10,35,36)</sup>.

RT aims to deliver the optimal radiation dose to the target while sparing OAR. OAR are structures that require dose constraints to minimize RT-induced toxicity <sup>(37,38)</sup>. Radiation dose to OAR can affect neural structures and networks that support neurocognitive development <sup>(39,40)</sup>. Delineation of OAR is a

crucial component of RT planning, as irradiation of the brain can lead to visual, auditory, hormonal, neurological, and neurocognitive impairments (<sup>37,38</sup>). More severe impairment has been reported after craniospinal irradiation, particularly for IQ, attention, working memory, and processing speed (<sup>3,4,10,34</sup>). In a long-term follow up, processing speed impairments were the most common impairment in adults receiving craniospinal irradiation. Neurocognitive impairments were linked to reduced educational attainment, unemployment, and non-independent living in adulthood (<sup>3</sup>).

Advancements in RT, especially proton RT, have enabled more precise tumor targeting and reduced RT doses to OAR (<sup>11-13,41</sup>). Photon RT has been the most common modality and is associated with an increased risk of neurocognitive decline including impairments in IQ, working memory, learning and processing speed (<sup>13,15,42</sup>). Gamma knife treatment (focused high dose radiation) generally spares normal tissue but is only suitable for smaller tumors (<sup>43</sup>). Proton RT is increasingly used, as it is suitable for a wide range of pediatric tumors and often minimizes the irradiated volume, thereby sparing OAR. Consequently, RT-induced injury may be reduced by protecting OAR (<sup>14,44,45</sup>). Several studies report favorable global and academic neurocognitive outcomes following proton RT (<sup>12,13,15,35</sup>). Still, domain-specific neurocognitive vulnerabilities remain, particularly processing speed have been reported, consistent with disturbed white-matter microstructure, impaired neural synchrony, and reduced network efficiency (<sup>5,12,13,46,47</sup>). Despite advances in RT techniques, the contribution of radiation dose distributions to specific OAR to neurocognitive outcomes remains poorly understood, particularly given that neurocognitive sequelae may unfold over many years (<sup>12,15,37,48</sup>).

Modern RT techniques enable more conformal dose delivery, allowing for increased sparing of OAR. This can be achieved with photon RT, using intensity-modulated RT (IMRT) or volumetric, modulated arc therapy (VMAT) (<sup>35,45,49</sup>). This is especially suitable for those receiving WBRT with photon RT and/or when proton RT is not available or appropriate (<sup>49-51</sup>). When proton RT is possible and appropriate, a sparing dose approach to OAR can be achieved with intensity modulated proton RT (IMPT) (<sup>35,45,49,52</sup>). Beneficial sparing with IMPT compared with IMRT has been demonstrated across a wide age range in patients with medulloblastoma and ependymoma, with reduced dose to OAR such as cochlea, optic nerve, hippocampus, brainstem, hypothalamus and pituitary gland (<sup>45,53,54</sup>).

Prescribed RT dose and planning target volume (PTV) dose metrics are commonly used measures when investigating neurocognitive late effects, primarily because they are readily available in clinical records. However, these measures provide only coarse estimates on actual RT exposure and do not account for spatial dose heterogeneity<sup>(38,40)</sup>. In contrast, mean RT dose to OAR may offer more specific information on radiation-related neurocognitive decline, as it reflects dose-volume heterogeneity<sup>(40,55)</sup>. Although research in this area has increased in recent years, the relationship between mean RT dose to specific OAR and neurocognitive outcome remains insufficiently characterized.

### Radiotherapy to organs at risk

Previously established OAR includes structures primarily associated with sensory, endocrine or neurological complications, including cochleae, optic chiasm, optic nerve, pituitary gland, hypothalamus, and brainstem. In addition, the hippocampus has more recently been delineated as an OAR due to its role in learning and memory and its sensitivity to cranial irradiation<sup>(8,37,56,57)</sup>. While several OAR are defined based on well-established clinical toxicities, their potential contribution to neurocognitive impairment remains incompletely understood. Moreover, brain regions not routinely delineated as OAR may also be relevant to radiation-related neurocognitive effects. Among these, but not limited to, are the cerebellum, vermis, thalamus and frontal regions, which are involved in visuospatial, visuomotor and attentional processing, and form part of cortico-subcortical networks that support neurocognitive function<sup>(58-60)</sup>.

Eye movements provide a sensitive window into visuospatial and visuomotor processes. Oculomotor and saccadic control engage cerebellar, frontal, brainstem and thalamic regions<sup>(61-63)</sup>. Pro-antisaccade paradigms can therefore serve as functional probes of visuomotor and attentional performance<sup>(61,63,64)</sup>. Eye-tracking approaches thus offer a means to investigate potential subtle neurocognitive effects of RT that may not be readily detected using traditional NPA.

The chiasma and optic nerves are defined as OAR due to the risk of RT-induced optic neuropathy. The optic nerves may be especially sensitive because they can be damaged many years after RT (delayed radiation toxicity), and such damage may affect neurocognitive function through connections to the CNS<sup>(37,38,65)</sup>. The cochleae are defined as OAR because they are highly sensitive to toxicity and higher RT dose to cochleae can result in hearing loss

(<sup>37,66</sup>). Hearing loss has also been associated with neurocognitive impairments (<sup>66-69</sup>), including intellectual impairment and lower academic performance in children treated for medulloblastoma (<sup>69</sup>). A dose-sparing approach to the hypothalamus and pituitary gland is important to prevent hypothalamic-pituitary disorders (<sup>70</sup>). Endocrine diseases that develop over time may mediate and aggravate neurocognitive impairment. Hypothalamic-pituitary disorders have been associated with neurocognitive decline, such as lower IQ and memory performance (<sup>71,72</sup>). However, associations between RT dose to the chiasma, optic nerves, cochleae, hypothalamus or pituitary gland and neurocognitive outcomes remain understudied.

The hippocampus is now established as an OAR. Because brain metastases are relatively uncommon in the hippocampus, sparing approaches have become feasible (<sup>57</sup>). The hippocampus is highly sensitive to WBRT in PBTS. RT-induced injury impairs hippocampal neurogenesis, which is critical for learning and memory. RT may also accelerate neurocognitive aging, including early onset dementia (<sup>2,36</sup>). Reducing RT dose and avoiding the hippocampi during WBRT have been recommended, as these approaches have been associated with preservation of memory and improved quality of life (<sup>37,73,74</sup>).

The cerebellum and vermis (midline of cerebellum) are not typically defined as OAR. The cerebellum has complex interactions with the cerebral cortex through neurocognitive networks such as the cortico-ponto-cerebellar pathway and cerebello-thalamo-cortical pathway (<sup>59,75</sup>). The cerebellum and vermis play important roles in sensorimotor and neurocognitive functions such as perception, attention, language, executive function, emotional and social behavior (<sup>76,77</sup>). These structures may be particularly sensitive to RT. Higher mean RT dose to the cerebellum in patients with ependymoma has been associated with decline in IQ and academic achievement (<sup>77,78</sup>). Increased blood-brain barrier damage and reduced blood flow in the cerebellum have also been reported in rats receiving WBRT, compared with other brain regions (<sup>79</sup>). The vermis may be sensitive to higher radiation since it has several connections with the pons, hippocampus, and limbic structures through multiple neural networks in the brain, and lesions in this region have been associated with psychosocial and neurocognitive problems (<sup>59,76</sup>). The cerebellum also connects to the pons and thalamus (<sup>59,75</sup>). The pons is part of the brainstem and is regarded as an OAR. However, there is lack of studies that have investigated associations between RT dose to the pons and neurocognitive outcomes. Cellular changes in the pons, thalamus, hippocampus, prefrontal grey matter, and white matter tracts have been reported in patients with posterior fossa tumors

treated with surgery and chemotherapy. These pathways seem more vulnerable to neurotoxicity when injured earlier in development<sup>(32)</sup>. Thalamus is not defined as an OAR, lesions in thalamus have been associated with late effects on visual attention and memory through cortico-subcortical networks<sup>(60)</sup>. The cerebello-thalamo-cerebral pathway links cerebellar and thalamic structures to frontal regions that support executive functions, and attentional control. Reduced anisotropy and increased radial diffusivity within this pathway have been associated with lower working memory in PBTS, particularly among those receiving RT<sup>(80)</sup>. Higher RT dose to white matter tracts in the frontal lobes has also been associated with slower processing speed<sup>(81)</sup>.

## Pro- and anti-saccades

Eye tracking enables high-temporal-resolution assessment and can capture subtle visual and neurocognitive impairments and, together with standardized NPA, may provide insight into fundamental mechanisms underlying complex behavior. Eye movements (saccades, fixations, smooth pursuit) provide information about attention, processing speed, working memory and cognitive control<sup>(61,64,82)</sup>. Eye tracking has been applied across a wide range of developmental and clinical groups including autism spectrum disorder<sup>(83,84)</sup>, ADHD<sup>(85-87)</sup>, anxiety<sup>(88)</sup>, preterm birth<sup>(89,90)</sup>, traumatic brain injury<sup>(91,92)</sup>, and typical development<sup>(93-95)</sup>. In traumatic injuries, saccade and smooth pursuit deficits may reflect white damage and functional network alternations in regions responsible for oculomotor control, with longer anti-saccade latencies, increased premature pro-saccades, directional errors, and switching difficulties<sup>(91,92)</sup>. Eye tracking may also reveal eye movement dysfunction and impairments in higher cortical functions such as reading<sup>(91)</sup>. A few eye-tracking studies in PBTS with posterior fossa tumors have reported cerebellar-related oculomotor impairments, including reduced visual scanning, smooth pursuit, and gaze stabilization, suggesting cerebellar dysfunction that can lead to deficits in reading<sup>(96-98)</sup>. These findings highlight the relevance of oculomotor assessment in PBTS, but have focused on basic oculomotor metrics rather than task-based paradigms as pro-antisaccades.

Oculomotor control provides a sensitive window into attentional and executive processes, domains frequently affected in PBTS<sup>(61)</sup>. Saccade measurements, particularly pro-saccades and anti-saccades, have shown promise as potential biomarkers of brain disorders across the lifespan<sup>(99-103)</sup>. From a developmental perspective, visuomotor and gaze control mature throughout childhood and adolescence, reflecting developing perception-action coupling,

predictive control and executive regulation (<sup>93,95</sup>). Oculomotor measures therefore provide a sensitive window into cognitive processes such as attention and inhibitory control, frequently affected in PBTS. Saccades are rapid eye movements that shift gaze to a new target and center the visual focus to a new target. Saccades, fixation and visual attention are closely interlinked, as saccades enable rapid shifts of gaze between objects and attentional targets (<sup>61</sup>). Pro-saccades reflect largely reflexive response directed toward appearing stimuli. Anti-saccades are voluntary movements directed away from a stimulus and require inhibition of the reflexive response and redirection of gaze, engaging higher executive control (<sup>61,99–103</sup>). Abnormalities in these tasks, including increased latency and error rates, have been reported across neurodevelopmental and neurological conditions, indicating the tasks' sensitivity to deficits in visual attention, processing speed and inhibitory control (<sup>100,102–105</sup>). A previous bedside study in craniopharyngioma patients reported anti-saccade difficulties associated with impaired attention and processing speed following proton RT, but without eye-tracking measures (<sup>106</sup>). To date, no studies have applied a pro- and antisaccade task using high-precision eye-tracking in PBTS. This thesis therefore investigates this previously unexplored approach to assessing oculomotor and cognitive performance.

The brain tumor itself, surgery, chemotherapy and RT can alter the anatomy of visual, sensory, and oculomotor pathways, resulting in visual deficits and impaired gaze control (<sup>2,6,82</sup>). These effects likely arise from white matter lesions affecting neurocognitive networks, including the optic radiations (white matter tracts that transmits visual information), primary visual cortex (V1), and cuneus (smaller lobe in the occipital lobe) (<sup>5,47</sup>). Disrupted white matter microstructure in these regions may disturb neural synchrony and thereby contribute to reduced processing speed, and has also been associated with slower reaction times in PBTS treated with WBRT (<sup>5</sup>). There are several neural networks that can be affected after RT. The optic nerves, chiasma, frontal lobes, cerebellum, vermis, thalamus, and pons are important for saccadic, smooth pursuit, velocity, precision, and visual attention through interconnected pathways (<sup>61,62</sup>). RT-induced lesions in these areas may affect information processing and storage in subcortical and cortical networks (<sup>5,58,63,77,107</sup>). However, the frontal lobes, cerebellum, vermis and thalamus are not routinely considered OAR in current RT planning. These structures form part of neurocognitive networks and oculomotor networks and may therefore be relevant for late effects following RT. To date, no study has examined associations between mean RT doses to these structures important for neurocognitive and

oculomotor networks and performance on a pro-antisaccade task using a high-precision eye-tracker in PBTS.

