Two different sides of ‘chemobrain’: determinants and nondeterminants of self-perceived cognitive dysfunction in a prospective, randomized, multicenter study

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Abstract

Objective: Complaints of cognitive dysfunction are frequent among cancer patients. Many studies have identified neuropsychological compromise associated with cancer and cancer therapy; however, the neuropsychological compromise was not related to self-reported cognitive dysfunction. In this prospective study, the authors examined if confounding factors masked an underlying association of self-perceived cognitive function with actual cognitive performance. Determinants of self-perceived cognitive dysfunction were investigated.

Methods: Self-perceived cognitive function and cognitive performance were assessed before treatment, at the end of treatment, and 1 year after baseline in 101 breast cancer patients randomized to standard versus intensified chemotherapy. Linear mixed-effects models were applied to test the relationships of performance on neuropsychological tests, patient characteristics, and treatment variables to self-reported cognitive function. Change of cognitive performance was tested as a predictor of change in self-reports.

Results: Self-perceived cognitive function deteriorated during chemotherapy and had partially recovered 1 year after diagnosis. The personality trait negative affectivity, current depression, and chemotherapy regimen were consistently related to cognitive self-reports. No significant associations with performance in any of the 12 cognitive tests emerged. Change of cognitive performance was not reflected in self-reports of cognitive function.

Conclusions: Neuropsychological compromise and self-perceived cognitive dysfunction are independent phenomena in cancer patients. Generally, cancer-associated neuropsychological compromise is not noticed by affected patients, but negative affectivity and treatment burden induce pessimistic self-appraisals of cognitive functioning regardless of the presence of neuropsychological compromise. Clinicians should consider this when determining adequate therapy for patients who complain of ‘chemobrain’.

Keywords: oncology; cancer; cognition disorders; adverse effects; neuropsychological tests; antineoplastic combined chemotherapy protocols
subjective cognitive functioning was assessed with questionnaires or interviews [7,9]. Nevertheless, associations of subjective and objective measures of cognitive functioning have been sporadically reported: In a study with breast cancer patients who were receiving chemotherapy, Downie and colleagues found an association of tests and self-reports in the domain of memory but not in any other cognitive domain [9]. Bender et al. reported several significant positive, but even more significant negative correlations of self-reports and test results in breast cancer survivors receiving endocrine therapy [17]. This pattern of results raises the question of whether the reported significances that have not been corrected for multiple testing are really meaningful.

The lack of association between subjective and objective evaluations of cognitive functioning suggests that the group of patients who feel cognitively impaired is different from the group of patients who show impairment in cognitive tests and that the overlap of the two groups is not greater than a chance overlap.

In search of an explanation for this puzzling finding, researchers have doubted the validity of the neuropsychological testing. The tests might fail to detect subtle cognitive compromise [7] or they may lack ecological validity [9,17]. However, the tests are sensitive enough to find cognitive compromise in patients who typically do not complain, and the lack of correspondence with subjective measures is not smaller with tests that possess face validity such as paragraph recall tests. Furthermore, it has been suggested that patients who experience daily-life cognitive problems still may not demonstrate any impairment in highly structured test situations [7]. However, all patients profit equally from the favorable circumstances of the neuropsychological testing. Therefore, the different levels of the patients’ cognitive functions in daily life should be mirrored in the test results.

While the incongruence of subjective and objective assessments has been ascribed to failure of the neuropsychological testing, subjective reports are often considered veridical indicators of cognitive functioning. Such an attitude toward symptom reports has been termed ‘naive realism’ by Costa and McCrae as early as 1985 [18]. The psychology of symptom reporting has been thoroughly investigated in the 1980s [19], and while cognitive symptoms were not included then, there are indications that the findings of that research are not limited to somatic symptoms.

