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Cognitive impairment and posttraumatic stress in breast cancer patients during the first year after diagnosis

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Content

1. Summary / Zusammenfassung

1.1 Summary

Cancer patients frequently report symptoms of cognitive impairment and posttraumatic stress. Until recently, it was assumed that cognitive deteriorations in cancer patients are attributable to neurotoxic effects of chemotherapy. However, new research indicates that cognitive impairment cannot be caused by cancer treatment alone – most likely also cancer-related posttraumatic stress affects cognition. Elucidating the causes of cognitive dysfunction and posttraumatic stress in cancer patients is crucial for prevention and effective psychological intervention.

This cumulative dissertation summarizes two publications of the prospective, longitudinal and controlled COGNICARES-study, which were published in peer-reviewed international journals with current impact factors that rank among the top 80% in the Journal Citation Report. COGNICARES is the first large study that applied an extensive neuropsychological test battery and a validated clinical interview at three assessment times, to measure cognitive functioning and posttraumatic stress in women with mamma carcinoma and in a control group. Prior to the start of any cancer treatment, limited cognitive impairment was found in cancer patients, which was mediated by posttraumatic stress. Only few patients were diagnosed with a full-blown acute or posttraumatic stress disorder (ASD, PTSD) but shortly after the cancer diagnosis, more than 80% of patients experienced symptoms of PTSD, which did not completely resolve during the first year after cancer diagnosis in the majority of patients. Implications of the findings are discussed in the context of the recently published Diagnostic and Statistical Manual of Mental Diseases-V (DSM-V).

1.2 Zusammenfassung

Krebspatienten klagen häufig über kognitive Probleme und Symptome einer posttraumatischen Belastungsstörung. Bis vor kurzem wurde die Beeinträchtigung kognitiver Funktionen ausschließlich auf die neurotoxische Wirkung von Chemotherapie zurückgeführt. Jüngste Studien weisen hingegen darauf hin, dass kognitive Störungen bei Krebspatienten nicht ausschließlich durch Chemotherapie verursacht sein können – vermutlich beeinflusst zusätzlich krebsspezifischer, posttraumatischer Stress die kognitiven Fähigkeiten. Die Aufklärung der Ursachen von kognitiver Dysfunktion und posttraumatischem Stress bei Krebspatienten ist relevant für Prävention und Therapie.

Diese kumulative Dissertation fasst zwei Artikel der prospektiven, kontrollierten Längsschnittstudie COGNICARES zusammen, die in referierten (peer-reviewed) Fachzeitschriften von internationalem Niveau veröffentlicht wurden. Die Zeitschriften haben jeweils einen fachspezifischen Impact-Faktor, der dem Journal Citation Report zufolge zu den besten 80% zählt. COGNICARES ist die erste großangelegte Studie, in der eine umfangreiche neuropsychologische Testbatterie und ein validiertes klinisches Interview zu drei Messzeitpunkten eingesetzt wurden, um kognitive Funktionen und posttraumatischen Stress bei Patientinnen mit Mamakarzinom und bei einer Kontrollgruppe zu untersuchen. Vor Therapiebeginn wurden bei den Patientinnen lediglich geringfügige kognitive Defizite festgestellt, die durch posttraumatischen Stress beeinflusst waren. Eine geringe Anzahl an Patientinnen wurde mit einer voll ausgeprägten akuten Belastungsreaktion (ABR) oder posttraumatischen Belastungsstörung (PTBS) diagnostiziert. Allerdings zeigten mehr als 80% der Patientinnen kurz nach der Diagnose posttraumatische Belastungssymptome, die bei der Mehrheit der Patientinnen ein Jahr nach der Diagnose noch vorhanden waren. Die Relevanz der Ergebnisse wird im Kontext des in 2013 erschienen Diagnostic and Statistical Manual of Mental Diseases-V (DSM-V) diskutiert.

2. Publications

2.1 Study I (see Appendix A):

Kerstin Hermelink, Varinka Voigt, Judith Kaste, Franziska Neufeld, Rachel Wuerstlein, Markus Bühner, Karin Münzel, Dorothea Rjosk-Dendorfer, Susanne Grandl, Michael Braun, Franz Edler von Koch, Kristin Härtl, Stephan Hasmüller, Ingo Bauerfeind, Gerlinde Debus, Peter Herschbach, Nadia Harbeck. (2015). Elucidating Pretreatment Cognitive Impairment in Breast Cancer Patients: The Impact of Cancer-related Post-traumatic Stress. *JNCI J Natl Cancer Inst* 107(7): djv099. doi: 10.1093/jnci/djv099. https://academic.oup.com/jnci/article/doi/10.1093/jnci/djv099/913443/Elucidating-Pretreatment-Cognitive-Impairment-in.

