SUMMARY

The first chapter of this thesis (Chapter 1) provides a general introduction to the work described in this thesis.

In Chapter 2 cognitive function and brain structure and function were studied prior to adjuvant treatment. We assessed overall cognitive performance by calculating the Mahalanobis distance, a method that assesses deviant profiles, taking into account correlations between tests and variance within the tests in the control group. In addition, cognitive domain scores were analyzed to assess whether differences in cognitive performance were global or more restricted to a specific cognitive domain. Following recommendations of the International Cancer and Cognition Task Force, we also calculated cognitive impairment compared to the no-cancer control group and subsequently tested the proportion of patients classified as impaired. Multimodal MRI was acquired to allow for assessment of regional grey matter volume, white matter integrity, brain metabolites, and brain activation. To control for potentially confounding psychosocial factors, patient-reported outcomes as well as hair cortisol were collected.

We found that breast cancer patients, regardless of required treatment (BC+SYST, n=32; BC, n=33), showed significantly worse cognitive performance compared to no-cancer controls (NC, n=38), as measured with the Mahalanobis distance. When assessing specific cognitive domains, no differences between the groups were found. Also, no significant difference in proportion of impaired patients was found. Taken together, these analyses suggest a global cognitive impairment with subtle differences across the entire battery of tests. The findings of worse overall cognitive performance were no longer significant when scores of fatigue, perceived stress or anxiety and depression were included. We found prefrontal hyperactivation with increased task load on a planning task, but not during a memory task, in both patient groups compared to no-cancer controls. These differences in brain activation were no longer significant when fatigue was included in the model, while other patient-reported outcomes did not elicit the same effect. Widespread lower white matter integrity was found in both patient groups compared to no-cancer controls. However, no differences in white matter integrity were found when fatigue was included in the model. Groups did not show differences in regional grey matter volume, brain metabolites or white matter macrostructure. This was the first study in breast cancer patients that combined multimodal MRI, neuropsychological measurements and patient-reported outcomes before administration of systemic therapy. This allowed us to additionally assess the effects of psychosocial factors on different modalities, and thereby identify the role of fatigue in the pretreatment differences between breast cancer patients and no-cancer controls.
In Chapter 3 we studied the effects of systemic treatment on cognitive function. Assessments took place at approximately six months after the last cycle of chemotherapy, or at matched intervals. Cognitive performance was analyzed using two methods: 1) differences per test at the group level at follow-up, adjusted for pretreatment scores, were analyzed; 2) multivariate normative comparisons (MNC), a method adequate for small sample sizes, were performed to identify cognitively impaired patients. MNC compares test scores against the distribution of those scores in the control group. Calculations were based on performance residual scores, the difference between an individual’s scores and her predicted scores, based on baseline performance, age and IQ. In addition, confounding effects of psychosocial and biological factors were assessed. We hypothesized lower cognitive performance in breast cancer patients who had received systemic treatment, compared to both other groups. We also expected to find a relation between follow-up performance and measures of fatigue.

No significant differences in neuropsychological performance were found at the group level. However, effect sizes (range: 0.41 - 0.71) indicated worse performance on tests of attention, verbal memory, and executive function in breast cancer patients who received systemic treatment (BC+SYST, n=31) compared to breast cancer patients who did not require systemic treatment (BC, n=24), as well as no-cancer controls (NC, n=32). Assessing overall cognitive performance using MNC, a higher proportion of the patients who received systemic treatment were classified as cognitively impaired (16%), compared to the patient group that did require systemic treatment (4%) and no-cancer controls (6%). Further investigating those patients classified as cognitively impaired and comparing them to unimpaired patients, we found that premorbid verbal IQ was lower in impaired patients. Lower premorbid IQ has been related to a higher risk of developing cognitive impairment following systemic treatment. Also, impaired patients showed worse functioning on several measures of quality of life. However, given the relatively small number of impaired patients, these observations on vulnerable patients need further exploration in larger studies. Given the strong relation between fatigue and several outcome measures prior to treatment, we studied the role of fatigue, as well as several other psychosocial and biological factors on cognitive performance. However, none of these factors affected the results of our analyses. Taken together, these results show that cognitive impairment occurs in a subset of patients receiving systemic treatment. Although differences in several clinical and psychosocial factors between impaired and unimpaired patients were apparent, the predictive value for the development and course of cognitive impairment after systemic treatment should be further investigated.