The ‘naive realism’ approach turned out to be insufficient for the understanding of symptom report. In more complex integrative models, symptom reporting was found to be strongly influenced by sociodemographic and psychological factors the most prominent, besides gender, being negative affectivity [18,20,21], i.e. the disposition to experience aversive feelings like guilt, shame, irritability, or hostility [22]. In previous studies of cancer-related cognitive complaints, negative affectivity as a personality trait has not been considered. Virtually all of these studies reported an association of cognitive complaints with depression and anxiety [2,4,7,8,10,13–16]; however, these negative emotional states may be the cause as well as the consequence of subjective cognitive complaints.

Furthermore, the reporting of physical symptoms was found to be promoted if individuals held a concept that the symptoms fit in [19]. Recently, Schagen and colleagues demonstrated that the mere availability of the ‘chemobrain’ concept increases the reporting of cognitive symptoms; breast cancer patients who had been given brief information about this concept reported more cognitive complaints [23].

In our multicenter study COGITO—Cognitive Impairment in Therapy of Breast Cancer—we assessed cognitive function and subjective cognitive problems in breast cancer patients before the start of cancer therapy and up to 1 year after diagnosis. In two previous reports, we focused on the effects of chemotherapy [8] and therapy-induced hormonal changes [24] on cognitive performance. In this report, we explore the factors that determine self-reported cognitive functioning.

Using sophisticated statistical methods, we tested the hypothesis that confounding factors, particularly negative affectivity and therapy burden, mask an underlying relationship between objective and subjective evaluations of cognitive function. For this purpose, we determined the effects of the factors negative affectivity, chemotherapy regimen, positive affectivity, current depression and anxiety, age, premorbid intelligence, erythropoietin medication, and induced menopause on subjective cognitive functioning. Then we tested whether objectively assessed cognitive function predicted subjective reports if the effects of the confounding factors were taken into account. Lastly, we examined whether objectively assessed cognitive change was reflected in subjective reports.

**Methods**

**Patients**

All patients were participants of the Preoperative Epirubicin Paclitaxel Aranesp trial [25] in five gynecologic or oncologic centers [8] in Germany. The patients were aged ≤65 years at the start of the study, had invasive breast carcinomas without evidence of metastasis, and had been randomized to receive either a standard chemotherapy regimen (arm A: epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² on day 1 every 21 days for 4 cycles; paclitaxel 175 mg/m² on day 1 every 21 days for 4 cycles), or an intensified
Committees of all the universities involved. The study was approved by the ethics committee. The first two assessments were included in this analysis. Previously [8].

GnRH agonists. Full details of the participation (anastrozole or letrozole) with or without tamoxifen or aromatase inhibitors (no antiestrogen medication/antiestrogen therapy (no antiestrogen medication/antiestrogen therapy). When appropriate, patients received antieostrogen treatment with tamoxifen or aromatase inhibitors (anastrozole or letrozole) with or without GnRH agonists. Full details of the participation criteria and patient accrual have been reported previously [8].

Only the data of patients who completed at least the first two assessments were included in this analysis.

Written informed consent was obtained from all patients. The study was approved by the ethics committees of all the universities involved.

**Assessments**

The test sessions took place before the start of preoperative chemotherapy (T1), before the last cycle of chemotherapy (T2, about 5 months later), and about 1 year after baseline (T3) [24].

Subjective perceptions of cognitive function were assessed with two instruments:

- The Cognitive Function Scale of the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire C30, version 3.0, [26,27] (EORTC-CFS) is composed of two items that globally cover memory and concentration problems. The answers score from 1 to 4 and the combined scores are linearly transformed into a scale ranging from 0 (seriously impaired function) to 100 (full unimpaired function).

- The Questionnaire of Experienced Deficits of Attention (Fragebogen erlebter Defizite der Aufmerksamkeit, FEDA [28]) is a validated instrument that is widely used in Germany to assess attention problems experienced in daily life. It consists of 27 statements, such as ‘I sometimes forget what I was about to do’ (item 7); ‘When I fill in a form, e.g. a bank transfer, I have to think a long time’ (item 20); ‘It’s hard for me to understand long sentences when I read’ (item 27). Answers are scored from 1 (never) to 5 (very often) and form a scale with a range of 108. The scale was inverted and shifted, resulting in a scale that ranged from 0 to 108 with higher numbers signifying better function.