2.2 Study II (see Appendix B):

Varinka Voigt, Franziska Neufeld, Judith Kaste, Markus Bühner, Philipp Sckopke, Rachel Wuerstlein, Karin Hellerhoff, Anikó Sztrókay-Gaul, Michael Braun, Franz Edler von Koch, Eliane Silva-Zürcher, Stephan Hasmüller, Ingo Bauerfeind, Gerlinde Debus, Peter Herschbach, Sven Mahner, Nadia Harbeck and Kerstin Hermelink. (2015). Clinically assessed posttraumatic stress in patients with breast cancer during the first year after diagnosis in the prospective, longitudinal, controlled COGNICARES study. *Psycho-Oncology* 1–7 (2016). doi: 10.1002/pon.4102. http://onlinelibrary.wiley.com/doi/10.1002/pon.4102/full.

Both articles were published in peer-reviewed international journals with current impact factors that rank among the top 80% in the Journal Citation Report.

3. Theoretical introduction

Breast cancer is the most common malignant tumor and the leading cause of cancer-related death in women worldwide (1). In Germany approximately 70.000 women are diagnosed with breast cancer each year, which can deeply affect patients' psychological wellbeing and functioning in life.

This dissertation analyses the prevalence and causes of cognitive impairment in breast cancer patients soon after the diagnosis, and posttraumatic stress during the first year after diagnosis. It relates the two articles published (*Elucidating Pretreatment Cognitive Impairment in Breast Cancer Patients: The Impact of Cancer-related Post-traumatic Stress (2)*; *Clinically assessed posttraumatic stress in patients with breast cancer during the first year after diagnosis in the prospective, longitudinal, controlled COGNICARES study (3)*), which describe cognitive functioning and posttraumatic stress in breast cancer patients in great detail. The main focus lies on posttraumatic stress in breast cancer patients, which most likely contributes to cognitive impairment. The following sections summarize the current state of research, describe the COGNICARES-study and explain general implications in the context of the recently published Diagnostic and Statistical Manual of Mental Diseases-V (DSM-V) (4).

3.1 Cognitive impairment in breast cancer patients

Cancer patients often report impaired cognitive functioning. Up to 94% of cancer survivors report clinically significant deterioration (5). They complain about feelings of 'fuzzy headedness' or 'mental slowness'(6), cannot remember words, have difficulties concentrating on long conversations and misplace their keys or glasses. Since the early 1980s a growing number of studies has investigated the relationship of different domains of cognitive functioning – including memory, attention, concentration, processing speed and executive functioning – and cancer (7-17). The prevalence of perceived cognitive dysfunction is higher than the prevalence of impairment assessed with objective measurements, which varies from 16% (14) to 75% (17) depending on the type of study design (10, 18) and on the definition for cognitive impairment (12, 18, 19). If the different definitions of cognitive impairment, that were used in cancer patients, are applied to non-cancer controls, rates of impairment vary

between 5% and 65% (19). Perceived and objective cognitive performance do not necessarily correlate (5, 6, 11, 18, 20-22). Perceived cognitive impairment may be more indicative of psychological distress instead of objective cognitive functioning (18, 21).

Cognitive dysfunction in cancer patients is mostly subtle and mild (8, 13, 15, 23-26) and not as severe as impairment found with acute amnesia or presenile dementia (6, 25). But even if it is subtle, it may seriously afflict patients' lives, undermining quality of life and daily functioning (8, 26, 27). Cognitive impairment influences the acquisition of information; treatment, educational and career decisions and the performance of self-care activities (8, 23, 26, 28) and inhibits a smooth transition from treatment back to normal life (12). Until now it is unclear at what time cognitive deteriorations emerge (23, 26). Many studies found evidence of impaired functioning during or shortly after medical treatment and improvements after treatment cessation (15, 29, 30). Cognitive impairment may persist for months and years (11, 15-17, 23, 26, 29).