## Pupillometry and arousal regulation

Fatigue and processing speed impairments are among the most common late effects following RT in PBTS. Disrupted network synchrony, largely attributed to RT-induced neurocognitive white matter disruption has been proposed to underlie difficulties in processing speed, fatigue, and cognitive overload (<sup>47,108,109</sup>). Given that fatigue and processing speed impairments are common in PBTS, systematic assessment of fatigue and related symptoms is essential for clinical follow-up outcomes (<sup>7,110,111</sup>). Pupillometry may provide complementary physiological information about arousal regulation and cognitive effort that is not captured by self-reported questionnaires or performance-based neuropsychological measures, and may therefore enhance characterization of fatigue-related difficulties in PBTS. Pupil dilation measured with an eye-tracker provides an objective and non-invasive index of autonomic nervous system activity and may serve as a biomarker of arousal, attention, memory and cognitive control (<sup>17,112-115</sup>). Fatigue and reduced processing speed co-occur and may share underlying mechanisms related to arousal and attentional control. Identifying objective markers of these processes could improve the characterization of late effects and inform targeted interventions in PBTS.

Several risk factors for fatigue have been identified in PBTS, including tumor location, age at diagnosis, RT exposure, depressive symptoms and slower processing speed (<sup>7,111,116</sup>). Cognitive fatigue has been associated with slower processing speed after RT and appears to increase with longer time since diagnosis (<sup>7,111</sup>). This may reflect arousal dysregulation.

Difficulties regulating arousal and cognitive effort may contribute to these impairments. Under constant luminance, pupil dilation provides an index of sensory stimulation, attentional orienting and cognitive effort. Altered responses reflect dysregulated arousal and attentional control. Consistent with this, pupil dilation to brief auditory stimuli has been demonstrated in both typical and clinical populations (<sup>85-87,117</sup>). Pupil dilation also increases during executive control tasks such as anti-saccades (<sup>118</sup>). Task-evoked pupil dilation reflects increased sympathetic activation mediated via the locus-coeruleus norepinephrine (LC-NE) system (<sup>115,117</sup>). Pupillometric measures may therefore capture differences in arousal regulation relevant to fatigue and processing speed

in PBTS. However, fatigue, arousal regulation, and processing speed have not been examined in PBTS in relation to RT doses to OAR important for visual and neurocognitive networks.

Taken together, studies integrating eye-tracking measures, standardized NPA and detailed RT dosimetry in PBTS are lacking. Such multimodal approaches may provide new insight into late effects on neurocognitive, oculomotor and arousal-related functions, and may ultimately support earlier identification of PBTS at risk for neurocognitive late complications and inform future rehabilitation efforts.

# Aims of this thesis

The overall aim of this thesis was to improve understanding of neurocognitive late effects after RT in PBTS by evaluating associations between RT doses to established and potential new OAR, and neurocognitive outcomes, as well as exploring additional risk factors, using both traditional NPA and eye-tracking metrics. Across all studies, associations with clinical risk factors (e.g., tumor size, age at RT, tumor location, IICP, time since RT, and non-radiation treatments) were examined where relevant.

The specific study aims were:

- I. To describe neurocognitive functions before and after RT across different treatment approaches, and to examine associations between IQ performance, clinical risk factors, and radiation-related risk factors including PTV dose and WBRT.
- II. To examine associations between mean RT dose to established and potential new OAR and IQ performance.
- III. To investigate oculomotor performance in long-term PBTS using a pro-antisaccade task compared with an age-matched healthy control group, and within PBTS to examine associations between saccadic latency, processing speed and mean RT dose to brain structures involved in visual and neurocognitive networks.
- IV. To further examine arousal regulation in PBTS through task-evoked pupil dilation and self-reported fatigue, and within PBTS to evaluate associations between arousal-related measures, processing speed and mean RT dose to established and potential new OAR.

# Methods

## Design

The retrospective studies evaluated neurocognitive function before and after RT (Study I) and examined associations between mean RT doses to OAR and intellectual outcomes (Study II). The prospective studies assessed processing speed in PBTS, oculomotor control (Study III), and pupillary responses and self-reported fatigue (Study IV) in PBTS compared with age-matched controls. Across studies, associations with radiation-related factors were examined while accounting for relevant clinical variables. Table 1 provides an overview of the study populations, designs, and data collection procedures in the four studies.

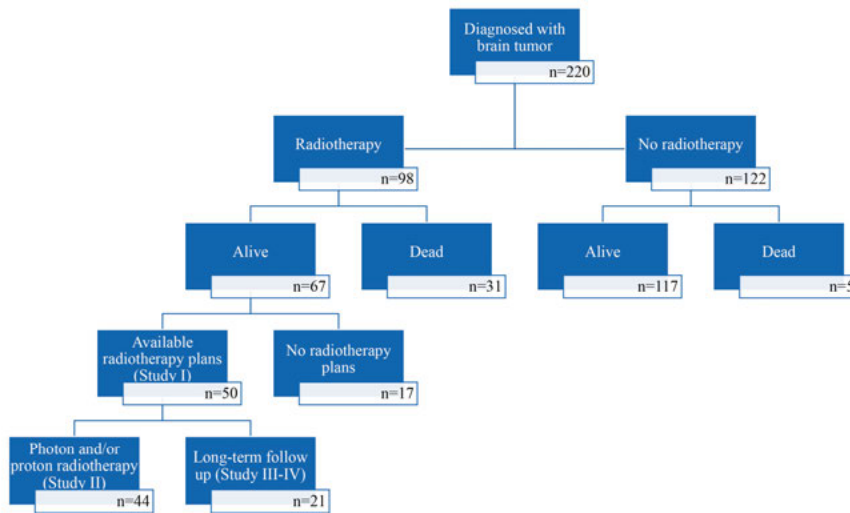
Table 1. *Study overview*

<b>Study</b>	<b>Population</b>	<b>Design</b>	<b>Data collection</b>
<b>I</b>	50 PBTS before and after RT	Retro-spective study	Clinical data and NPA before and after RT
<b>II</b>	44 PBTS after RT	Retro-spective study	Mean RT doses to OAR and IQ measurements after RT
<b>III</b>	21 PBTS and 50 age-matched controls	Prospective study	Pro-antisaccades (eye tracking), processing speed and mean RT doses to OAR
<b>IV</b>	21 PBTS and 50 age-matched controls	Prospective study	Pupillometry (eye tracking), fatigue, processing speed and mean RT doses to OAR

## Participants

Participants in the four studies included in this thesis were PBTS diagnosed between January 2003 and June 2015 at Uppsala University Children's Hospital in Sweden. During this period, 220 patients with CNS tumors were diagnosed of whom 184 were alive at data collection (five-year overall survival rate, 84%; Figure 1). Within this cohort, 98 patients received RT, of whom 67 were alive at data collection (68%). Eligible participants were treated with partial-brain RT (PBRT) or WBRT. Seventeen patients were excluded due to RT outside the study period (n=7), treatment abroad (n=4), unavailable treatment data (n=4), or missing data (n=2).

Study I included 50 participants treated with photon RT, proton RT and/or gamma knife treatment  $\geq 5$  years prior to inclusion. Study II included 44 participants treated with photon and/or proton RT from the same cohort as in Study I, excluding those treated with gamma knife only (n= 6). Studies III and IV comprised a long-term follow-up of 21 participants from study II, along with an age-matched control group of 50 participants. Exclusion criteria among PBTS were blindness or severe visual impairment (n = 3) and relapse after June 2015 (n = 2). Of the remaining eligible participants, 18 did not participate (declined, no response, or could not be reached). Exclusion criteria for the control group were a neuropsychiatric disorder and/or learning difficulties. Written informed consent was obtained from all participants. Sex distribution was comparable between the PBTS group and the control group (PBTS: 9 females, 12 males; controls: 24 females, 25 males, one non-binary participant).



*Figure 1.* Flowchart illustrating patient identification, eligibility inclusion for Studies I-IV among children diagnosed with brain tumors and treated with radiotherapy at Uppsala University Children's Hospital, Sweden, between January 2003 and June 2015.

## Study procedures

Study I-II were based on retrospective data. In study I, clinical information was retrieved on neurological debut symptoms, neurocognitive functions before and after RT, and potential clinical, and radiation-related risk factors. In Study II, IQ measurements after RT were combined with radiation treatment plans, including delineation of established and potential new OAR, to examine associations between mean RT doses to OAR and neurocognitive outcome.

Studies III and IV constituted a long-term follow-up (8-20 years after RT) of a subset of participants from the same underlying cohort included in Studies I and II. These studies involved fewer participants and included a full-day clinical visit for PBTS. In Studies III and IV, survivors underwent comprehensive NPA in addition to completing questionnaires and eye-tracking measures, whereas controls completed questionnaires and eye-tracking measures only. For the control group, the assessment consisted of a 2-hour visit.

## Clinical characteristics

Clinical data, including medical information, NPA, and radiation treatment plans, were collected from the medical records, neuropsychological test

protocols, and radiation treatment systems, and were compared with data from the Swedish Childhood Cancer Registry, including the Radtox Quality Registry (a former national RT registry for children).

Clinical variables included sex, age at diagnosis, age at RT, tumor type, tumor location (supratentorial/infratentorial), tumor size (widest diameter in cm), IICP (yes/no), sensory function before RT (vision and hearing, yes/no), surgery and chemotherapy (yes/no), as well as age at assessment and time since RT. NPA were available pre- and/or post-RT, depending on study.

Post-RT sensory function could not be assessed. Ophthalmological examinations were available for most patients approximately one-year post-RT as part of routine clinical follow-up. These data were not aligned in time with the prospective neurocognitive assessments and were therefore not used analytically.

In Study I, 30 participants (60%) had documented visual impairments and six (12%) had hearing impairments prior to RT. In Studies III–IV, nine PBTS (43%) had documented and/or self-reported visual impairments, of whom seven (33%) had impairments not correctable with glasses.

Radiation-related variables included RT distribution (WBRT vs PBRT), RT modality (photon, proton, combined proton-photon, and Gamma Knife), PTV dose (Gray; Gy), and mean RT dose to OAR (Gy; Studies II–IV). Gamma Knife and PTV were only included in Study I.

For descriptive purposes, clinical and radiation-related variables were reported in their original form, whereas for correlation analyses they were treated as categorical or continuous measures as appropriate. In Study I, clinical characteristics were presented in the Results section due to the descriptive aim of the study. For consistency across studies and to facilitate comparison, clinical and radiation-related characteristics for all cohorts (Studies I–IV) are summarized here in the Methods section of the thesis.

In this thesis, variables with potential relevance for neurocognitive outcomes are grouped into clinical risk factors and radiation-related risk factors. Clinical risk factors include background variables (e.g., age, sex), disease-related variables (e.g., tumor localization, IICP) and non-radiation treatment-related variables (e.g., surgery, chemotherapy). Radiation-related factors include RT modality, distribution (WBRT vs PBRT) and RT dose to OAR. In Studies I–III,

these variables were referred to as confounding risk factors in a broad clinical sense. In the present thesis, the updated terminology is used to emphasize a clinical–conceptual framing rather than statistical confounding. Time since RT was included as a clinical follow-up variable and reflects duration of exposure to potential late effects.

Tumor classification followed the pre-molecular WHO CNS criteria in use during the study period (2003-2015), corresponding to the WHO 2007 CNS classification. Across Studies I-IV, the most common tumor types were embryonal (including medulloblastoma, 30-43%), ependymal (20-24%), and astrocytic tumors (5-16%), followed by germ cells tumors (10-14%), tumors of the sellar and pineal regions (5-14%). A small number of optic nerve sheath tumors and unclassified meningioma were also included (2-4%). Tumors were further grouped as low-grade (WHO grade I-II) and high-grade (WHO grade III-IV). Table 2 summarizes the clinical and radiation-related characteristics of the cohort across Studies I-IV. These were considered in the subsequent analyses of neurocognitive outcomes.

Table 2. *Clinical and radiation-related characteristics of pediatric brain tumor survivors across Studies I-IV. Values presented as mean  $\pm$  SD (range) or percentage*

<b>Variable</b>	<b>Study I (n = 50)</b>	<b>Study II (n= 44)</b>	<b>Study III-IV (n= 21)</b>
<b>Male/female (%)</b>	58/42	55/46	57/43
<b>Age at diagnosis (years)</b>	9.5 $\pm$ 4.5 (0-17)	9.6 $\pm$ 4.3 (1-17)	9.3 $\pm$ 4.1 (2-17)
<b>Age at RT (years)</b>	10.3 $\pm$ 4.1 (2-17)	10.4 $\pm$ 3.97 (3-17)	9.7 $\pm$ 3.8 (2-17)
<b>Infra-/supratentorial (%)</b>	38/60 <sup>a</sup>	43/55 <sup>a</sup>	57/43
<b>IICP (%)</b>	62	66	71
<b>Tumor size, widest diameter (cm)</b>	4.0 $\pm$ 1.7 (0.8 – 9.5)	4.1 $\pm$ 1.7 (0.8-9.5)	4.3 $\pm$ 2.1 (0.8-9.5)
<b>Surgery (%)</b>	90	75	90
<b>Chemotherapy (%)</b>	72	80	86
<b>WBRT %</b>	34	39	48

Abbreviations: RT, Radiotherapy; IICP, Increased intracranial pressure; WBRT, Whole-brain radiotherapy.