Cognitive function was examined using 12 neuropsychological tests [8,29–33] (Table 2).

Premorbid intelligence was estimated using a language-related test, the MWT-B [34]. Current levels of depression and anxiety were measured with the Hospital Anxiety and Depression Scale (HADS) [35]. Trait negative and positive affectivity were assessed once at T1 with the Positive and Negative Affectivity Schedule (PANAS) [36–38]. It consists of two scales, each of them composed of 10 adjectives, e.g. hostile, guilty, ashamed, irritable (negative affectivity), or excited, proud, interested, active (positive affectivity). The scales were conceptualized to be independent, with low negative affectivity meaning the absence of negative emotions rather than the presence of positive emotions and vice versa. Indeed, moderate correlations of the scales have been reported [38]. Participants indicated on a five-point scale, ranging from ‘slightly or not at all’ to ‘very much’, the extent that they generally experienced the respective emotions.

**Statistical analysis**

Linear mixed models were used to determine factor effects on cognitive self-reports. The analyses were conducted for the dependent variables EORTC-CFS and FEDA, the two cognitive self-report measures.

As a first step, a model was constructed that included all variables that might confound an association of the dependent variables and the cognitive tests, i.e. age, premorbid intelligence, HADS anxiety, HADS depression, negative affectivity, positive affectivity, induced menopause (present/not present), concomitant erythropoietin medication (no/yes), and the interaction of time (T1/T2/T3) with therapy arm (standard/intensified). A stepwise backward procedure using the Akaike Information Criterion was applied for factor selection. We hypothesized that negative affectivity and the interaction of time with therapy arm were confounding factors; therefore, these variables were not subjected to factor selection. In the second step, the cognitive tests were introduced into the model. Since the tests were strongly intercorrelated, their effects were assessed with separate models, each comprising the factors that were selected prior plus one of the cognitive tests.

Eventually, we determined whether the change of cognitive self-reports was related to change of cognitive performance. The dependent variables were cognitive self-reports at T2 corrected for cognitive self-reports at T1, and cognitive self-reports at T3 also corrected for cognitive self-reports at T2. Initially, all aforementioned independent variables, except the cognitive tests, were included in the models and selected as described above. In the T3 models, we included antieostrogen therapy (no antieostrogen medication/tamoxifen/aromatase inhibitors; patients had...
received antiestrogen therapy only at T3). In the second step, the differences of the cognitive test results were introduced as factors into the models, i.e. in the T2 models we introduced the difference of the T2 results minus the T1 results, and in the T3 models we introduced the difference of the T3 results minus the T1 results. Again, separate models were created for each of the cognitive tests with each model comprising the previously selected factors plus the difference of results in one test.

Additionally, t-tests, Chi-square-tests, and the Pearson product-moment correlation were used. Analyses were carried out with the Statistical Package for the Social Sciences (SPSS, version 16: SPSS, Chicago, Ill). All statistical tests were two-sided and significance was calculated with a 5% type I error.

**Results**

Of the 101 patients who partook in the T1 and T2 assessments [8,24], 48 patients received standard chemotherapy (arm A) and 53 patients received intensified chemotherapy (arm B). About half of the patients in each therapy arm were treated with concomitant erythropoietin medication (arm A: 22 patients, 45.8%; arm B: 28 patients, 52.8%). At T3, two patients in arm A and seven patients in therapy arm B discontinued study participation [24]. For full demographic characteristics of the patients, readers are referred to our previous reports [8,24]. The chemotherapy groups did not significantly differ in terms of age (arm A, mean: 49.9, SD: 8.9; arm B, mean: 47.1, SD: 10.1, N = 101), premorbid intelligence (arm A, mean: 108.6, SD: 13.9; arm B, mean: 106.9, SD: 15.5, N = 101), negative affectivity (arm A, mean: 18.8, SD: 4.8; arm B, mean: 18.3, SD: 5.1, N = 100), or positive affectivity (arm A, mean: 39.0, SD: 5.6; arm B, mean: 38.7, SD: 4.7, N = 95).