In Chapter 4 we report on the results of analyses on brain activation during cognitive task performance. While previous prospective studies administered a single cognitive task, we employed two tasks. This allowed us to draw conclusions about the effects of cancer and cancer treatment on the two most commonly affected cognitive domains, memory and executive function. Given the relation between prefrontal hyperactivation and lower levels of fatigue at baseline, we assessed the relation between patient-reported outcomes and brain activation at follow-up as well as changes in brain activation between baseline and follow-up. We hypothesized
that patients who received systemic treatment would show larger deviations in brain activation, regardless of cognitive task, compared to breast cancer patients who did not receive systemic treatment and to no-cancer controls. Given the relation between prefrontal hyperactivation and levels of fatigue before treatment, we expected to find an effect of fatigue on brain function at the follow-up assessment.

Following systemic treatment (BC+SYST, n=28), breast cancer patients showed increased activation of parietal brain regions with increasing task difficulty of an executive functioning task, compared to their pretreatment baseline. Patients who did not require systemic therapy (BC, n=24) showed a decrease in parietal activation during executive functioning compared to patients who received systemic treatment as well as to no-cancer controls (NC, n=32). These results might indicate decreased neural integrity as a result of neurotoxic side effects of systemic treatment, leading to parietal over-recruitment to maintain performance. No significant differences in brain activation or task performance during episodic memory performance were found between the groups. It could be that the task was too difficult to detect subtle differences. However, previous studies by our group did show differences in brain activation during episodic memory ten years after treatment. This suggests that it could also be that the effects of cancer and cancer treatment are specific to the task employed, and become more generalized after a longer period of time. Prior to treatment, a relation between frontal activation during executive functioning and fatigue was found. After treatment, a relation between pretreatment fatigue scores as well as their change over time and parietal activation was found in the patient group not receiving systemic treatment. No relation between psychosocial factors and brain activation was found for patients who received systemic treatment.

In Chapter 5 we describe analyses of brain white matter macro- and microstructure after systemic treatment. Prior to treatment, breast cancer patients showed widespread lower white matter integrity compared to no-cancer controls. These results were associated with higher levels of fatigue. We subsequently acquired DTI data in the same group of subjects at six months after the last cycle of chemotherapy, or at matched intervals. We hypothesized that patients receiving systemic treatment would show a stronger decrease in white matter integrity compared to BC patients not requiring systemic treatment, as well as no-cancer controls. In addition, we expected baseline measures of fatigue to be related to changes in white matter integrity in patients.

White matter macrostructure was not severely affected (according to Fazekas ratings) in any of the groups. No significant group differences were found, although a clear shift from Fazekas 0 to Fazekas 1 was apparent in the patient groups (BC+SYST, n = 26; BC, n=23), which was absent in the no-cancer control group (NC, n=30). A decline in white matter microstructure, assessed using DTI, over time was found in all groups. White matter integrity in the right superior longitudinal fasciculus and corticospinal tract showed a larger decline in patients who received systemic therapy compared to patients who did not require systemic treatment. Patients who had received systemic treatment also reported worse physical functioning, higher levels of fatigue and more cognitive complaints. We did not find an association between cognitive decline and decline in
white matter integrity. This is in contrast to a previous study by Deprez et al.\textsuperscript{2}. It could be that the cytostatic agents administered in our sample have smaller effects on white matter integrity than other agents, such as 5-fluorouracil. Another explanation could be that some recovery had already occurred at the moment of the second assessment. Also, the applied statistical methods might be less sensitive to these subtle changes.

Taken together, these results show that cognitive impairment and impaired brain function and structure may already exist prior to adjuvant treatment for breast cancer. These pretreatment differences between breast cancer patients and no-cancer controls were associated with fatigue. We also found a relation between pretreatment cognitive function and perceived stress as well as symptoms of anxiety and depression. Also, other studies have shown that other psychosocial and biological factors, such as worry\textsuperscript{3}, stress, and time since surgery\textsuperscript{4-6}, may also play a role in pretreatment cognitive and brain function. It could be that these biological and psychosocial factors represent another underlying nonspecific factor, which can be expressed in different measures. After treatment, breast cancer patients who received systemic treatment showed more cognitive impairment, changes in brain activation and stronger declines in white matter integrity than patients who did not require systemic treatment as well as no-cancer controls. This shows that systemic treatment for breast cancer has adverse effects on cognitive function as well as brain function and structure. We found differences between impaired and unimpaired patients on clinical and psychosocial factors, but given the small sample size, these findings should be further investigated.