Exercise the brain

Effects of exercise on cognition and the brain in chemotherapy-treated breast cancer patients

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Chapter 1

General introduction

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Breast cancer is the most common cancer type diagnosed in women. Incidence rates are still increasing, with over 15.000 new cases diagnosed in the Netherlands in 2022. Fortunately, the number of patients surviving breast cancer is also growing, due to earlier detection and advances in treatment. In 1970, the 10-year survival of all patients with breast cancer was only 40%, while in 2020 this percentage has increased to 80% [1]. Unfortunate consequences of this increase are that many patients have to deal with (late) effects of cancer and cancer treatment, including fatigue, depression, anxiety, lower quality of life, reduced physical fitness, and cognitive problems (Figure 1) [2–5]. In this thesis, we will focus on these cognitive problems.

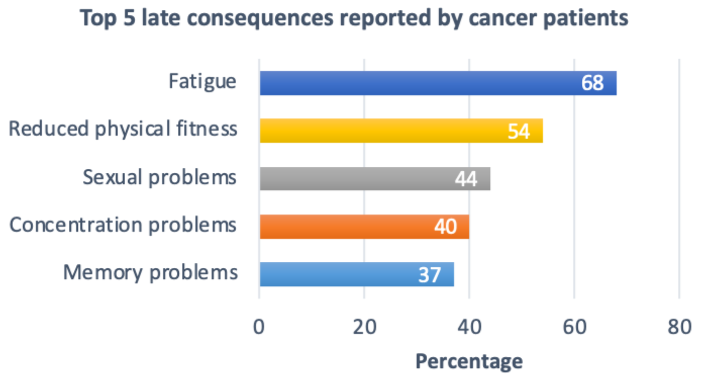


Figure 1. Top 5 late (late) effects of cancer (treatment), reported by cancer patients. *Adjusted from figure in report NFK (2017)* (171214-Generieke-rapportage-DJE-Late-gevolgen_artikel_final.pdf (nfk.nl).

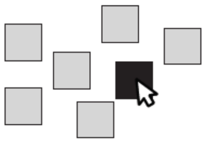
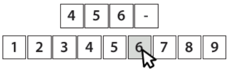
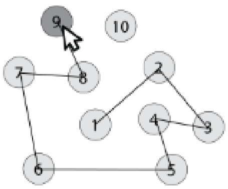
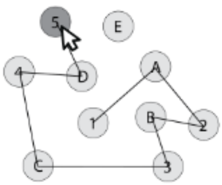
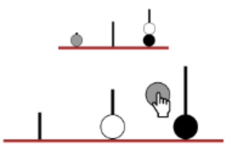
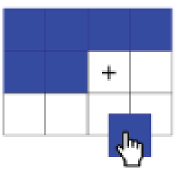
Box 1. Measuring cognition

Cognitive functioning can be assessed as cognitive complaints and cognitive problems. A questionnaire can be used to measure cognitive complaints (self-reported cognitive functioning), and cognitive problems can be measured with a neuropsychological assessment (tested cognitive functioning).

Recently, an online cognitive test battery was designed for cancer patients to formally assess cognitive functioning, the Amsterdam Cognition Scan. The content of the Amsterdam Cognition Scan is based on traditional neuropsychological tests and contains computerized tasks in the following cognitive domains: attention, information processing speed, learning and memory, executive functioning, and psychomotor speed [6] (Table 1).

continuation Box 1.

Table 1. Content of the Amsterdam Cognition Scan.

Test domain	Online test	Main outcome measures	Traditional equivalent
Learning and memory		Total number of correct responses (Learning: trials 1 to 5)	Dutch version of Rey Auditory Verbal Learning Test (immediate recall, delayed recall, and recognition)
Attention and working memory		Total number of correctly repeated sequences	Corsi Block-Tapping Test
		Total number of correctly repeated sequences	WAIS-III Digit Span forward WAIS-III Digit Span backward
Processing speed		Mean reaction time (msec)	Visual Reaction Time (subtest FePsy)
		Completion time (sec)	Trail Making Test A
Executive functioning		Completion time (sec)	Trail Making Test B
		Total number of extra moves	Tower of London, Drexel University (ToL-dx)
Motor functioning		Completion time (sec)	Grooved Pegboard

Breast cancer and the prevalence of cognitive problems

On average, 44% of breast cancer patients report cognitive complaints post-treatment [7]. Formal assessment of cognitive problems in patients treated for breast cancer has shown prevalence rates between 21% and 34% after diagnosis and treatment [7,8]. Even 20 years after treatment, breast cancer patients treated with chemotherapy showed worse performance than age- and sex-matched controls in several cognitive domains, including learning and memory, information processing speed, executive functioning, and psychomotor speed [9]. Although these problems are typically of mild to moderate nature, they may profoundly affect quality of life [5,10,11].