There were no significant differences in depression between the treatment groups at any of the assessment points and no significant differences in anxiety at T1 and T2. However, at T3 patients in arm B reported more anxiety (arm A, mean: 4.7, SD: 3.4; arm B, mean: 6.5, SD: 3.7; p = .019, N = 92).

The cognitive test results and the factors influencing cognitive test results have previously been reported. Neither therapy arm nor concomitant medication with erythropoietin significantly affected the performance in any of the cognitive tests [8,24].

Both self-report measures of cognitive functioning showed deterioration at T2 and partial recovery at T3 (EORTC-CFS, mean/standard deviation T1: 84.3/19.6; N = 101; T2: 76.6/21.0, N = 101; T3: 78.6/21.4; N = 92; FEDA, mean/standard deviation T1: 89.8/11.8 N = 101; T2: 83.1/16.3; N = 100; T3: 85.0/16.3, N = 92). For the course of subjective cognitive function relative to therapy arm, see Figure 1 (EORTC-CFS) and Figure 2 (FEDA).

EORTC-CFS and FEDA correlated significantly at all assessment points (T1: r = 0.623, p < 0.001, N = 101; T2: r = 0.649, p < 0.001, N = 100; T3: r = 0.679, p < 0.001, N = 92).

**Factors predicting self-reported cognitive functioning**

Both measures of subjective cognitive function were significantly predicted by the following

![Figure 1](image1.png)

**Figure 1.** The course of self-reported cognitive function: EORTC-CFS by therapy arm. Blue: arm A, standard chemotherapy, N = 46; red: arm B, intensified chemotherapy, N = 46. EORTC-CFS: European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire–Cognitive Function Scale. T1, prior to chemotherapy; T2, toward the end of chemotherapy; T3, 1 year after baseline. Higher values indicate better cognitive function. Boxplots show interquartile range and median

![Figure 2](image2.png)

**Figure 2.** The course of self-reported cognitive function: FEDA by therapy arm. Blue: arm A, standard chemotherapy, N = 45; red: arm B, intensified chemotherapy, N = 46. FEDA, Questionnaire of Experienced Deficits of Attention. T1, prior to chemotherapy; T2, toward the end of chemotherapy; T3, 1 year after baseline. Higher values indicate better cognitive function. Boxplots show interquartile range and median
‘Chemobrain’ determinants and nondeterminants

The analysis of change of subjective cognitive function relative to baseline, as predicted by the change of the cognitive test results relative to baseline, showed a significant effect of changed performance in a test of executive function, the Regensburg Word Fluency test subtest Category Fluency with Switch of Category [8,33] on the FEDA score at T2 (p = 0.049). There was no other significant effect of changed test performance on the FEDA score or the EORTC-CFS at either T2 or at T3, i.e. 1 of 48 statistical tests (effects of changes in 12 cognitive tests on two self-report measures at two assessment points, respectively) produced a significant result.

In the analysis of change, additional effects of factors other than cognitive tests were found: At T2, higher levels of trait positive affectivity were associated with less deterioration of EORTC-CFS (p = 0.031) and older age was associated with less deterioration of FEDA (p = 0.012). At T3, there was an unfavorable effect of antiestrogen therapy (p = 0.028) and a favorable effect of previous erythropoietin medication (p = 0.028) on EORTC-CFS.