3.1.1 What causes cancer-related cognitive impairment?

Early research assumed that cognitive impairment in cancer patients is caused by cytotoxic effects of chemotherapy (31). Patients and scientists called the phenomenon "Chemobrain" or "Chemofog". Many studies found evidence that patients who received chemotherapy, especially high-dose chemotherapy (32), scored lower on neurocognitive tests than published norms or control groups without cancer (7-17). Thus, the phenomenon of chemofog was almost universally accepted (12) until it was challenged by new studies that revealed similar cognitive difficulties in patients prior to or without chemotherapy (6, 15, 16, 20, 25, 28, 33-38). Today it is assumed that approximately 30% to 40% of cancer patients show cognitive impairment before the initiation of cancer therapy (15, 16, 25, 34, 39, 40). Thus, chemotherapy cannot be the only cause for cognitive deteriorations. Various alternatives have been discussed to trigger cognitive impairment: Cancer itself (12), possibly by stimulating proinflammatory cytokine production (25, 41); hormonal changes due to cessation of hormone replacement therapy, endocrine therapy or premature menopause (6, 12, 14, 23, 29, 42); a common disposition or risk factors for cancer and cognitive disturbances (25). Fatigue, anxiety, depression and changes in quality of life have also been proposed as negative influences on cognitive functioning (14, 36) but no consistent explanation for cognitive

impairment before the initiation of medical treatment has yet been found (26). Today it is assumed that a variety of mechanisms interact (8). It is likely that psychological factors contribute to cognitive impairment. This would explain why patients suffering from other diseases (for example, chronic kidney disease (43) or musculoskeletal pain (44)) also experience cognitive deteriorations. Generally speaking, all physically ill patients might be at risk for psychological instability, mainly disease-related stress.

3.2 Cancer – a traumatic event?

During the last decades researchers recognized that cancer can be a traumatic event, triggering stress disorders in some patients (45-51). According to the American Psychiatric Association (APA) a trauma is the "exposure to actual or threatened death, serious injury, or sexual violence" (4, 52). The direct experience and the witnessing of an event or the information that a traumatic event occurred to a beloved person can be traumatic and cause posttraumatic stress disorder (PTSD) and acute stress disorder (ASD) (4, 52). In 1994, the APA added chronic diseases to the list of potential traumas in the DSM-IV (52). Since then a growing body of research has investigated and discussed the traumatic characteristics of cancer, of which some are very similar and others are very different to those of other traumatic events, such as war experiences, accidents and violent abuse.

Cancer is a life-threatening disease and may trigger fear of imminent death. A cancer patient – possibly diagnosed with incurable metastases – may be as anxious for his survival as a soldier during war or a motorcyclist during an accident. Cancer is an internally induced event, not conducted by others (50, 53). In most cases it is associated with a multitude of potentially traumatic experiences (50, 54-57), which can be highly pervasive in the daily lives of patients. Cancer patients often receive regular treatment and medical examinations and frequently face side effects or physical changes to their body. Those stimuli are difficult to avoid and regularly trigger the memory of the disease (46, 50, 53, 54). For other trauma victims it might be easier to avoid reminding stimuli. War veterans, for example, might be able to hide from loud noises or war reports on TV. In contrast to most other traumatic events cancer is associated with a long-lasting threat and with future-oriented, realistic und justifiable fears, most of all the fear of disease progression and death (46, 50, 53, 55, 58-60). Despite these

distinctive features of cancer as a traumatic event, symptoms that cancer patients and victims of other traumas experience are similar (61). They include among others recurrent, intrusive and distressing recollections and problems with sleep and concentration. Since life-threatening diseases have been acknowledged potential traumas in the DSM-IV (52), cancer patients can be diagnosed with PTSD or ASD.

3.2.1 Stress disorders in breast cancer patients

According to the DSM-IV, PTSD is diagnosed if patients have experienced a traumatic event and suffer from specific symptoms, that afflict their lives and did not occur before the trauma (52). Specified numbers of symptoms from three clusters must persist for at least one month (52). The clusters are 1. Re-experiencing the trauma (e.g. intrusive thoughts or distressing dreams), 2. Avoidance/Numbing in response to reminders of the trauma (e.g. efforts to avoid activities, places, or people that arouse recollections of the trauma) and 3. Hyperarousal (e.g. difficulty falling or staying asleep). ASD is diagnosed if symptoms of derealisation or dissociation are present in addition to symptoms of the three symptom clusters of PTSD during the first month after the traumatic event (52).