Cancer treatment effects on cognition

Accumulating evidence has shown neurotoxic effects of chemotherapy on the brain, affecting cognitive functioning [12]. The associated cognitive problems were initially called 'chemobrain' or 'chemofog'. However, various factors seem to contribute to the development of these cognitive problems, including other treatment strategies, cancer itself, but also co-occurring symptoms, such as fatigue [10]. Therefore, the term cancer-related cognitive impairment has been adopted by researchers. Still, up till now, the effects of chemotherapy on cognitive functioning and the brain have been studied most extensively and have been demonstrated repeatedly [10].

Both direct and indirect mechanisms have been proposed by which chemotherapy affects cognitive functioning [5,12–15]. The most frequently studied mechanisms are highlighted here. Note that these mechanisms can interact and are not mutually exclusive. Direct neurotoxicity includes effects on neuronal cells, including neural progenitor cells (undifferentiated neural cells), and effects on glia cells such as (mature) oligodendrocytes, which are cells that form myelin in the central nervous system to accelerate signaling of white matter tracts [13,16–19]. Among the suggested indirect mechanisms are vasculature damage [20–23], oxidative stress [24,25,] and inflammation, reflected by an increase of pro-inflammatory cytokines (e.g., IL-1b, IL-6, TNF-a, IL-10) [26–29], which have been related to brain-derived neurotrophic factor (BDNF) levels [30]. At this moment, inflammation is the most cited mechanism. Even 20 years after treatment, chemotherapy-treated patients showed higher levels of inflammatory markers than controls, and higher levels of inflammation were related to worse cognitive functioning [31]. The mentioned direct and indirect mechanisms can reduce neurogenesis, which is the growth of new neurons, and/or can result in impaired myelination causing reduced white matter integrity [18].

Chemotherapy and brain changes: results from neuroimaging studies

Neuroimaging studies examining the neural substrates of cognitive deficits after chemotherapy observed structural changes in grey matter volume and white matter connectivity [32–34]. In some studies, it was found that these brain alterations are directly associated with cognitive functioning [35].

For grey (and white) matter volumetric analysis, voxel-based morphometry calculated from T1-weighted magnetic resonance images is most commonly used [32]. After chemotherapeutic treatment, global and local grey matter volume reductions have been reported [32,33] and these alterations seem most prominent in the temporal and frontal regions [34]. In the medial temporal lobe, the hippocampus is situated, which is an important neural structure for learning and memory functioning. The hippocampus is one of the few regions in the brain where neurogenesis occurs in adults, although the functional relevance in adult humans is hotly debated [36,37]. In breast cancer patients, three studies specifically investigated the effect of chemotherapy on the hippocampus [29,38,39]. These studies observed a volume reduction in the posterior hippocampus [38] and left hippocampus [29], but also hippocampal deformities were seen [39].

Although not all studies have found similar effects, detrimental effects of chemotherapy on white matter microstructure have been reported [32]. Changes in white matter microstructures, such as axonal cell membranes, myelin sheaths, and neurofilaments, which are necessary to restrict molecular movement [40], are often non-invasively measured with a neuroimaging modality called diffusion tensor imaging (DTI) [41]. DTI is a magnetic resonance imaging technique to visualize and characterize white matter tracts, based on the diffusion of water molecules. Both cross-sectional and longitudinal studies have observed impaired white matter microstructure in chemotherapy-treated cancer patients [32]. Even years after chemotherapy treatment, some studies have reported impaired white matter microstructural integrity in cancer patients compared to controls [42,43], but not Billiet et al. [44]. Additionally, several studies in cancer patients showed that worse white matter microstructural integrity is associated with lower cognitive performance [45–47].

Few studies have investigated the effects of chemotherapy on the delivery of oxygen and nutrients to tissue using blood, or cerebral blood flow/brain perfusion. Cerebral blood flow is one of the parameters to measure brain function and has been associated with cognitive functioning [48]. A magnetic resonance imaging technique to non-invasively measure cerebral blood flow is Arterial Spin Labeling (ASL). One month after chemotherapeutic treatment, Nudelman et al. found increased regional cerebral blood flow, in the right precentral gyrus in breast cancer patients, and Chen et al. described a widespread increase in cerebral blood flow (hyperperfusion) [49,50]. Results from studies using functional magnetic resonance imaging, another measure of brain function depending on cerebral blood flow [51], are in agreement with Arterial Spin Labeling literature. They observed increased activation after chemotherapy use, which indicates that more neuronal activity is necessary to reach the same cognitive performances [52–55].