Conclusions

In an analysis of self-perceived cognitive function before chemotherapy for breast cancer and throughout the first year after diagnosis, depression, trait negative affectivity, and chemotherapy regimen emerged as consistent predictors of self-reports both of global cognitive problems and of specified attention problems experienced in daily life. By contrast, data from none of the 12 cognitive tests predicted self-reported cognitive function. Moreover, when changes of self-reported cognitive

Table 1. Factor effects on self-reported cognitive function

<table>
<thead>
<tr>
<th>Factor</th>
<th>EORTC-CFS</th>
<th>p-Value</th>
<th>FEDA</th>
<th>p-Value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Estimate</td>
<td>Confidence Interval 95%</td>
<td></td>
<td>Estimate</td>
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<tr>
<td>Negative affectivity: PANAS-N</td>
<td>-0.85 ± 0.69</td>
<td>0.015</td>
<td>-0.62 ± 0.47</td>
<td>0.011</td>
</tr>
<tr>
<td>Positive affectivity: PANAS-P</td>
<td>0.18 ± 0.65</td>
<td>0.581</td>
<td>0.32 ± 0.45</td>
<td>0.162</td>
</tr>
<tr>
<td>Depression: HADS-D</td>
<td>-1.96 ± 0.87</td>
<td>&lt;0.001</td>
<td>-1.94 ± 0.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Premorbid intelligence: MWT-B</td>
<td>0.02 ± 0.22</td>
<td>0.887</td>
<td>Factor not included</td>
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<tr>
<td>Induced menopause</td>
<td>0.14 ± 0.53</td>
<td>0.960</td>
<td>Factor not included</td>
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<tr>
<td>Erythropoietin medication</td>
<td>-3.79 ± 5.65</td>
<td>0.188</td>
<td>2.48 ± 3.63</td>
<td>0.179</td>
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<tr>
<td>Interaction of time with therapy arm</td>
<td></td>
<td>0.011</td>
<td></td>
<td>&lt;0.001</td>
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<tr>
<td>T1 and therapy arm A</td>
<td></td>
<td>0</td>
<td></td>
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<tr>
<td>T1 and therapy arm B</td>
<td>-9.47 ± 7.68</td>
<td>0.148</td>
<td>-2.47 ± 5.17</td>
<td></td>
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<tr>
<td>T2 and therapy arm A</td>
<td>-7.67 ± 8.46</td>
<td>0.873</td>
<td>-5.44 ± 5.46</td>
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<tr>
<td>T2 and therapy arm B</td>
<td>-17.18 ± 7.09</td>
<td>0.162</td>
<td>-14.41 ± 3.91</td>
<td></td>
</tr>
<tr>
<td>T3 and therapy arm A</td>
<td>-8.71 ± 8.50</td>
<td>0.148</td>
<td>-6.43 ± 5.50</td>
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<tr>
<td>T3 and therapy arm B</td>
<td>-15.03 ± 6.79</td>
<td>0.179</td>
<td>-13.20 ± 4.06</td>
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</tbody>
</table>

EORTC-CFS, European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire–Cognitive Function Scale; FEDA, Questionnaire of Experienced Deficits of Attention; PANAS-N, Positive and Negative Affect Schedule–Negative affectivity scale; PANAS-P, Positive and Negative Affect Schedule–Positive affectivity scale; HADS-D, Hospital Anxiety and Depression Scale–Depression; MWT-B, Multiple Choice Vocabulary Test of Intelligence; T1, before treatment; T2, toward the end of chemotherapy; T3, one year after baseline.

*Estimated change on EORTC-CFS score or FEDA score, respectively, effected by one score point of the factor (continuous variables), or by presence of the factor (categorical variables). Range of scales: EORTC-CFS, 0–100; FEDA, 0–108; PANAS-N and PANAS-P, 0–40; HADS-D, 0–21; MWT-B, 61–145. Positive estimates signify favorable effects, negative estimates signify unfavorable effects.

bSignificant effect.
function were examined in relation to changes of cognitive performance, only 1 out of 48 statistical analyses yielded a marginally significant result. This is within the rate of false-positive results to be expected given the number of statistical tests.