The prevalence of stress disorders in breast cancer patients seems to be relatively low, 2.4% for ASD (54) and between 2.4% (54) and 6% (62) for PTSD. However, PTSD symptoms that do not meet the criteria for a diagnosis were found to be common, with up to 36% of women experiencing three or more symptoms (49, 63, 64). Most PTSD symptoms seemed to occur shortly after the trauma (4, 46, 53, 65) and decline or vanish over time (54, 56, 58, 66). In some patients, however, they were found to persist long-term (67-69), up to 20 years after the diagnosis (70), or to have a late onset (59, 71). The nature, course and consequences of posttraumatic stress in cancer patients have not yet been studied extensively – especially not longitudinally. Reliable information on posttraumatic stress associated with cancer is therefore limited. No matter if a patient's posttraumatic stress fulfills diagnostic criteria or not, it deeply affects the patient's life. PTSD symptoms are associated with low quality of life (49) and impaired functioning (72).

3.3 Can posttraumatic stress cause cognitive impairment?

As studies with victims of other traumas have shown, PTSD is associated with disturbed cognitive functioning (73-81). If the same were true for cancer patients, this would explain why some studies found cognitive impairment in patients before medical treatment. Currently, the role of cancer-related posttraumatic stress on cognitive functioning has rarely been examined in hypothesis-driven investigations (27, 82, 83).

4. The COGNICARES-study

The project COGNICARES is a prospective, longitudinal, controlled and multisite study with the aim to identify the influence of cancer-related stress on cognitive functioning in women with breast cancer. The acronym stands for Cognition in Breast Cancer Patients: The Impact of Cancer-related Stress. It is the first large study in which an extensive neuropsychological test battery and a validated clinical interview are applied at three assessment times to measure cognitive functioning and posttraumatic stress in breast cancer patients and in a control group. The study was conducted between 2011 and 2014. To date, parts of the data have been analyzed, interpreted and published, including the prevalence of cognitive impairment and the mediation effect of posttraumatic stress on cognitive functioning at baseline and the course of PTSD symptomatology during the first year after diagnosis. The following paragraphs will summarize the study's rationale, design and results. For more details, see the publications in appendix A and B. Further publications will follow.

4.1 Rationale

The primary goal of the study was to identify the role of posttraumatic stress in cognitive functioning in women with breast cancer. The main hypothesis that cognitive impairment in breast cancer patients is mediated by cancer-related posttraumatic stress was tested. Understanding the causes for cancer-related cognitive impairment is necessary to accurately inform patients, prevent and treat cognitive problems and to preserve patients' quality of life.

The secondary objective was to analyze the prevalence of cancer-related stress disorders and subsyndromal stress symptoms, and to determine the effects of time, mastectomy and

chemotherapy on cancer-related PTSD symptom severity. The prevalence, course and moderators of posttraumatic stress during the first year after diagnosis were assessed. Elucidating the different factors influencing PTSD symptoms and understanding the symptoms' course over time is crucial to offer psychological support at the right time.

4.2 Design

Women newly diagnosed with stage 0 to III breast cancer and women without cancer as control patients were recruited at six breast centers in the area of Munich, Germany. Eligible women who agreed to be contacted were fully informed by the COGNICARES-staff and asked to participate. The assessment sessions took place after definite cancer diagnosis for patients and after a negative mammogram or ultrasound for controls (T1), approximately seven months after the first assessment (T2) and four to six months after the second assessment (T3). The same procedure was applied at T1, T2 and T3[1]. Each session was conducted by one of five designated psychologists and took approximately two to three hours. It comprised a neuropsychological test battery, PTSD diagnostics with the Structured Clinical Interview for DSM-IV (SCID) (71), self-report measures of cognitive functioning and psychological morbidity, and demographic and medical data that were additionally extracted from medical records. To allow a dimensional assessment of PTSD symptomatology, all symptoms were assessed, disregarding the general skipping rules of the clinical interview. Depressive and anxiety disorders were assessed with the German version of the Patient Health Questionnaire (PHQ-D) (84, 85). For the analysis, the IBM SPSS Statistics 22 and 23 (Armonk, NY: IBM Corp.) and the software R (86) were used.

4.3 Results

226 participants (166 patients and 60 controls) were included in the study. The overall attrition rate was 8.8% (patients: 9.6%, controls: 6.7%).