Physical exercise as a potential intervention

Evidence-based interventions directed at improving cognition in cancer patients are needed, but unfortunately, are limited [12]. Potential interventions can be divided into interventions directed at improving cancer-related cognitive problems (problem-directed) and interventions targeting the underlying causes of cognitive decline (mechanism-directed). Some problem-directed interventions (both pharmacological and behavioral (such as brain training)) do not show convincing beneficial effects on cognitive functioning [56,57]. However, the most common interventions, such as cognitive rehabilitation approaches, can effectively help patients manage cognitive problems in daily life [58]. Next to the problem-directed interventions, several mechanism-directed interventions exist that show promise. These include pharmacological interventions and physical exercise [12].

Potential mechanisms that link physical activity with cognition

Cellular processes, including neurogenesis and angiogenesis, that seem affected by chemotherapy, may benefit from physical exercise [59]. Several growth factors, including BDNF, insulin-like growth factor (IGF-1), and vascular endothelial growth factor (VEGF), are affected by physical exercise and increase these cellular processes [60] (Figure 2). Other effects of exercise may be the reduction of oxidative stress [61] and support of the immune system, by decreasing vascular inflammation and regulating circulating cytokines [60,62]. Additionally, physical exercise might reduce cancer-related cognitive impairment by improving other co-occurring psychosocial factors such as fatigue and distress [63,64].

Exercise effects on cognition

Physical exercise interventions have been extensively studied in healthy elderly and populations with mild cognitive impairment, and have shown promising effects on cognitive functioning. In healthy elderly, results of a systematic review and meta-analysis including 48 studies indicated that exercise ameliorates cognitive function [65]. Furthermore, in older adults with mild cognitive impairment, a recent systematic review and meta-analysis including 2,077 participants from 27 studies concluded that physical exercise can improve cognitive functioning [66]. Moreover, results from a systematic review and meta-analysis in adults with mild cognitive impairment investigating exercise effects on memory functioning, suggested beneficial effects of exercise in this cognitive domain [67].

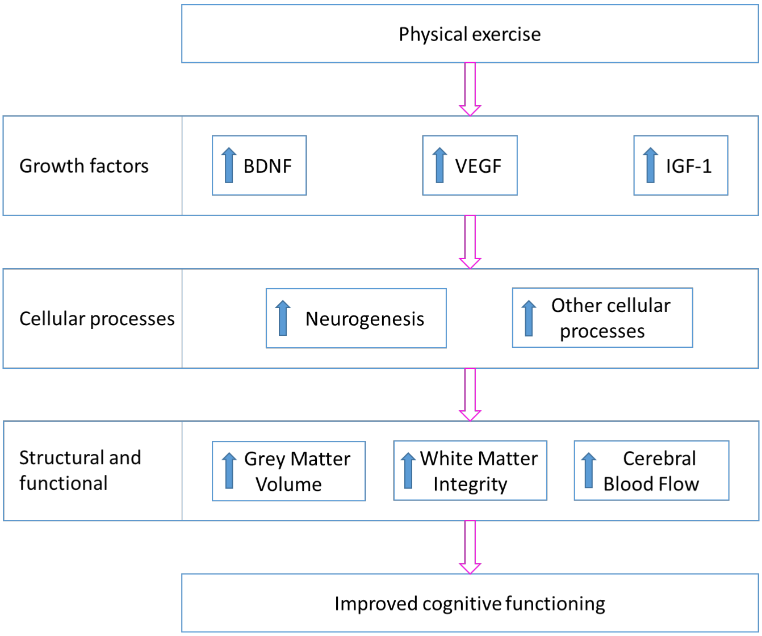


Figure 2. The theoretical framework of physiological and structural mechanisms underlying the potential beneficial effect of exercise on long-term cognitive problems.

Abbreviations: BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor; IGF-1, insulin-like growth factor 1.