<sup>a</sup>One patient had multifocal disease but lacked neuropsychological data and was therefore not included in the analyses

## Radiotherapy and dosimetry

In Studies I-IV RT was categorized according to distribution into WBRT and PBRT, where WBRT was generally delivered as part of craniospinal irradiation. RT was further classified as photon RT, proton RT, combined proton-photon RT, or Gamma Knife therapy. Photon RT was delivered using linear accelerators at Uppsala University Hospital in Sweden. Proton RT was administered as a single fixed horizontal beam (180 MeV) at the former Svedberg Laboratory, Uppsala University. Proton doses were converted using a relative biological effectiveness (RBE) of 1.1 to allow comparison with photon doses. Gamma Knife treatment was delivered with ionizing radiation (Leksell gamma knife) at Karolinska University Hospital (only included in Study I).

In Studies II–IV analyses focused on radiation dose to previously established OAR (left and right cochleae, optic chiasm, left and right optic nerve, pituitary gland, left and right hypothalamus, left and right hippocampus and pons) and potential new OAR (cerebellum, vermis and thalamus). OAR were delineated on CT images according to Radiation Therapy Oncology Group (<sup>119</sup>) and European Society of Radiotherapy and Oncology guidelines (<sup>120</sup>), and contoured in either Treatment Management System (TMS) or Oncentra Treatment Planning (OTP) (<sup>121</sup>), depending on the original treatment plan. In the thesis, the term “dose to” OAR is used, following established clinical RT conventions. Biologically, this refers to absorbed dose within the tissue (Gy).

Mean physical RT doses to each OAR were extracted and converted to equivalent dose in 2 Gy fractions (EQD2) using the linear–quadratic model ( $\alpha/\beta=3$ ). In Study III analyses were restricted to mean RT dose to the optic nerves, chiasm, frontal lobes, cerebellum, vermis, thalamus and pons. For one participant, dose to the right optic nerve was unavailable and treated missing in all relevant analyses. In Study IV the hippocampi, hypothalamus, pituitary gland and cochleae were additionally included as OAR. For bilateral OAR, a single mean dose value was computed across the pair to facilitate analysis. Mean RT dose was calculated for the frontal lobes, optic nerves, cochleae, hippocampi and hypothalamus. For the missing data of the right optic nerve, the available unilateral value was used as a proxy for mean RT dose. To facilitate comparison across studies, mean RT dose to OAR is summarized in Table 2.

Table 3. Mean radiotherapy dose (Gy) to organs at risk across Studies II-IV

<b>Organs at risk</b>	<b>Study II<sup>a</sup> (n=44)</b>	<b>Study III<sup>a</sup> (n=21)</b>	<b>Study IV (n=21)</b>
<b>Chiasma</b>	26 ± 17 (0-53)	26 ± 16 (0-53)	26 ± 16 (0-53)
<b>Optic nerves<sup>b</sup></b>	14 ± 13 (0-38)	17 ± 13 (0-38)	17 ± 13 (0-38)
<b>Frontal lobes</b>	Not assessed	19 ± 16 (0-54)	19 ± 16 (0-54)
<b>Cochleae</b>	21 ± 20 (0-55)	Not assessed	27 ± 20 (0-55)
<b>Hippocampi</b>	28 ± 18 (0-55)	Not assessed	32 ± 15 (1-54)
<b>Pituitary gland</b>	28 ± 19 (1-53)	Not assessed	27 ± 17 (0-53)
<b>Cerebellum</b>	28 ± 23 (0-65)	36 ± 22 (0-65)	36 ± 22 (0-65)
<b>Vermis</b>	30 ± 23 (0-56)	37 ± 21 (0-56)	37 ± 21 (0-56)
<b>Pons</b>	31 ± 17 (0-61)	37 ± 17 (0-55)	37 ± 17 (0-55)
<b>Thalamus</b>	28 ± 17 (0-57)	31 ± 16 (0-51)	31 ± 16 (0-51)
<b>Hypothalamus</b>	29 ± 19 (0-54)	Not assessed	33 ± 18 (0-54)

<sup>a</sup> Bilateral values in Studies II-III are presented for descriptive purposes in this thesis. These values were not used in the original analyses. In Study IV we used bilateral means in the primary analyses.

<sup>b</sup> Right optic nerve missing; unilateral value used.

In Study I, the PTV dose was 50 Gy on average (SD=9; range 24-60). WBRT doses were available in Studies I-II (n=17, mean 29 Gy, SD=7, range 23-40) and Studies III-IV (n=10, mean 30 Gy, SD=6, range 23-36). WBRT was generally part of craniospinal irradiation.

Comparisons between RT modality were not feasible due to small and non-comparable groups, and because proton RT was delivered exclusively as PBRT, whereas photon RT included both PBRT and WBRT treatments. In Studies I-II, the cohort included 21 patients treated with photon RT (WBRT=

11; PBRT= 10), 11 treated with Proton RT (WBRT=0; =PBRT=11), 12 treated with combined photon and proton RT (WBRT=6; PBRT=6), and 6 treated with gamma knife (PBRT only). In study III-IV, the cohort included 11 patients treated with photon RT (WBRT=7; PBRT= 4), 6 treated with proton RT (WBRT=0, PBRT=5), and 5 treated with combined photon and proton RT (WBRT=3, PBRT=2).

## Neurocognitive assessments

In Study I and II, neuropsychological data were obtained retrospectively from clinical records and neuropsychological test protocols as part of routine clinical follow-up in Sweden during this period. Assessments were recommended before treatment, 1, 3 and 5 years after treatment. These data were collected prior to implementation of the common Nordic neuropsychological protocol; consequently, local test procedures and follow-up schedules varied over time. The composition of test batteries differed across PBTS due to changes in clinical routines and individual clinical considerations. Depending on age and assessment time point, different versions of the Wechsler intelligence scales were used (<sup>122-128</sup>). All IQ indexes of the Wechsler intelligence scales were included and consisted of Full-scale IQ (FSIQ); Verbal Reasoning Index (VRI), assessed using Similarities and Vocabulary; Perceptual Reasoning Index (PRI), assessed using Matrix reasoning and Block Design; Working Memory Index (WMI), assessed using Digit Span and Letter-Number Sequencing; Processing Speed Index (PSI), assessed using Coding and Symbol Search (normative mean=100, SD=15). Both index scores and individual subtest scores were included as outcome measures in the analyses. When the complete set of IQ subtests had not been administered, estimated index scores were calculated. Subtests scores were converted to age standardized scores (SS; mean=10, SD=3).

To capture a broader range of neurocognitive sequelae in Study I, the full NPA before and after RT was analyzed and categorized as severe/moderate problems ( $\leq -2$  SD), mild problems ( $> -2$  SD to  $-1$  SD), or no documented problems ( $\geq -1$  SD). Due to limited availability of recommended neuropsychological follow-up assessments, the most recent assessment for each individual was used in post-RT analyses. The time span varied between two months and nine years and eight months. Before RT, Raven Progressive Matrices was administered as part of the more comprehensive NPA, but was not included in the longitudinal analyses after RT. Terminology for IQ indexes reflects the most commonly administered test versions (WISC-IV/WAIS-IV).

In Studies III and IV processing speed was assessed using the Processing Speed Index (PSI) and included the subtests Coding and Symbol Search from the Wechsler intelligence scales (<sup>122,126</sup>). In Study IV, fatigue was additionally measured for the PBTS and controls, with the Swedish self-report version of the PedsQL Multidimensional Fatigue Scale (MFS). The scale comprises general fatigue, sleep-rest fatigue and cognitive fatigue subscales, which are linearly transformed to a 0-100 scale (higher scores indicating less fatigue) (<sup>129</sup>). Study IV also expanded the assessment of processing speed by including timed executive subtests from the D-KEFS Trail Making Test; Visual Scanning, Number Sequencing, Letter Sequencing, Number-Letter Sequencing, and Color-Word Interference Tests; Naming, Reading, Inhibition, and Inhibition Switching (SS; mean = 10, SD = 3) (<sup>130</sup>). A mean composite score from these D-KEFS subtests was combined with Coding and Symbol Search (PSI) and was computed as an overall index of processing speed.

Although the Trail Making Test and Color-Word Interference Test have executive demands, performance in pediatric RT cohorts is strongly influenced by processing speed demands. In this thesis, these measures were therefore interpreted primarily within the processing speed domain. The motor speed condition was not included, and performance was within the normative range for all participants.

In all studies, comparisons of neurocognitive function before and after RT were not feasible due to variability in the timing of pre-treatment assessments.

In Studies I-IV NPA after RT were conducted at varying time points. In Study I, 84% underwent NPA both before and after RT (follow-up mean 5 years, range 0-11). In Study II, 80% underwent NPA after RT (mean 5 years, range= 0-11). In Study III-IV, all participants underwent NPA after RT (mean 13 years, range 8-20).

Age at NPA after RT differed across studies:

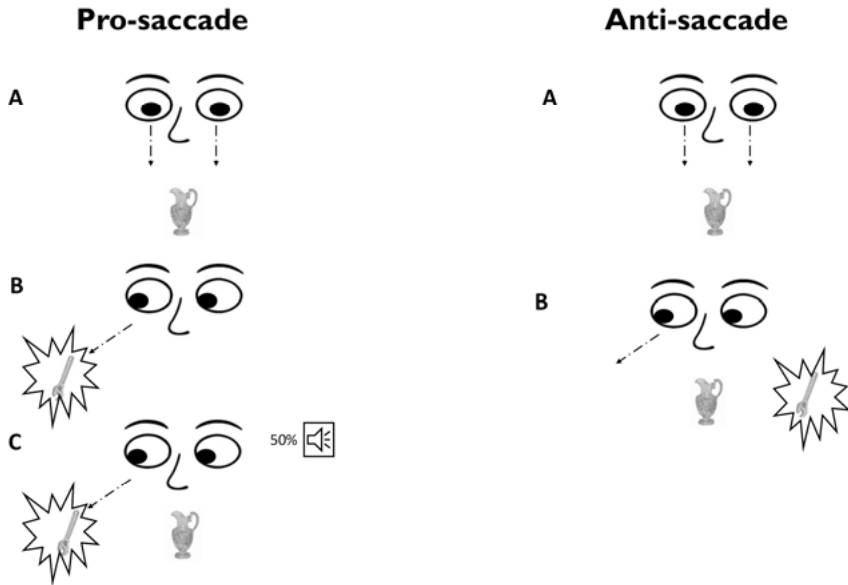
- Study I: 15 years (range 7-19)
- Study II: 15 years (range 8-19).
- Study III-IV: 23 years (range 15-34).

The age-matched control group in Studies III-IV had a mean age of 26 years (range 18-34).

## Eye-tracking procedures

In both Study III and Study IV, stimuli were presented using custom MATLAB scripts implemented with the Psychtoolbox library (<sup>131</sup>). Each trial began with a central fixation stimulus, followed by a peripheral picture presented 7.9° to the left or right. Participants completed 60 randomized pro-saccade trials, evenly distributed across *gap*, *silent overlap*, and *cued overlap* conditions (20 trials per condition; see Figure 2). Immediately after the pro-saccade task, participants completed 20 *anti-saccade* trials. In this condition, participants were instructed to shift their gaze as quickly as possible in the opposite direction of the peripheral stimulus. The anti-saccade trials followed the same structure as the silent overlap condition, except for the instruction to look away from, rather than towards, the peripheral stimulus. Instructions were provided both visually on the screen and orally, and were repeated when necessary.

On pro-saccade trials, participants were instructed to first fixate on the central stimulus and then look as quickly as possible toward the peripheral stimulus. In the *gap* condition, the central stimulus was extinguished shortly before the onset of the peripheral stimulus, and a gap interval drawn from a Gaussian distribution (mean=200 ms, SD=50 ms) was presented between central stimulus offset and peripheral onset. In the overlap conditions (*silent overlap* and *cued overlap*), the central stimulus remained on the screen for 1000 ms plus a variable time interval drawn from a Gaussian distribution (mean=400 ms, SD=200 ms) before peripheral stimulus onset. In the *cued overlap* condition, brief auditory warning cues (simple beeps) were presented on 50% of the overlap trials, 500 ms before peripheral stimulus onset; the remaining overlap trials were silent (*silent overlap* condition).



*Figure 2. Pro-antisaccade task. Pro-saccade task:* Each trial began with a central image (A), followed by a peripheral image (B-C). In the gap condition (B), the central stimulus was extinguished before peripheral onset, creating a temporal “gap”. In the overlap condition (C), the central stimulus remained on screen when the peripheral image appeared. Half of the overlap trials included an auditory warning cue, presented shortly before the offset of the peripheral stimulus. *Anti-saccade task:* Trials followed the overlap structure (A) but participants were instructed to shift their gaze as quickly as possible in the direction opposite to the peripheral target (B).

In Study IV, pupil cue effect and pupil anti-saccade effect were further analyzed: the pupil cue effect was defined as the difference in pupil dilation between the brief auditory cued overlap (auditory warning cue) and silent overlap conditions, reflecting visual attention-driven arousal in response to auditory alerting cues, and the pupil anti-saccade effect was defined as the difference in pupil dilation between the anti-saccade and silent overlap conditions, reflecting executive control-driven arousal during voluntary response inhibition and increased cognitive effort.