4.3.1 Cognitive functioning in breast cancer patients before treatment

The first article reports the findings on cognitive functioning at the initial assessment conducted prior to any local or systemic cancer treatment. Patients and controls showed near-identical deviations from population norms in their cognitive functioning. Both groups scored

[1] With one exception: The test of premorbid intelligence was only applied once (T1).

significantly below or above the population norms on more than a third of cognitive indices. Case patients scored worse than control patients on two indices of one attention test. Only PTSD symptoms and age significantly predicted the errors. PTSD symptoms mediated the effect of having cancer on errors at the attention test and predicted performance on these indices, while the effect of patient versus control status was statistically not significant if PTSD symptoms were accounted for. Cancer patients showed limited cognitive compromise prior to any treatment that was apparently mainly caused by cancer-related posttraumatic stress. They did not have an increased risk of overall cognitive impairment. Self-reported cognitive problems were more pronounced in patients.

4.3.2 Stress disorders in breast cancer patients during the first year after diagnosis

The second article focuses on the prevalence of cancer-related stress disorder, subsyndromal stress symptoms and moderators of PTSD symptoms in breast cancer patients during the first year after diagnosis. The results confirm previous findings of low rates of PTSD diagnoses in breast cancer patients. Only a small proportion developed a stress disorder (3.62%, T1; 1.9%, T2; 2.0%, T3). Compared to controls (no case of stress disorder), patients showed higher rates of full-blown diagnosis of stress disorders and a substantially higher PTSD symptom burden. More than two-thirds of the patients met the criteria for the re-experiencing cluster (70.5%) and more than one-third the criteria for the hyperarousal cluster (40.4%). Only a few patients met the criteria for the avoidance cluster (7.2%). Most symptoms occurred right after the diagnosis (82.5%, T1) and declined over time. Nonetheless, they were not fully resolved in more than half of the sample by one year (57.3%, T3). The greatest decline was observed between the first and the second assessment. The number of PTSD symptoms could not be explained by any demographic or medical characteristics that were tested (age, education, partnership, tumor stage, past PTSD, type of operation, chemotherapy) or by time. However, university education significantly predicted the decline of PTSD symptoms over time. Highly educated women seem to quickly develop coping skills, which prevent the manifestation of long-lasting psychological disturbances after a cancer diagnosis. Of 71 patients who had already experienced a traumatic event prior to the cancer, almost 40% rated having cancer as the more severe stressor.

5. General implications

5.1 Cognitive functioning in breast cancer patients

In the study, breast cancer patients did not have an increased risk of overall cognitive impairment prior to cancer treatment. They only showed limited difficulties in specific neuropsychological tests (attention), which were mediated by posttraumatic stress. Further analysis of the COGNICARES-data will provide insight in patients' cognitive functioning shortly after chemotherapy and one year after the diagnosis. If cognitive functioning actually is attributable to posttraumatic stress, it is assumed to improve, since in our study posttraumatic stress declined over time. If this were true, observed impairment in patients prior to or without chemotherapy could at least to some extent be explained.

5.1.1 DSM-V: New diagnosis of mild neurocognitive disorder

Since impairment of cognitive functioning is rather subtle in cancer patients, researchers have raised the question of whether we should even speak of impairment (25). The recently published DSM-V includes a new diagnosis named "mild neurocognitive disorder (NCD)" (4), which may apply to some cancer patients. Mild NCD is diagnosed if patients report modest cognitive decline in one or more cognitive domains and subtle or no inferences with function. The diagnosis is based on "a concern about cognition on the part of the individual, a knowledgeable informant, or the clinician, and performance on an objective assessment that falls below the expected level or that has been observed to decline over time" (4). Estimates of the prevalence of mild cognitive impairment among older individuals are fairly variable, ranging from 2% to 25% between the age of 65 and 85 (4). According to the DSM-V, NCDs often occur in the setting of medical illnesses but cancer is not explicitly named.

5.1.2 Cognitive rehabilitation

Currently there is no standard therapy for cancer patients with cognitive impairment, but different cognitive rehabilitation approaches have proven effective in enhancing subjective and objective cognitive functioning, reducing stress and improving cancer patients' quality of life (26, 87-89). Researchers recommend to acknowledge perceived problems as real, develop educational programs that inform patients about cognitive functioning, address specific

stressors, help reduce social constraints, promote effective coping strategies and train memory and attention techniques (87, 89-91). In-clinic and home-based cognitive training, group and individual sessions are effective, but not every intervention may be suitable for all patients, for example individuals with more severe deficits (26, 87, 88). The best time to approach cognitive problems may be after chemotherapy has been completed and other issues have been resolved (91) but many patients return to work around this time and might not be able to focus on cognitive rehabilitation. The optimal timing remains unaddressed in current literature (26).