In cancer patients, physical exercise interventions have shown beneficial effects on physical fitness, depression, fatigue, and quality of life [68–70]. Evidence for positive effects on self-reported cognitive functioning, and especially on tested cognitive functioning, is scarce [71]. A few studies with small sample sizes showed promising exercise effects on tested cognitive functioning (after treatment). In a proof-of-concept randomized controlled trial with a total study sample of 19 breast cancer patients with self-reported cognitive dysfunction, a 24-week aerobic exercise intervention showed a significant beneficial effect on processing speed. However, the effect size was small, and effects on other cognitive tests did not reach significance [72]. Furthermore, in a pilot study including seventeen female cancer survivors randomized in three groups (high-intensity interval training; moderate-intensity continuous training; or wait-list control group), moderate to large statistically non-significant effects on episodic memory, working memory, and executive functioning were found following 12 weeks of high-intensity interval training, compared to the moderate-intensity continuous training group and a wait-list control group [73]. Finally, Hartman et al. investigated with a randomized controlled trial the effects of a 12-week physical activity program in a total sample of 87 sedentary patients treated for breast cancer, and showed significant improvements in processing speed for patients diagnosed within the last two years [74]. More sufficiently powered randomized controlled studies with (tested) cognitive functioning as a primary outcome measure are needed to investigate the potential beneficial effects of exercise on cognition [71].

Studies on exercise effects on the brain

Neuroimaging studies investigating the effects of physical exercise on the brain have shown several structural and functional changes. In several populations, including healthy elderly [75] and patients with mild cognitive impairment [76], grey matter volume increase or maintenance, and more specifically hippocampal volume increase or maintenance, has been reported after physical exercise. Neurogenesis is one of the proposed underlying mechanisms for hippocampal volume increase, but also an increase in whole brain volume and reduced brain atrophy have been reported after physical exercise [77]. In breast cancer patients, a cross-sectional study showed that higher physical fitness was associated with larger hippocampal volume, suggesting the benefit of physical exercise on brain health [78]. However, the effects of a physical exercise intervention on brain structure, including hippocampal volume, in chemotherapy-exposed breast cancer patients are unclear.

Previous research suggests that physical exercise might improve white matter integrity, although evidence is limited. Several studies have found a positive cross-sectional association between physical fitness and white matter integrity [79–85]. Additionally, in patients with schizophrenia, a 6-month exercise intervention has improved white matter integrity, and also in patients with amnestic mild cognitive impairment individual gains in physical fitness were related to improved regional white matter integrity [86]. However, not all studies investigating exercise effects on white matter integrity have found significant intervention effects [87,88].

Physical exercise might improve cognitive functioning by changing brain blood flow [89]. Research on the effects of physical exercise on cerebral blood flow in cancer patients is limited. A pilot study in 17 female cancer survivors showed moderate to large positive effects of high-intensity interval training on cerebral blood flow. However, in this small study, this effect was not significant [73]. In other populations, (aerobic) exercise training increased global and regional brain perfusion, including in the hippocampal and cingulate cortex regions [90,91], which was in some studies related to improved memory functioning [92–94]. However, the opposite effect of physical exercise on cerebral blood flow has been found as well. In some studies, such as in patients with mild cognitive impairment, hyperperfusion has been reported before the intervention [95]. Alfini et al. and Thomas et al. found a decrease in perfusion in some areas after the intervention, indicating that physical exercise does not simply increase perfusion, but might normalize cerebral blood flow [94,95].

Aim and outline of this thesis

The study described in this thesis was designed to determine if a physical exercise intervention can diminish cognitive problems in cancer patients treated with chemotherapy, and to investigate how the brain is affected by this intervention. In **chapter 2**, the design of the randomized controlled physical activity and memory (PAM) study is described in detail. In the PAM study, the effects of physical exercise on cognitive functioning and the brain are investigated in relatively inactive chemotherapy-exposed breast cancer patients, with both self-reported cognitive problems and lower-than-expected performance on neuropsychological tests. In **chapter 3,** the effects of the physical exercise intervention on tested cognitive functioning and self-reported outcomes, including subjective cognitive complaints, fatigue, depression, anxiety, and quality of life are described. Additionally, adherence to the exercise protocol and its effects on physical fitness are included. **Chapter 4** is the first in-depth chapter on the effects of a physical exercise intervention on the brain. The effects of physical exercise on the hippocampus are investigated in detail and in addition to that, the effects on global volumetric measures such as cortical thickness and grey matter are included. We also investigated more generally if physical fitness and brain measures such as hippocampal volume, cortical thickness, and grey matter volume are associated. In **chapter 5** the effects of the physical exercise intervention on white matter microstructure are described and in **chapter 6** intervention effects on brain perfusion are reported. In **chapter 7** main results of previous chapters are interpreted, and placed in the context of previous research on this subject. Additionally, methodological considerations, future directions, and the potential impact on the research field and society are discussed.

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