### Eye tracking data recording and analysis

Eye-tracking data were recorded with a Tobii Pro Spectrum (1200 Hz) following five-point calibration at a university lab and an outpatient pediatric clinic. Data were processed using the R package kollaR<sup>(132)</sup>.

### **Saccade measures (Study III)**

Gaps shorter than 75 ms were linearly interpolated, and eye position data (X and Y coordinate vectors) were smoothed using a moving median filter (15 ms window). Fixations and saccades were then identified with an I-VT filter (velocity threshold =  $35^\circ/\text{s}$ ) (<sup>132,133</sup>). Saccadic latency (saccadic reaction time) was defined as the time in ms from the onset of the peripheral stimulus to the initiation of a saccade in the correct direction. Trials in which participants did not initiate a saccade in the correct direction but maintained gaze on the screen were coded as no-shift trials. Trials were excluded if latency was  $<100$  ms or if central fixation was not maintained prior to peripheral onset. Participants contributing fewer than four analyzable trials were excluded from latency analyses. Five PBTS participants were excluded from the anti-saccade condition due to failure to shift gaze (0–2 trials), and one participant with hearing impairment was excluded from the cued-overlap condition.

### **Pupillometry (Study IV)**

Pupil data were pre-processed by removing physiologically implausible sample-to-sample changes ( $>\pm$  MAD from the mean). Gaps shorter than 200 ms were linearly interpolated and signals smoothed using a moving average filter (100 ms window). Pupil dilation was defined as the mean pupil diameter (mm) during the 1000 ms interval following peripheral onset minus baseline diameter during 700 to 500 ms interval preceding central onset (<sup>87</sup>). The baseline interval preceded the auditory alerting cues.

## **Data analyses**

As most clinical and RT data were non-normally distributed, Spearman rank correlation coefficient ( $r_s$ ) was used in Study I-IV to compare potential risk factors, radiation-related risk factors, and neurocognitive outcomes after RT. In study I performance on IQ assessments was compared with clinical and radiation-related risk factors before and after RT. Correlations of  $r_s = \pm 0.7$  to  $\pm 1.0$  were regarded as strong,  $r_s = \pm 0.6$  to  $\pm 0.4$  as moderate, and  $r_s = \pm 0.1$  to  $\pm 0.3$  as weak (<sup>134</sup>).

In study II, one-sample t-test was used to compare the sample mean on IQ index to the normative mean scaled score of 100 (SD=15) and IQ subtests to the normative mean scaled score of 10 (SD=3). An alpha level of  $<0.05$  was regarded as significant. The statistical analyses in Studies I and II were performed with SPSS (27 and 28; IBM Corp).

In study III eye tracking measures were averaged across valid trials for each participant and condition. Saccadic latency data were log-transformed prior to analysis due to positive skewness, with back-transformed values reported. Normality was assessed using the Shapiro-Wilk test, and outliers were identified using box plot criteria, one PBTS and one control participant were excluded. Group differences in saccadic latency were analyzed using independent t-tests, with effect sizes estimated using Cohen's *d*. To complement group level analyses, we examined the proportion of PBTS that could be classified as impaired on the pro-antisaccade task (e.g., saccadic latency and did no-shift in the correct direction). Each individual PBTS score was tested against the control group using the modified Crawford-Howell t-test with 1 degree of freedom. A significant result at  $p < 0.05$  indicates that the individual score is reliably below the control distribution. The Crawford-Howell procedure enables single-case comparisons against small control samples by adjusting for sample size and variability, and is regarded as more robust than conventional z-score norms when normative datasets are unavailable. This approach is often used in neuropsychological research to quantify individual-level impairment and estimate the proportion of cases showing clinically meaningful deficits. It is especially valuable in rare clinical populations where population norms do not exist and group-level analyses may mask individual variability (<sup>135</sup>). Associations between eye-tracking measures, processing speed, and mean RT doses to OAR were examined using Spearman's correlations. Sensitivity analysis was performed with and without potential outliers that were very slow on saccadic latency compared to the others. An alpha level of  $< 0.05$  was regarded as significant.

In study IV, group differences between PBTS and controls were analyzed using independent t-test, with effect sizes reported as Cohen's *d*. Normality was assessed using the Shapiro-Wilk test and box plot inspection. Within the PBTS group, associations with pupil dilation, fatigue, processing speed and mean RT doses to OAR were examined using Spearman's correlations. An alpha level of  $< 0.05$  was applied, with Bonferroni correction for multiple comparisons across processing speed subtests (adjusted  $\alpha = 0.004$ ). Statistical analyses in Study II and IV were performed using R Studio (version 4.3.2) and SPSS (version 30; IBM Corp.)

Given the exploratory nature of the studies and the limited sample sizes, correction for multiple comparisons was generally not applied. In Study IV, Bonferroni correction was used to account for the large number of processing speed outcomes analyzed.

## Ethical considerations

All studies in this thesis were approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2018/404 and 2020-05301), and it has been performed in accordance with the Declaration of Helsinki.

Several ethical considerations must be taken into account when conducting research involving a clinical population. In the retrospective studies, most data had already been approved for inclusion in clinical registries. We considered it inappropriate to contact all PBTS for additional consent, as this could be more inconvenient and a breach of their integrity. All data were de-identified and results were reported at a group level. On this basis, and in accordance with approval from the Regional Ethical Review Board in Uppsala, informed consent was not required for the retrospective studies.

In the prospective studies involving NPA and eye-tracking measures, participation could be emotionally challenging, as testing might remind some participants of their previous illness and treatment. However, since late complications may emerge or become more pronounced over time, participation could also provide new and clinically relevant information regarding neurocognitive sequelae. In those cases, they were referred to appropriate follow-up and support procedures. Neuropsychological testing might also be experienced cognitively demanding. While participants were informed that they could pause or stop the testing at any time, some may have continued due to perceived expectations. The NPA was conducted over one day, with several breaks and pauses as needed. For participants with moderate to severe impairments, testing was divided into two half days. All participants were offered a summary of their assessment result along with individualized recommendations. Routines for neuropsychological follow-up are typically limited to individuals up to 18 years of age in Sweden. As most of the participants in the prospective studies were adults, the absence of assessment could itself be considered ethically problematic, given the known risk of long-term neurocognitive sequelae. With participants' consent, neuropsychological test protocols were stored in their hospital charts to allow future clinical use if needed. The teenagers who participated were assessed at clinically appropriate time points. For the control group, assessment duration was shorter, and no significant burden or inconvenience was anticipated.

# Results

## Overall outcomes

The results of this thesis demonstrated that PBTS exhibited neurocognitive impairments that were present prior to RT and became more pronounced with increasing time since RT. Comprehensive NPA identified broader and more diverse and severe impairments than IQ measurements alone, underscoring the value of multidimensional assessment. Neurocognitive outcome was influenced by multiple tumor- and treatment related factors. Among these, mean RT doses to OAR (both established and potential new) and WBRT showed clearer and more consistent associations with neurocognitive impairment, compared with PTV dose and other examined risk factors. Whereas PTV dose was associated with performance on only one IQ subtest (Study I), mean RT doses to several OAR were associated with poorer IQ performance and slower processing speed (Studies II-IV). Slower processing speed was also associated with higher levels of fatigue in Study IV. Beyond traditional neuropsychological tests, PBTS demonstrated impairments in saccadic eye movements, altered pupil responses, and higher levels of fatigue. These outcomes were likewise associated with higher mean RT doses to OAR and WBRT.

Taken together, these findings indicate that neurocognitive late effects in PBTS are multifactorial and shaped by interacting clinical and radiation-related factors. Although radiation-related factors showed the most consistent dose-outcome patterns across neurocognitive, oculomotor, and arousal-related outcome domains, tumor-related vulnerabilities also contributed to outcome.

## Study I

Neurocognitive impairments were prevalent before RT and became more pronounced after treatment. Before and after surgery, a substantial proportion of patients performed  $\geq 1$  SD below normative means, with more extensive impairments detected when comprehensive NPA were considered rather than IQ measures alone (Figure 3a). After RT, neurocognitive impairment increased with longer follow-up time, particularly in processing speed and working memory, and was most pronounced among those who received WBRT (Figure

3b). Comprehensive NPA revealed more frequent and severe impairments than IQ measurements alone, both before and after RT.

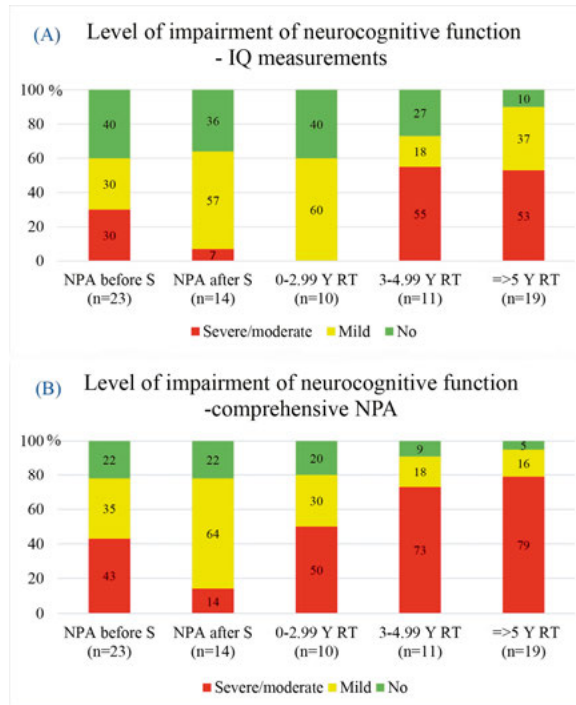


Figure 3. Level of impairment of neurocognitive function before surgery (S), after surgery, and after radiotherapy (RT), neuropsychological assessment (NPA) at 0-2.99, 3-4.99, and  $\geq 5$  years after RT. A: IQ test results categorized as severe/moderate ( $\leq -2$  SD), mild ( $> -2$  to  $-1$  SD), or no impairment ( $\geq -1$  SD). B: Comprehensive neuropsychological assessment categorized as severe/moderate ( $\leq -2$  SD), mild ( $> -2$  to  $-1$  SD), or no documented impairment.

The most common neurological debut symptoms at diagnosis included headache, visual problems, nausea, vomiting, and motor deficits. Before RT, the most prevalent neurocognitive impairments, in descending order, were documented problems with fatigue, learning, attention, memory, processing speed, executive and psychosocial functioning. After RT, the most frequent neurocognitive impairments, in descending order, consisted of documented problems with processing speed, memory, executive functions, attention, fatigue, psychosocial functions and visual perception. Notably, fatigue was not assessed using a standardized questionnaire but was documented through clinical observations observed by a neuropsychologist.

### **Clinical-related risk factors before and after radiotherapy**

Before RT, larger tumor size, IICP and vision impairment were correlated with lower performance on specific IQ subtests (Block Design, Similarities, and Vocabulary). No significant correlations were observed between IQ measures and sex, age at diagnosis, tumor location, or hearing impairment.

After RT, several potential risk factors demonstrated moderate correlations with lower performance on IQ measures, including larger tumor size, IICP, infratentorial tumor location, surgery, and chemotherapy. Tumor size was associated with lower performance on one subtest within each index, except processing speed. IICP correlated with reduced performance on one processing speed subtest. Surgery was associated with lower performance on WMI and one verbal subtest. Older age at RT was associated with higher working memory span and faster processing speed (one subtest).

Longer time since RT correlated with lower PSI and WMI. Infratentorial tumors was associated with lower FSIQ, WMI and PSI compared with supratentorial tumors.

### **Radiation-related risk factors**

Higher RT dose to the PTV correlated moderately with lower performance on WMI. Within the WBRT group, lower performance on WMI correlated strongly with WBRT dose, and moderately with FSIQ, PRI and PSI.

## **Study II**

PBTS performed below the normative mean on FSIQ, VRI, WMI, and PSI after RT (one-sample t-test). The time from RT to the last NPA ranged from nine months and eleven years and seven month (139 months). Of the 44 children, 35 had undergone an NPA after RT.

### **Radiation-related risk factors**

Higher mean RT doses to established and potential new OAR correlated strongly and moderately with lower performance on several IQ measurements.

Higher mean RT dose to the cochleae (left and right) correlated moderately with lower performance on all IQ indexes. Higher mean RT dose to the optic nerves (left and right) correlated moderately with lower performance on FSIQ, PRI, PSI, and WMI (for the left optic nerve). Higher mean RT dose to the hippocampi (left and right) correlated moderately with PSI and one working memory subtest.

Higher mean RT doses to the pons and cerebellum correlated moderately with all IQ subtests, and within the WBRT group the correlations were strong. Higher mean RT dose to the vermis correlated moderately with FSIQ, PRI, and PSI. WBRT dose correlated moderately with all IQ indexes. No significant correlations were observed between IQ measurements and mean RT doses to the chiasma, hypothalamus (left and right), or thalamus.

### **Clinical risk factors and follow-up time since RT**

Tumor size correlated moderately with verbal, visuospatial reasoning and working memory subtests. Surgery correlated moderately with lower performance on WMI and visuospatial reasoning.