Sporadic effects of further factors were found: Older patients and patients with higher levels of positive affectivity showed less increase in cognitive complaints during chemotherapy; erythropoietin medication during chemotherapy was associated with fewer cognitive complaints six months later; and current tamoxifen or AI medication increased cognitive complaints. All of these associations neither emerged consistently across the two different measures of subjective cognitive function nor were highly significant. Therefore, they should be interpreted with caution.

Even though we applied a battery of 12 validated and widely used cognitive tests that cover a broad range of cognitive domains, we cannot fully exclude that the failure to detect an association of subjective cognitive functioning with cognitive performance is due to insufficient sensitivity of the neuropsychological assessment. Some, but not all, other studies have detected more cognitive decline following chemotherapy. Furthermore, the sample size of our study may have been too small to detect subtle associations of objective and subjective cognitive function.

Many studies have found an association of self-reported cognitive function with negative emotional states, primarily depression and anxiety. Our study confirms the association of self-perceived cognitive function and depression, while anxiety had no further effect when depression was accounted for. However, while depression appears to increase the reporting of cognitive symptoms, self-perceived cognitive symptoms may actually increase depression. In our study, we demonstrated that the personality trait negative affectivity, assessed before the start of chemotherapy, increases cognitive complaints throughout the first year after diagnosis.

This finding concurs with research that found a substantial role of negative affectivity in the reporting of physical symptoms [18,20,21]. Negative affectivity acts as a bias particularly if the symptoms are rather vague [39]. This applies to the cognitive symptoms reported by cancer patients. In a large-scale interview study, the vast majority of cognitive complaints were slips and lapses that could happen to anybody [7]. Apparently, persons with high levels of negative affectivity tend to report more pessimistic evaluations of such incidences.

Furthermore, we identified treatment burden as a determinant of self-perceived cognitive function: Patients randomly assigned to receive an experimental dose-intensified, dose-dense chemotherapy regimen reported more cognitive symptoms before the first chemotherapy session and at the following assessments; however, chemotherapy regimen had no effect on the performance in any of the cognitive tests [8,24]. It is possible that the experience and even the anticipation of an extraordinarily toxic treatment may promote the general concept of the chemotherapy’s harmfulness, boosting expectations of somatic and cognitive side effects alike and thus aggravating self-perceived cognitive dysfunction.

Even if cancer patients’ self-perceived cognitive symptoms generally do not appear to be based on neuropsychological compromise, we strongly advocate taking these complaints seriously. First,
self-perceived cognitive dysfunction and neuropsychological impairment are not mutually exclusive and may of course exist simultaneously in individual patients. Second, self-perceived cognitive dysfunction causes suffering and needs treatment even if it is not based on neuropsychological impairment. However, it will not help cancer patients to simplify the problem of cancer-related cognitive compromise and ignore the divergence of objective and subjective cognitive functioning. Encouraging the notion that cancer-related cognitive symptoms are generally based on chemotherapy-inflicted damage may even exacerbate patients' self-perceptions of cognitive dysfunction.

In our prospective, randomized study, self-reports of cognitive dysfunction did not reflect neuropsychological compromise but were associated with the personality trait negative affectivity, therapy burden, and current levels of depression. These findings imply that the cancer-associated neuropsychological compromise detected by research generally remains unnoticed by affected patients. Cancer patients' self-perceptions of cognitive dysfunction instead appear to be pessimistic interpretations of their cognitive functioning that are induced by treatment burden and negative affectivity regardless of whether or not neuropsychological compromise is actually present.

References

25. Untch M, Fasching PA, Bauerfeind I et al. The PREPARE trial A randomized phase III trial comparing preoperative, dose-dense, dose-intensified chemotherapy with epirubicin, paclitaxel and CMF with