Further research is needed to explore if early interventions could prevent cognitive decline and which therapies are most effective at what times. Additionally, research needs to further explore causes of cognitive dysfunction in cancer patients. If there was proof that cognitive impairment does not worsen during or after medical treatment, patients could be reassured that chemotherapy is not accountable for cognitive problems. Furthermore, if more evidence for the mediating effect of posttraumatic stress was found, psychological counseling should be offered to reduce stress – and simultaneously cognitive impairment.

5.2. Posttraumatic stress in breast cancer patients

Full-blown diagnoses of PTSD or ASD are rare in breast cancer patients – less than four percent in the study. These results are consistent with earlier studies. Nevertheless, many patients experienced several PTSD symptoms during the first year after diagnosis, which can deeply afflict their lives.

5.2.1 DSM-V: Only sudden, catastrophic medical incidents are traumatic

In the recently published DSM-V chronic diseases were removed from the list of potential traumatic events that can trigger stress disorders (4). Since its publication in 2013, only medical incidents that involve sudden, catastrophic events (e.g. waking during surgery, anaphylactic shock) qualify as trauma (4). Thus, if DSM-V criteria are applied, cancer does not count as potential traumatic event anymore and PTSD or ASD related to cancer cannot be diagnosed – even if enough PTSD symptoms are prevalent. More cancer patients will receive

an adjustment disorders diagnosis[2] in the future, which is given "when an individual exhibits symptoms of either ASD or PTSD that do not meet or exceed the diagnostic threshold for either disorder […] and for individuals who have not been exposed to a traumatic event but who otherwise exhibit the full symptom profile of either ASD or PTSD" (4).

Even if the prevalence of stress disorders is low in cancer patients, those who suffer from ASD or PTSD symptoms should not be neglected and denied adequate treatment for their symptoms. It is questionable if patients with PTSD symptoms but without a diagnosis of stress disorder will be treated with the same therapeutic techniques that have been proven effective in victims of other traumas. Breast cancer substantially increases the load of posttraumatic stress – a fact that clinicians need to be aware of.

5.2.2 Psychological interventions

Ideally, cancer patients would be regularly screened for posttraumatic stress but this is currently not feasible. Thus, all patients should be informed about their vulnerability and encouraged to seek help if they experience PTSD symptoms. Clinicians need to make psychological support available – preferably early after diagnosis to promote problem-solving skills and the initial process of adjustment. Evidence on the effectiveness of interventions is currently limited (45). Non-directive supportive counseling and cognitive behavioral therapy have been shown to reduce posttraumatic stress symptoms, anxiety and depression in head and neck cancer patients (92). Cognitive behavioral therapy was more effective than non-directive supportive counseling in a 12-month follow up (92). Patients seem to prefer individual sessions over group sessions, although they have not been proven more effective in reducing stress symptoms (93). Psychologists working in clinical settings, where workload does not allow long-term therapy, should refer patients to psychotherapists in private practice. Future research is needed to identify, which interventions should be applied at what time.

[2] Adjustment disorder is diagnosed when emotional or behavioral symptoms occur in response to an identifiable stressor and if symptoms are out of proportion or significantly impair normal functioning. Adjustment disorders are common accompaniments of medical illness.

5.3 Does a reduction in posttraumatic stress improve cognitive functioning?

As the study has shown, cognitive impairment in breast cancer patients is mediated by posttraumatic stress. Coping with stress-response symptoms related to cancer and its treatment could require many cognitive resources that do not leave enough capacity available for other neurological processes. Psychotherapy may therefore not only help patients reduce posttraumatic stress but also cancer-related cognitive problems.

6. The author's contribution

I was one of five designated psychologists who carried out the interviews and neuropsychological assessments with patients and controls. I recruited participants, collected data, documented all information and controlled for correctness. I was involved in data analysis and interpretation, article drafting, writing and revising of the first article (2). I conducted data analysis and interpretation and wrote the second article (3). I approved the final versions of both articles. Each co-author contributed to the successful execution of this research project and the compilation of the articles. The declaration for cumulative dissertation is signed by all co-authors and separately submitted. Further publications of our study will be published in the near future.

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9. List of abbreviations

ASD	= Acute stress disorder
DSM	= Diagnostic and Statistical Manual of Mental Diseases
NCD	= Neurocognitive disorder
PHQ	= Patient Health Questionnaire
PTSD	= Posttraumatic stress disorder
SCID	= Structured Clinical Interview for DSM
T1, T2, T3	= First, second, third assessment of the study