Longer time since RT correlated moderately with poorer performance on WMI and PSI. As shown in Figure 4, working memory and processing speed scores were lower with increasing time since RT.

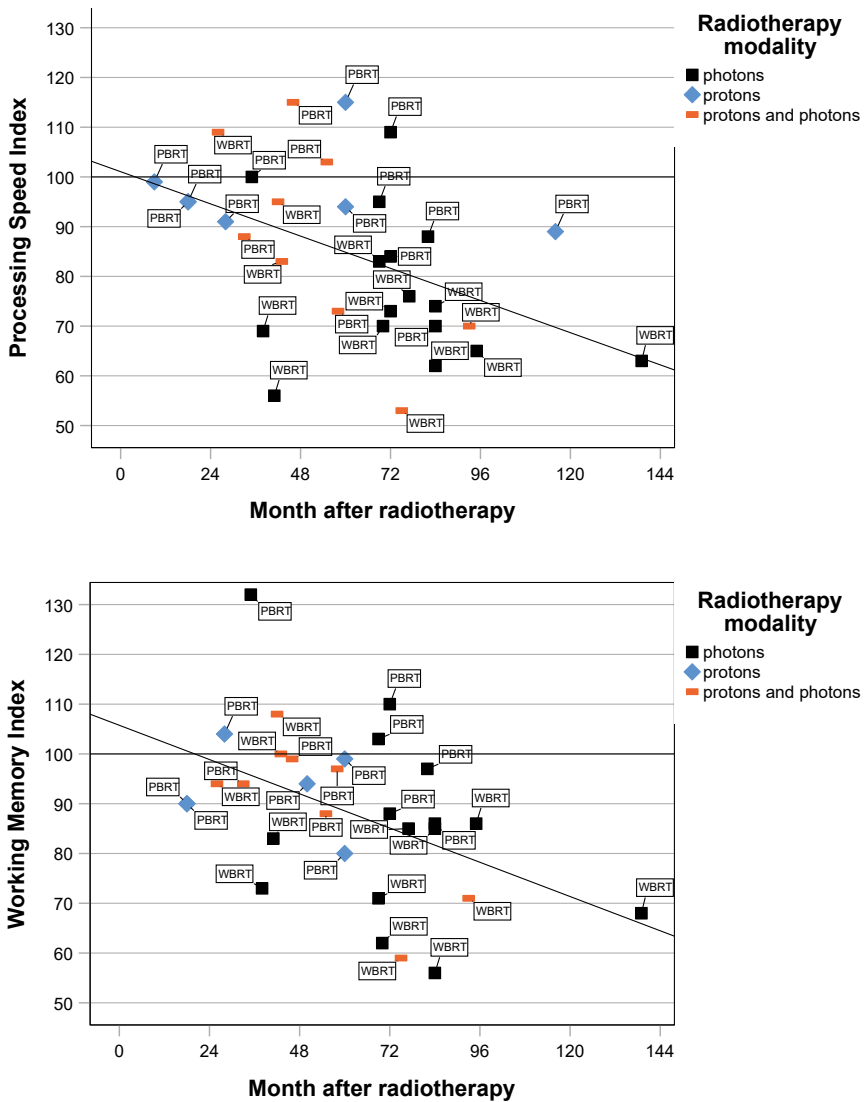


Figure 4. Scatterplots of performance on working memory and processing speed index ( $M=100$ ,  $SD=15$ ) against months after radiotherapy. Lower scores indicate lower performance and longer time since radiotherapy. The shapes define radiotherapy modality. WBRT= whole-brain radiotherapy and PBRT= partial brain radiotherapy. The least squares regression line is included for illustrative purposes.

### Study III

PBTS showed oculomotor impairments on the pro-antisaccade task compared with age-matched controls. As a group, PBTS had significantly longer saccade latencies in the gap and anti-saccade conditions, with large effect sizes for the gap and small for the anti-saccade condition (independent t-tests; Cohen's  $d$ ).

Those who had received WBRT showed significantly longer saccade latencies across all four conditions (gap, silent overlap, cued overlap and anti-saccade) with large effects for the pro-saccade conditions (gap, silent overlap and cued overlap) and moderate effects for anti-saccades. Modified t-tests indicated that both the PBRT and WBRT groups showed impairments on the pro-antisaccade task relative to controls, although difficulties were more pronounced after WBRT. Impairments on the cued overlap condition were predominantly present in the WBRT group, whereas the gap, silent overlap and anti-saccade conditions showed similar proportions of impairment across both RT groups. Nearly half of the PBRTs (48%) had significantly prolonged anti-saccade latencies and difficulties on no-shift trials (i.e., not initiating a saccade in the correct direction). See figure 5 for an overview of group differences on the four saccadic latency conditions; gap, silent overlap, cued overlap and anti-saccade.

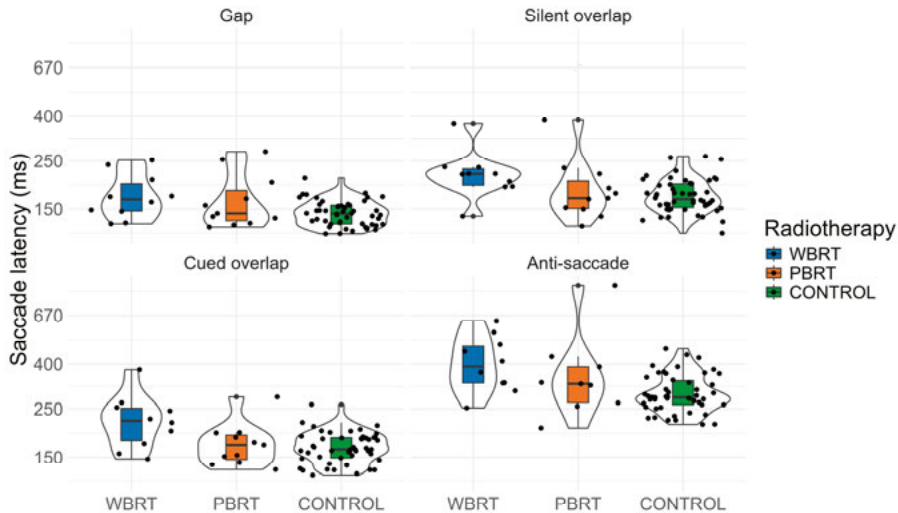


Figure 5. Group differences on saccade latency. WBRT denotes whole-brain radiotherapy and PBRT denotes partial-brain radiotherapy.

In PBRTs, longer saccadic latencies were moderately associated with poorer processing speed (PSI; Coding and/or Symbol Search) across all conditions except saccadic latency cued overlap.

### Radiation-related risk factors

Mean RT doses to the optic nerves were associated with longer pro-saccade latencies (silent and cued overlap conditions). These associations remained

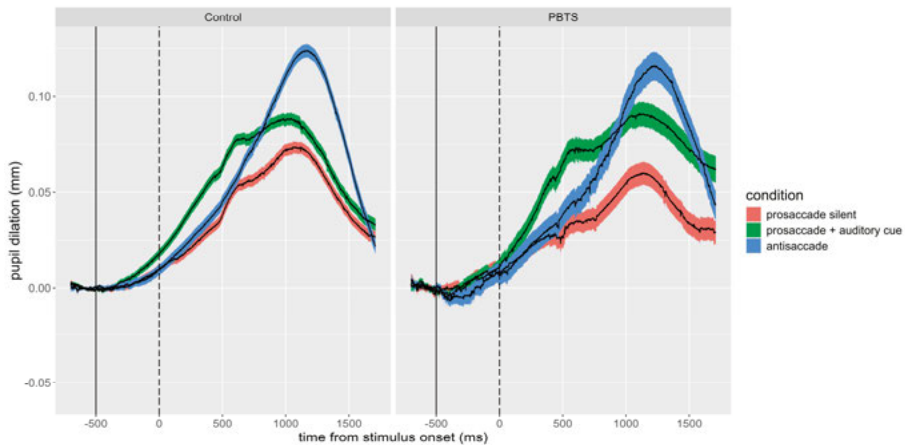
when individuals with pronounced visual impairments were excluded (sensitivity analysis). When one PBTS with pronounced visual impairment - who had received high RT doses to the optic nerves but low dose to the pons (in the PBRT group) - was excluded, a moderate association between higher mean RT dose to the pons and longer saccadic latency in the silent overlap condition became apparent. No significant associations were found between saccadic latency and mean RT doses to the chiasma, cerebellum, frontal lobes or thalamus, as well as WBRT dose.

### Clinical related risk factors and follow-up time since radiotherapy

Larger tumor size was moderately associated with longer saccadic latency in the silent overlap condition. Age at RT, time since RT, tumor location, and IICP were not significantly related to oculomotor performance.

### Study IV

PBTS showed increased pupil dilation to alerting cues (pupil cue effect) compared with age-matched controls, with a medium effect size and stronger effect size for the WBRT group (independent t-tests; Cohens'd). In contrast, there were no significant group differences in pupil dilation during anti-saccades (anti-saccade pupil effect); effect sizes were small. See Figure 6 for pupil dilation in controls and PBTS by condition.



*Figure 6.* Task-evoked pupil dilation in controls and pediatric brain tumor survivors (PBTS) by condition. Pupil dilation was baseline-corrected using the mean pupil size during -700 to -500 ms prior to peripheral stimulus onset (solid line). Auditory warning cues were presented 500 ms before stimuli onset of the peripheral stimuli (dashed line). Red indicates pro-saccade trials, green pro-saccade trials with auditory cue, and blue anti-saccade trials.

PBTS reported higher levels of cognitive fatigue compared with controls (medium effect size), while general, sleep-rest and total fatigue did not differ between groups. Within the WBRT group, PBTS reported higher levels of general (medium effect size) and cognitive fatigue (large effect size) compared with controls.

Within PBTS, increased pupil dilation correlated moderately with general fatigue, sleep-rest fatigue and total fatigue. Slower processing speed correlated strongly and moderately with higher levels of general fatigue, cognitive fatigue and total fatigue.

### **Radiation-related risk factors**

Higher mean RT dose to the cerebellum and vermis correlated moderately with lower pupil dilation on the anti-saccade pupil effect. No significant correlations were found between pupil dilation and WBRT dose.

Higher level of general fatigue was strongly and moderately correlated with higher RT dose to the frontal lobes, optic nerves and WBRT dose. Cognitive fatigue correlated moderately with higher RT doses to the frontal lobes and WBRT dose. Total fatigue correlated moderately with higher RT dose to the frontal lobes. No significant correlations were found between fatigue and RT dose to other OAR.

Slower processing speed was moderately associated with higher RT dose to most investigated OAR (established and potential new OAR). No association was observed for the hypothalamus, and the association with thalamic dose did not remain statistically significant after Bonferroni correction. Slower processing speed was additionally associated with higher WBRT dose. See figure 7 for correlations between mean processing speed and mean RT doses to OAR.

### **Clinical related risk factor and follow-up time since radiotherapy**

Larger tumor size correlated with higher levels of total fatigue, sleep-rest fatigue, and slower processing speed.

No significant correlations were observed between pupil dilation, fatigue or processing speed and sex, age at RT, time since RT, localization, or IICP. Neither did pupil dilation show any significant associations with tumor size.

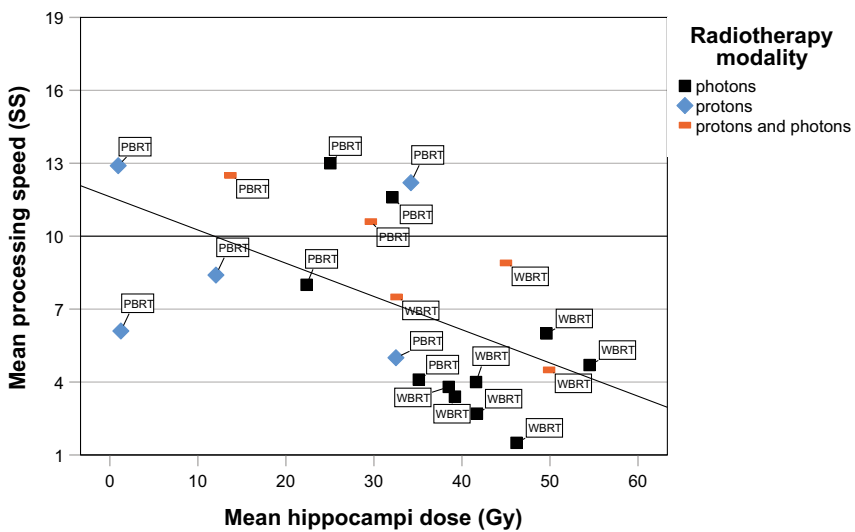
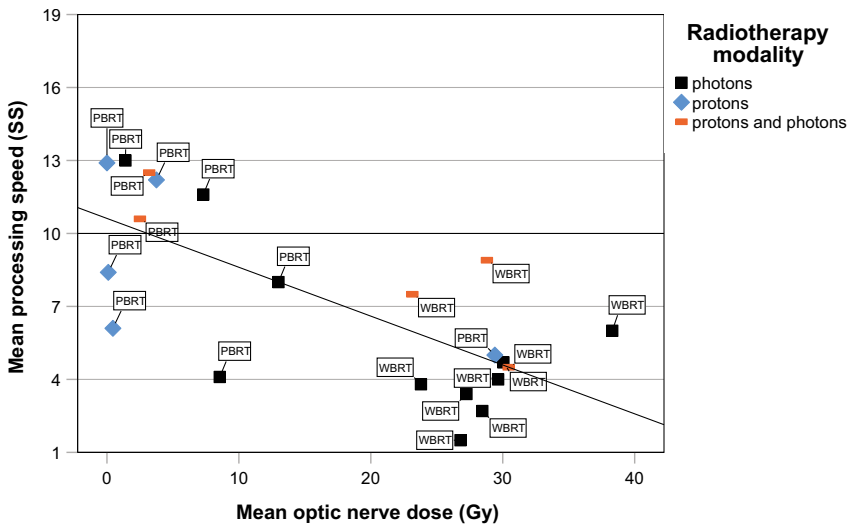


Figure 7. Scatterplots illustrating the associations between mean processing speed ( $M = 10, SD = 3$ ) and mean radiotherapy dose to organs at risk (optic nerve and hippocampi). The shapes define radiotherapy modality. WBRT=whole-brain radiotherapy and PBRT= partial-brain radiotherapy. The least squares regression is included for illustrative purposes.

# Discussion

Taken together, the findings of this thesis indicate that neurocognitive impairments in PBTS are present prior to RT and become more pronounced with increasing time since treatment. Neurocognitive outcome was multifactorial and related to both tumor- and treatment-related factors. Radiation-related factors, particularly WBRT and mean RT dose to OAR, showed clearer and more consistent associations with outcome than other examined factors or PTV dose. Across the included studies, higher mean RT doses to several established and potential new OAR were associated with poorer IQ performance and slower processing speed. These associations were evident across processing speed measures derived from both WISC/WAIS and D-KEFS. In long-term follow-up, slower processing speed was also associated with prolonged saccadic latency and higher levels of fatigue. In addition, PBTS demonstrated impairments in saccadic eye movements and altered pupil responses, which, along with fatigue, were associated with higher mean RT doses to OAR and WBRT.

Against this background, the following sections discuss these findings in relation to clinical risk factors, assessment timing, long-term trajectories, and radiation-specific dose–response effects.

## Clinical risk factors and neurocognitive outcomes

Neurocognitive outcomes in PBTS are multifactorial and influenced by clinical, treatment-related, and developmental factors<sup>(2–4)</sup>. Previous studies have identified tumor size, IICP, visual impairment, sex, age at diagnosis, and tumor location as risk factors for neurocognitive impairment before RT<sup>(20,136,137)</sup>. Surgery alone and/or chemotherapy, irrespective of RT, may also affect neurocognition, including memory, processing speed, executive functioning, and motor function<sup>(20,138–140)</sup>.

Several of these risk factors were also observed in Study I. Larger tumor size, IICP and vision impairment were associated with lower performance on

several Weschler subtests, highlighting the importance of accounting for clinical vulnerability when interpreting baseline performance. After RT, multiple clinical risk factors continued to influence outcome. In Study I, younger age at RT, tumor size, surgery, IICP, infratentorial location and chemotherapy were associated with lower performance on IQ indexes and subtests. In Study II, larger tumor size and surgery remained associated with lower performance on several IQ subtests.

Across all four studies (I–IV), larger tumor size emerged as the most consistent clinical risk factor. It was associated with lower performance on IQ subtests, slower processing speed, longer pro-saccade latencies, and higher levels of fatigue. This pattern suggests that tumor burden, which also reflects larger treatment volumes, contributes to vulnerability across multiple outcome domains.

In contrast, in the long-term follow-up studies (III-IV), other clinical-related risk factors such as age at RT, time since RT, tumor location and IICP showed no strong independent associations with neurocognitive, oculomotor, or arousal-related measures when examined individually. Although such factors are known to influence outcome, the weak or absent associations observed here may partly reflect limited statistical power due to the smaller sample size.

Taken together, these findings underscore the clinical complexity in which tumor burden and treatment exposures co-occur and jointly shape vulnerability across domains, rather than supporting strong independent effects of multiple clinical risk factors. Identifying such vulnerability profiles before RT may support risk stratification, targeted rehabilitation, and planning of long-term follow-up.

## Baseline neuropsychological assessment and timing

Given the multifactorial risk profile observed in PBTS, systematic NPA before treatment, when clinically feasible, is recommended to establish a valid baseline, identify vulnerabilities and support subsequent monitoring and rehabilitation<sup>(9,18,19)</sup>. The timing of NPA requires consideration of tumor- and treatment related factors as well as the child's clinical status<sup>(4,18)</sup>. Current clinical guidelines recommend NPA within three months of diagnosis and indicate that it may be conducted before or after surgery and/or following urgent medical treatments<sup>(28)</sup>.

However, pre-surgical assessment may not always represent the optimal baseline, as neurological and neurocognitive functioning may already be affected by hydrocephalus (<sup>141</sup>). Visual impairment and fatigue, may also influence baseline performance, as observed in the present cohort. In Study I, NPAs were routinely conducted before surgery and fatigue was commonly documented at that time-point, likely affecting performance. Visual impairments were common prior to RT, affecting approximately 60% of the cohort, and may have influenced baseline performance, particularly on task with visuospatial and processing speed demands. In such cases, shorter assessments or repeated measures over time may yield a more reliable baseline for children scheduled to receive RT (<sup>142</sup>). Establishing an adequately timed baseline is essential for differentiating pre-morbid vulnerabilities from treatment-related decline (<sup>20,136,137</sup>), but was not feasible in the present thesis due to constraints in the clinical workflow.

Beyond timing, selection of neurocognitive measures is critical. IQ provides a global indicator of neurocognitive outcome (<sup>22</sup>), and domain-level indexes (e.g., processing and working memory) improve sensitivity to specific vulnerabilities that are common in PBTS (<sup>20,126,143</sup>). However, IQ alone does not capture the breadth of neurocognitive sequelae in PBTS, and comprehensive NPA is often required to assess attention, perceptual and visuomotor functions, processing speed, memory, and executive functions (<sup>18,22</sup>). In Study I, comprehensive NPA together with neurological reports revealed more diverse and frequent difficulties than IQ alone, highlighting the added value of domain-level assessment. Notably, processing speed, a domain frequently affected following RT, was already reduced before RT and may reflect interacting influences on fatigue, visual impairment, attentional difficulties, motor function and affective symptoms (<sup>9,138,144</sup>). Processing speed therefore appears to be a sensitive indicator of early vulnerability and a relevant domain for longitudinal surveillance.

## Long-term neurocognitive follow-up and trajectories

Long-term follow-up with periodic standardized NPA provides an important basis for detecting evolving or late-emerging decline, and for planning appropriate rehabilitation (<sup>8,9,21</sup>). Neuropsychological deficits often unfold slowly and may progress over time, underscoring the need for longitudinal monitoring to detect RT-induced decline (<sup>4</sup>). The Nordic protocol for neuropsychological follow-up of children treated with brain tumors recommend NPA at diagnosis, 2- and 5-years post-diagnosis (+/-3 months), with additional

assessments for rehabilitation needs, schools' transitions and adolescence (<sup>27,28,145,146</sup>). When comprehensive NPA is not feasible, assessment of core domains such as processing speed and working memory using widely available Wechsler scales is recommended (<sup>4,147</sup>).

Importantly, in Study I-II, retrospective follow-up varied widely and only 38% were assessed five years after RT, largely due to limited neuropsychological resources during the study period. Despite this, neurocognitive sequelae appeared progressively aggravated and longer time since RT was associated with lower working memory and processing speed performance. In Study III-IV, time since RT did not correlate with processing speed, which may indicate that the most pronounced variation in processing speed emerges within the first five years after RT. Nevertheless, slower processing speed remained prevalent 8-20 years after RT and was associated with longer pro-antisaccades and higher fatigue levels.

Adult PBTS remain at elevated risk of persistent neurocognitive difficulties, particularly in processing speed, attention, executive functions, and cancer-related fatigue (<sup>2,3,24</sup>). Early CNS abnormalities after cranial RT may contribute to chronic pathophysiological progressive impairment into adulthood (<sup>2,25</sup>). National care programs and updated national cancer strategy guidelines emphasize structured assessment of rehabilitation needs, long-term follow-up, registry-based data collection, and age-adapted rehabilitation services for children, adolescents and young adults with cancer (<sup>23,29</sup>). These priorities underscore the need for sustained neuropsychological monitoring and targeted support extending into adulthood (<sup>2,3,24,25</sup>).

## Radiotherapy dose to organs at risk and neurocognitive outcomes

Prescribed RT dose, or PTV dose is commonly used to evaluate neurocognitive risk after RT. However, it does not adequately capture dose-volume heterogeneity outside the target volume, and therefore is likely to underestimate exposure to structures involved in neurocognitive networks (<sup>37,40</sup>). In Study I, higher PTV dose was associated with lower performance on one working memory subtest only. By contrast, in Studies II-IV, higher mean RT doses to several established and potential new OAR showed clearer and more consistent associations with neurocognitive performance, including lower IQ scores, longer saccade latencies, reduced task-evoked pupil dilation, higher fatigue levels and slower processing speed. These findings suggest that

anatomically specific mean-dose metrics may provide greater sensitivity in detecting RT-related neurocognitive effects than PTV dose alone and therefore merit consideration in dose–response analyses in PBTS (<sup>40,77,148</sup>).

In Sweden, pediatric proton RT is centralized to Uppsala, where proton therapy is now the standard modality for most children. Photon-based techniques continue to be used for selected indications, and both modalities remain part of contemporary clinical practice. The establishment of the national proton center in Sweden (Scandion Clinic) has enabled more conformal dose distributions and strengthen the rationale for evaluating associations between dose to OAR and long-term neurocognitive outcomes. However, systematic dose-response studies remain scarce, and long-term follow-up is needed to determine whether contemporary dose-sparing approaches translate into improved neurocognitive trajectories. The retrospective cohort in this thesis reflects the transitional period, prior to Scandion, with mixed photon and proton techniques and heterogeneous dose distributions. Although a higher proportion of pediatric patients now receive proton therapy, both modalities remain clinically relevant. This mixed landscape limited direct modality comparisons in the presents cohort but enabled detailed examination of mean RT dose to OAR across treatment techniques.

Higher RT doses, larger irradiated brain volumes and exposure at younger age are well-established risk factors for neurocognitive late complications (<sup>4,15,35</sup>). In this thesis, children who had received WBRT consistently showed the most pronounced impairments across outcome domains, including global IQ, domain-specific measures, processing speed, saccadic performance, pupil responses and fatigue. In this cohort, those who received WBRT performed lowest overall. However, impairments were not limited to WBRT. Descriptive scatterplots and modified t-tests for the pro–antisaccade task showed that a substantial proportion of patients treated with PBRT also exhibited slower saccadic latencies and directional errors relative to age-matched controls.

Regarding mean RT dose to OAR, higher mean cochlear dose was associated with lower performance across IQ measures (Study II) and slower processing speed in long-term follow-up (Study IV). These findings suggests that radiation exposure to the cochleae may have broader relevance beyond auditory function alone. Many of the patients with higher cochleae dose had received WBRT, which is known to adversely affect processing speed. However, cochlear dose may contribute additively, either by reflecting more extensive radiation exposure or trough downstream effects on subclinical hearing

dysfunction on cognitive efficiency. Previous work has linked cochlear dose primarily to estimated IQ (<sup>149</sup>), whereas the present findings extend this literature by demonstrating associations with directly assessed neurocognitive performance, including processing speed.

Higher cochlear dose substantially increases the risk of severe hearing loss, particularly at mean doses  $\geq 36$  Gy (<sup>150</sup>). Severe hearing loss has been associated with worse neurocognitive outcomes and academic performance in survivors of childhood cancers treated with RT (<sup>150-153</sup>). In the present cohort, several patients received cochlear doses well above this threshold, in some cases exceeding 50 Gy, yet only one had a documented hearing impairment. This discrepancy suggests potential under-detection of hearing deficits, consistent with reports that sensorineural hearing loss may emerge or progress years after treatment. In medulloblastoma patients can severe hearing loss occur more than five years after of proton RT (<sup>150</sup>). Given the educational and psychosocial consequences of untreated hearing loss, systematic audiological screening, extending into long-term survivorship, appears warranted even when early post-treatment hearing is preserved.

Together, these findings indicate that cochlear dose may influence neurocognitive outcomes indirectly, through effects on sensory input and cognitive efficiency, as well as by indexing broader radiation exposure. Prior studies have highlighted the importance of reducing mean RT dose to the cochleae (<sup>66-69</sup>), and IMPT provides better sparing compared with IMRT (<sup>149</sup>). Incorporating cochlear dose considerations and audiological follow-up into survivorship care may therefore be clinically meaningful for protecting neurocognitive development.

Higher mean RT dose to the hippocampi was associated with lower working memory and processing speed (Study II), and in Study IV the associations were stronger for multiple processing speed measures, particularly reading (Color-Word Interference Test), a function highly relevant for daily academic performance in PBTS. These findings strengthen previous evidence that hippocampal dose should be minimized to preserve neurocognitive function (<sup>37,73,74</sup>). Proton RT can substantially reduce the mean hippocampal dose, and hippocampal sparing IMPT may further lower dose with minimal impact on whole-brain target coverage and an estimated reduction in risk of neurocognitive impairment (<sup>53,154</sup>). When proton RT is not feasible, hippocampal-sparing VMAT during WBRT can also reduce mean dose and should be considered as an alternative approach (<sup>49</sup>). Given the central role of the hippocampus for

learning and memory, these results support dose-sparing strategies to protect neurocognitive functions essential for academic functioning and developmental trajectories in PBTS.

A sparing radiation approach is also feasible for the hypothalamus and pituitary gland, either with IMPT (<sup>45</sup>) and VMAT (<sup>49</sup>), to reduce the risk of hypothalamic-pituitary dysfunction. In the present thesis, higher mean RT dose to the pituitary gland within the WBRT group was associated with lower performance on working memory in Study II and with slower processing speed in the long-term follow-up Study IV. These associations remained significant after correction for multiple comparisons, indicating a robust relationship between pituitary radiation dose and processing speed outcomes. These findings can be clinically relevant, as hypothalamic-pituitary dysfunction may indirectly affect neurocognitive function through endocrine pathways (<sup>71,72</sup>). These regions are important for social- and executive networks and a previous study has reported that craniopharyngioma patients who had received RT were less able to reliably identify the emotional content in vocal expressions (<sup>155</sup>). In contrast, mean RT dose to the hypothalamus did not show significant associations with neurocognitive outcomes in the present studies. In Study II, no significant correlation was found between mean RT dose to the hypothalamus or thalamus and IQ subtests. This may partly reflect that IQ measurements alone are not enough to detect all radiation-related neurocognitive complications as shown in Study I. In the long-term follow-up (Study IV), higher RT doses to the thalamus were associated with slower performance on two visual search measures. However, these associations did not remain significant after Bonferroni correction and should therefore be interpreted as exploratory. Nonetheless, a recent study has reported reduced thalamic volume following cranial RT and associations between higher thalamic dose and poorer verbal reasoning (<sup>107</sup>). Further studies are warranted to clarify dose-response relationships involving the hypothalamic-pituitary region and thalamus, as well as the clinical relevance of hypothalamic-pituitary dysfunction for long-term neurocognitive outcome and treatment planning (<sup>71,72</sup>).

Several of the OARs examined in this thesis form interconnected nodes within cortico-subcortical networks supporting visual processing, visuomotor control, attention and processing speed-domains highlighted in the introduction as particularly vulnerable following RT (5, 48-59-61). Rather than reflecting isolated regional effects, radiation-related associations across these structures point toward disrupted network functioning underlying neurocognitive late effects in PBTS.

Within these regions, the optic nerves represent the first major input pathway into cortical visual systems and are therefore critical for efficient transmission of visual information. The optic nerves appear particularly radiosensitive, likely due to their high oligodendrocyte content and vulnerability during myelination, predisposing to late or delayed radiation toxicity (<sup>5,37,38</sup>). In this thesis, higher mean RT doses to the optic nerves were associated with lower IQ performance (Study II) and slower processing speed at long-term follow-up (Study IV). Slower processing speed was in turn associated with longer saccade latencies, and higher optic nerve doses were associated with longer pro-saccade latencies. Together, these findings suggest that RT-related disruption of early visual pathways may affect downstream visuospatial and attentional networks, contributing to slowed processing speed and visuomotor inefficiency, consistent with network-level findings in PBTS (<sup>47</sup>).

The cerebellum and vermis are integral components of cerebro-cerebellar networks supporting visuomotor coordination, sensorimotor integration, attention and executive control (<sup>77,78,156</sup>). Although these posterior fossa structures are not routinely delineated as OARs, their proximity to brainstem pathways makes them susceptible to RT exposure. In this thesis, higher mean RT doses to cerebellum and vermis were associated with lower IQ (Study II), slower processing speed, reduced task-evoked pupil dilation and higher levels of fatigue (Study IV). This pattern suggests altered functioning within networks that support both cognitive processing and arousal regulation, rather than isolated cerebellar deficits.

The pons serves as a major relay within visuomotor networks, linking cerebellar, brainstem and cortical systems involved in saccade initiation and visual attention (<sup>157</sup>). In this thesis, higher mean RT doses to the pons were associated with lower IQ performance (Study II) and longer pro-saccade latencies (Study III), indicating slowed visuomotor processing. Higher RT doses to the pons was also associated with lower performance on FSIQ and indexes (Study II), and on several slower processing speed measures, particularly reading (Color-Word Interference Test). These findings further support vulnerability of sub-cortical relay structures within distributed visuomotor networks after RT.

Frontal regions contribute to control of saccadic eye movements, such as saccade generation (<sup>103</sup>). Although frontal lobe dose was not independently associated with saccadic latency in the present cohort, higher mean RT dose to the frontal regions was strongly associated with slower processing speed measures, particularly PSI and Color-Word Interference Test. Higher RT

doses to the frontal lobes was also associated with higher levels of fatigue (Study IV). These findings support the frontal lobes involvement in distributed neurocognitive networks affected by RT.

Taken together, associations across the optic nerves, cerebellum, vermis, pons and frontal regions suggest that radiation-related effects on processing speed, oculomotor control and fatigue in PBTS involve multiple interconnected components of visuomotor and attentional networks.

These findings indicate that mean RT doses to OAR provides a more sensitive measure of clinically relevant radiation exposure to neurocognitive networks than PTV dose alone.

## Eye-tracking measures as a complement

As a complement to standardized NPA, eye-tracking in Study III revealed systematic oculomotor disturbances after RT, with slower pro-antisaccades in PBTS compared with controls. Impairments were most pronounced after WBRT, but were also evident following PBRT. This indicates that oculomotor slowing is not restricted to diffuse irradiation. Higher mean RT doses to the optic nerves and pons were associated with slower processing speed. This supports the hypothesis that oculomotor control and cognitive efficiency rely on shared networks linking visual input, visuomotor relay, and higher-order processing. Pro-saccades primarily reflect reflexive visuomotor responses, whereas anti-saccades also require inhibition and executive control. This layered organization provides a mechanistic bridge between RT-related slowing of bottom-up transmission and top-down control<sup>(63)</sup>. The pattern observed in PBTS, prolonged latencies and increased directional errors is consistent with prior evidence of attentional and executive vulnerability in this group and is consistent with patterns observed in other clinical groups in which visuomotor and executive control systems are affected<sup>(101,158)</sup>.

Notably, stimulus-based alerting cues failed to normalize performance, indicating that attentional difficulties in PBTS are more likely driven by slowed information processing rather than isolated inhibitory dysfunction. In contrast to ADHD where external cueing often improves performance<sup>(85)</sup>, PBTS appear to exhibit a distinct neurocognitive profile characterized by reduced processing speed, which may limit the effectiveness of such alerting cues<sup>(159)</sup>. Prolonged saccadic latencies, particularly following WBRT and during anti-

processing speed, which may limit the effectiveness of such alerting cues (<sup>159</sup>). Prolonged saccadic latencies, particularly following WBRT and during anti-saccade conditions, further support this distinct neurocognitive profile and highlight saccadic measures as sensitive markers for longitudinal monitoring.

Eye-tracking (Tobii 1200 Hz system) allowed for high-precision saccadic recordings in PBTS. Despite common visual impairments, usable eye-tracking data were obtained, suggesting that eye-tracking may be feasible in this population. Eye-tracking provides sensitive measures of oculomotor function, (<sup>103</sup>) while findings should be interpreted in conjunction with ophthalmological assessments to account for visual and ocular factors that may influence performance (<sup>6</sup>) and neuroimaging can offer additional information on visual and network related alternations (<sup>108</sup>).

To date, no studies have applied a pro- and antisaccade task using high-precision eye-tracking in PBTS. This thesis therefore investigates this previously unexplored approach to assessing oculomotor and cognitive performance. However, a previous bedside study in craniopharyngioma patients reported anti-saccade difficulties associated with impaired attention and processing speed following proton RT, but without eye-tracking measures (<sup>106</sup>).

In addition to cognitive slowing, Study IV revealed that PBTS altered arousal regulation after RT. PBTS showed greater cue-evoked pupil dilation and reported higher levels of fatigue compared with controls, indicating inefficient phasic arousal response rather than adaptive task engagement (<sup>85,117,118</sup>). Within PBTS, reduced task-evoked dilation and slower processing speed were associated with higher RT doses to the cerebellum and vermis, regions implicated in cerebro-cerebellar networks supporting cognitive, sensorimotor and autonomic regulation (<sup>59,75,160</sup>).

Given that arousal regulation supports attentional control and processing speed, these findings provide converging evidence for a network-level mechanism in which RT-related injury to cerebellar–brainstem pathways contribute to both slowed information processing and increased fatigue. Similar alterations in pupil dynamics have been reported in ageing and early neurodegenerative disease (<sup>161,162</sup>), where alternations in arousal regulation and pupil dynamics have been described as early indicators of cognitive decline (<sup>161</sup>). Cancer survivors show increased vulnerability to accelerated ageing (<sup>162</sup>), raising the possibility of overlapping mechanisms in PBTS.

Clinically, survivors frequently describe fatigue that emerges during novel or multitask situations, or when rapid task switching is required. These contexts place demands on attentional control and arousal modulation, consistent with the inefficiencies observed in pupillometric and processing-speed measures in the present study. These findings are consistent with a model in which greater cognitive effort is required to maintain performance, reflecting reduced processing efficiency.

## Processing efficiency as a unifying framework

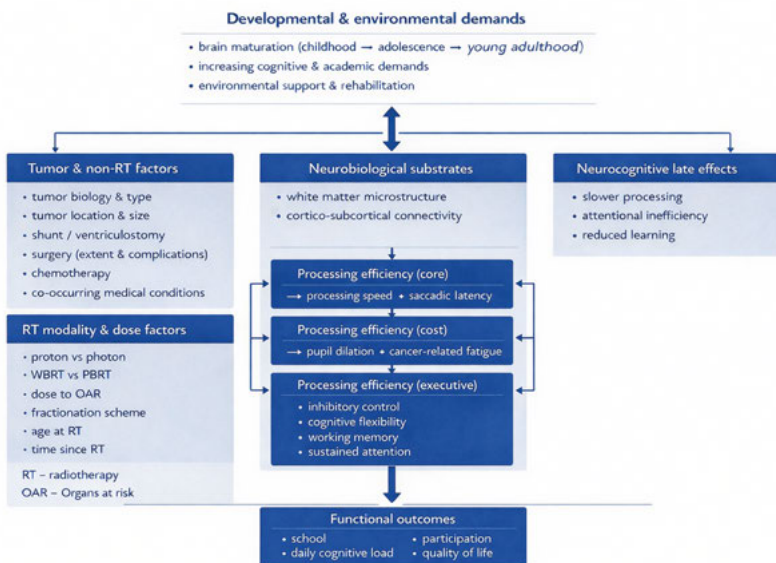
Processing speed was examined in detail in this thesis, as it represents one of the most consistently vulnerable neurocognitive domains after RT. Study I-IV assessed processing speed through multiple modalities, including behavioral performance, oculomotor control and arousal-related responses, to capture subtle impairments and to relate them to radiation exposure, fatigue and time since treatment. This multimodal approach positioned processing speed as an integrative indicator of neurocognitive integrity with relevance for dose-response analyses, rehabilitation and long-term follow-up.

However, processing speed does not operate in isolation. Working memory is theoretically linked to processing speed within a broader “processing efficiency” framework, and emerging literature suggests that these domains jointly index the efficiency of cognitive resource allocation<sup>(163)</sup>. Processing speed has been proposed as a central mediator of neurodevelopmental risk outcomes in pediatric brain tumors, particularly when RT occurs at a younger age. Disruption in processing speed may constrain other core skills, including attention span and working memory<sup>(164)</sup>. Within this framework, processing speed and saccadic latency can potentially be viewed as core timing measures, while altered arousal (task-evoked pupil dilation) and perceived fatigue could reflect the cost or cognitive effort required to maintain performance. Future analyses within this framework could be conducted within this cohort by first incorporating working memory and attention, already assessed in this cohort, alongside processing speed to examine processing efficiency as a joint construct, and then to investigate whether combined measures provide greater sensitivity to RT effects than either domain alone.

Positioning processing efficiency as a joint construct may provide a more ecologically valid understanding of late complications in PBTS, and may help explain why survivors often report fatigue and cognitive overload in complex or multitask contexts despite performing within one standard deviation on individual neuropsychological measures. Such analyses would clarify whether

processing efficiency supports more accurate identification of individuals at risk and whether it has utility for refining OAR delineation, rehabilitation planning and long-term survivorship care.

This framework should be regarded as a hypothesis-generating approach. It naturally motivates future research aimed at testing whether combined measures improve sensitivity, predictive validity and ecological relevance relative to traditional test performance alone, and whether they can be operationalized stepwise—first within the present cohort and subsequently in larger prospective samples. A hypothetical model of this framework is illustrated in Figure 8.



*Figure 8.* Hypothetical processing efficiency model for PBTS after RT. Conceptual framework linking radiotherapy mean dose to organs at risk and other risk factors with neurocognitive (processing speed, working memory, attention), physiological (task-evoked arousal) and behavioral (fatigue) domains to illustrate how reduced processing efficiency may relate to neurocognitive and functional outcomes in survivorship. This model was not empirically tested in the present thesis.

Persistent difficulties in processing speed, attention, working memory and fatigue highlight the relevance of neurocognitive rehabilitation in PBTS (23). Such challenges can affect participation, learning and everyday functioning. Eye-tracking and pupillometry may offer objective markers of cognitive effort and arousal that complement standardized NPA and may inform individualized follow-up and rehabilitation needs.

## Strengths and limitations

A major strength of this thesis is the population-based cohort with long-term follow-up of PBTS treated with multiple RT modalities during a transitional period in Swedish neuro-oncology. Detailed clinical data (e.g., tumor size, IICP, surgical interventions, chemotherapy, tumor location, age at RT, and time since RT) enabled examination of multiple tumor- and treatment-related risk factors across different time point relative to RT. The multimodal approach integrating detailed RT dosimetry, standardized NPA, eye-tracking and pupillometry enabled examination of neurocognitive, oculomotor and arousal-related outcomes through different but complementary methods. This made it possible to detect subtle late effects in PBTS. Another strength was the use of anatomically specific mean RT dose metrics for established and potential new OAR, which provided more sensitive dose–response associations with neurocognition than PTV dose. To our knowledge, these are the first studies to examine dose–response relationships for cerebellum, vermis, pons, thalamus, optic nerves and frontal regions using both traditional NPA and high-precision eye-tracking measures. Eye-tracking and pupillometry provided sensitive indices of visuomotor control, arousal regulation and fatigue that complemented traditional neuropsychological measures. In Studies III–IV, age-matched healthy controls provided essential normative comparison for saccadic and pupillometric measures, for which population norms do not exist. This enabled group comparisons and individual-level interpretation using modified t-tests and scatterplots. Although the WBRT group showed the most pronounced impairments, the PBRT group also showed prolonged saccade latencies and directional errors relative to controls, suggesting that oculomotor slowing was not solely driven by WBRT.

Several limitations should be considered. The retrospective design of Studies I–II introduced heterogeneity in diagnosis, treatment and follow-up, which limited statistical modelling and interpretation. Cohort size, heterogeneity and interrelated risk factors precluded multivariable regression and formal analysis of multicollinearity. Bivariate analyses were therefore preferred to avoid overfitting. Sample sizes further constrained subgroup comparisons of RT modality for the PBRT group. Given the small sample sizes and clinical heterogeneity of PBTS, the generalizability of these findings should be interpreted with appropriate caution. Larger multicenter cohorts will be needed to support multivariable dose-response analyses and assessment of risk.

Neuropsychological follow-up varied substantially, and only 38% completed a five-year post-RT assessment mainly due to limited clinical neuropsychological

capacity during the study period. Baseline NPA before RT were typically conducted before surgery or closely after surgery, which is not always optimal for malignant tumors due to fatigue, raised intracranial pressure or visual impairment. Neuropsychological test batteries also changed over time, reflecting evolving clinical routines and limited resources, which complicated longitudinal interpretation.

Although mean RT dose to OAR was informative, the dosimetric analyses relied on old CT-based planning data and delineation according to previously available atlases (<sup>119,120</sup>). Small structures such as cochlea and hypothalamus were contoured with anatomical margins, and variability CT image quality may have influenced mean dose estimates. Most OAR, except the frontal lobes, were delineated by the same person, ensuring internal consistency but not eliminating the risk of systematic bias. The use of updated neuro-contouring atlases, together with modern CT and MRI-based planning and emerging AI-based segmentation tools, could reduce both inter- and intra-observer variability. In particular, AI-assisted delineation may facilitate more accurate and time-efficient contouring of small and anatomically variable brain structures that are not routinely included in pediatric RT planning. More advanced dosimetric software incorporating linear energy transfer or variable relative biological effectiveness-weighted doses may further improve dose estimation. These methodological advances could enhance dose-response analyses in future studies (<sup>16,165,166</sup>).

In Studies III-IV, the sample of adult PBTS was relatively small, despite active recruitment. For several survivors, attending testing required support from family members and, in some cases, assessments had to be split across two days due to fatigue or cognitive load. This highlights practical barriers to research participation in adult PBTS and underscores the vulnerability of this group. Eye-tracking provides sensitive measures of oculomotor function (<sup>103</sup>). However, visual impairments were common in this cohort, and several patients had documented visual impairments that were not self-reported. No current ophthalmological examination was performed at the time of testing, complementary ophthalmological assessment would have been preferable (<sup>6</sup>). Future studies and clinical follow-up would benefit from including systematic ophthalmological assessment. Advanced neuroimaging techniques such as diffusion MRI and resting-state fMRI could also help characterize structural and functional network alterations following RT (<sup>108</sup>).

These four studies are based on PBTS that were treated one to two decades ago. Long-term follow-up is important to detect neurocognitive sequelae in survivors after childhood cancer. However, much has happened regarding treatments and future studies are needed to replicate and refine these findings.

# Conclusion

This thesis shows that PBTS are at elevated risk for long-term neurocognitive, oculomotor, and arousal-related difficulties following RT. Higher mean RT doses to established and potential new OAR important for neurocognitive and visual networks were associated with poorer outcomes across neurocognitive, oculomotor, and arousal-related domains. Processing speed, including performance on tasks with higher executive demands, was consistently affected and was associated with radiation-related factors, particularly mean RT doses to OAR and WBRT. Processing speed was also associated with clinical risk factors, such as tumor size and time since RT. In addition, slower processing speed was associated with prolonged saccadic latency and higher levels of fatigue. Mean RT dose to OAR showed clearer dose-response associations than PTV dose, indicating greater relevance for radiation-related neurocognitive outcomes in dose-response analysis.

These findings underscore the importance of systematic and structured NPA before and after RT. Baseline assessments prior to RT are important for identifying pre-treatment vulnerabilities, and differentiating tumor- and surgery-related effects from treatment-related decline. Long-term follow-up is required to detect late-emerging decline, particularly in processing speed and working memory, and to consider how interacting clinical risk factors may contribute to neurocognitive outcomes over time.

The findings in this thesis emphasize the importance of assessing mean RT doses to OAR in relation to neurocognition and indicate a need for further research on dose-response relationships. Integrating standardized clinical NPA with eye-tracking and pupillometry may enhance the early detection of subtle late effects and guide individualized long-term follow-up and rehabilitation. In this context, repeated eye-tracking assessments before, during, and directly after RT could be considered at the Skandion Clinic in Uppsala as a complementary research and monitoring tool, integrated alongside established clinical neuropsychological follow-up routines.

# Future research

## Multicenter studies and neuropsychological assessment

Future research should focus on multicenter and more homogeneous cohorts to clarify dose-response patterns, examine multicollinearity among clinical risk factors, and evaluate whether contemporary proton-based techniques translate into improved neurocognitive trajectories. International collaboration will be essential given the small population base, especially for proton RT, where common platforms for contouring, dosimetry and outcome evaluation are needed. For larger cohorts and systematic evaluation of clinical outcomes, national and/or international quality registries are highly recommended (<sup>44,167-169</sup>). The Swedish national quality registries provide unique opportunities for such research by enabling structured data collection across time points and treatment modalities (<sup>23</sup>).

## Processing efficiency framework

Future studies could integrate processing speed with working memory, attention and fatigue within a broader processing efficiency framework (<sup>163,164</sup>). In the current cohort, a stepwise exploratory approach could be applied by combining existing measures of processing speed, saccadic latency, attention and fatigue to examine whether such domains cohere statistically and clinically. This would provide initial hypothesis-generating evidence before testing the framework in larger or more homogeneous samples. Combining behavioral, oculomotor and pupillometric measures may increase sensitivity to radiation-related effects and improve prediction of long-term neurocognitive trajectories. Larger multicenter cohorts will be needed to determine whether such measures have utility for refining dose-response modelling, rehabilitation planning and survivorship care remains to be seen.

## Eye-tracking and multimodal outcomes

Eye-tracking and pupillometry warrant further investigation as potential objective biomarkers of neurocognitive and arousal-related late effects. Repeated assessments before, during and after RT may detect early dysfunction, monitor recovery and evaluate interventions. For proton RT specifically, the national centralization to the Skandion Clinic in Uppsala enables coordinated prospective research with repeated eye-tracking assessments before, during and after treatment. This may facilitate further research regarding neurocognitive outcome when integrating eye-tracking data repeatedly, tumor- and treatment-related data, detailed dosimetry, and standardized NPA collected from the national quality registry. Such coordinated approaches could help clarify whether contemporary dose-sparing strategies to organs at risk translate into improved neurocognitive trajectories in PBTS.

To further understand how RT dose contributes to late effects, network-based analyses combining dosimetry, neuropsychological data and eye-tracking measures may clarify pathways linking RT exposure to cognitive effort, reduced processing efficiency and functional outcomes.

## Rehabilitation and clinical translation

Neurocognitive rehabilitation is an essential component of PBTS survivorship. Many survivors experience persistent difficulties in processing speed, attention, working memory, fatigue and executive control that can affect education, participation and quality of life <sup>(23)</sup>. Evidence from adult cancer populations suggests that physical exercise, mindfulness-based interventions, cognitive-behavioral therapy have shown beneficial effects on cognitive function, but pediatric evidence remains scarce <sup>(23,170–172)</sup>. Although pediatric intervention studies remain scarce, structured and validated outcome measurement is needed to evaluate rehabilitation effects and to strengthen the evidence base in children and adolescents. Eye-tracking and pupillometry may contribute to rehabilitation research by providing objective markers of cognitive effort, arousal regulation and oculomotor control, and may be useful for monitoring change before and after rehabilitation. Preliminary evidence from other neurological populations suggest that eye-tracking based training also may enhance saccadic control, inhibitory function and processing speed, indicating a potential relevance for PBTS <sup>(173–175)</sup>. Structured neurocognitive follow-up prior to treatment is particularly important when intervention content varies by individual need. The Nordic protocol and national registers provide an emerging infrastructure for systematic outcome

collection from childhood into adolescence and adulthood, enabling prospective evaluation of rehabilitation trajectories in PBTS populations <sup>(23)</sup>.

## Sammanfattning på svenska

Personer som behandlas för hjärntumör löper en ökad risk för långvariga neurokognitiva sena komplikationer, särskilt efter strålbehandling. Nedsatt processhastighet är en av de vanligaste följderna och speglar sårbarhet i distribuerade neurokognitiva nätverk, vilket kan påverka flera kognitiva funktioner och vardagsfunktion. Strukturerad neuropsykologisk uppföljning rekommenderas efter strålbehandling på grund av risken för långvariga neurokognitiva sena effekter. Samtidigt finns begränsad kunskap om hur medelstråldoser till specifika riskorgan i hjärnan, i jämförelse med planerad stråldos till målvolymer (PTV), relaterar till neurokognitiv funktion på lång sikt.

Denna avhandling undersöker sena neurokognitiva, okulomotoriska och arousalrelaterade effekter efter strålbehandling hos personer som behandlats för hjärntumör under barndomen. Genom retrospektiva och prospektiva studier analyserades samband mellan medelstråldos till etablerade och potentiellt nya riskorgan samt neurokognitiv funktion, ögonrörelser och pupillrespons i relation till kliniska riskfaktorer och behandlingsrelaterade variabler. Vid långtidsuppföljning kombinerades neuropsykologiska test med ögonrörelsemätningar och pupillometri.

Resultaten visar att neurokognitiva nedsättningar identifierades i samband med diagnos och behandling samt att sämre neurokognitiv funktion observerades vid uppföljning efter strålbehandling, med särskilt tydlig påverkan på processhastighet. Högre medelstråldoser till flera riskorgan var associerade med lägre intellektuell funktion, långsammare processhastighet, nedsatt okulomotorisk funktion, förändrad pupillrespons och högre grad av fatigue. Strålning mot hela hjärnan var associerad med mer uttalade svårigheter, men även partiell strålning var associerad med okulomotoriska nedsättningar. Processhastighet framträdde som en central funktion och var associerad med förlångsammad initering av saccader, svårigheter med arousalreglering och fatigue. Utfallen påverkades även av kliniska riskfaktorer, framförallt tumörstorlek.

Sammantaget visar avhandlingen att medelstråldos till specifika riskorgan är mer informativ än planerad målvolymsdos vid analys av strålningsrelaterad

påverkan på neurokognitiv funktion. Resultaten understryker vikten av optimerad strålplanering samt systematisk och långsiktig neuropsykologisk uppföljning. Ögonrörelsemätningar och pupillometri kan fungera som känsliga komplement till traditionell neuropsykologisk bedömning vid identifiering av sena komplikationer och behov av individualiserad rehabilitering.

## Declaration about the use of generative AI

ChatGPT (OpenAI) was used as a language-editing tool to improve grammar, clarity and flow. All scientific content, analysis, and interpretations were developed and verified by the author(s).

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