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The Hormone-Brain-Emotion Axis in Endocrine Therapy for Early Breast Cancer: Insights from a Survivorship Cohort

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Research Article

Keywords: Early breast cancer, Endocrine therapy, Cognitive impairment, Fatigue, Emotional distress, Survivorship, Quality of life, Hormone-brain-emotion axis, Tamoxifen, Aromatase inhibitors

Posted Date: June 28th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9723767/v1

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Additional Declarations: No competing interests reported.

Abstract

Background:

Endocrine therapy (ET) is a cornerstone of treatment for hormone receptor-positive early breast cancer but may cause cognitive and emotional side effects that affect quality of life and adherence. This study investigated the interplay between cognitive complaints, fatigue, and emotional distress, the hormone-brain-emotion axis, during adjuvant ET.

Materials and methods:

We conducted a cross-sectional online survey of women undergoing adjuvant ET for early-stage breast cancer between January and June 2023. Eligible participants were identified from institutional pharmacy records of patients actively collecting ET prescriptions during this period. Data collection included the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog v3) for perceived cognition, the Patient's Disease Questionnaire for Breast Cancer (PDQ-BC) for distress, and a fatigue numeric scale. Clinical and demographic data were self-reported. Pearson correlations and multivariable linear regression models were used to evaluate associations among cognitive function, fatigue, distress, ET duration, and therapy type. Statistical analyses were conducted using IBM SPSS v27.

Results:

126 female patients filled the questionnaire, with a median age of 55.5 years (range 33–78) and a median ET duration of 37 months (IQR 6–140). Cognitive interference was prevalent: 91 (72.2%) reported at least occasional difficulty, and 27 (21.4%) reported frequent or very frequent interference with daily life. Mean global cognition (FACT-Cog total) indicated a clinically relevant decline in perceived function. Fatigue was widespread (mean 21.0 ± 12.2 on a 0–48 scale), strongly correlated with emotional distress ($r = 0.81$, $p < 0.001$) and moderately with cognitive complaints ($r = 0.58$, $p < 0.001$). Distress scores averaged 20.5 ± 13.2 (range 0–60), with 34 (27.0%) exceeding the clinical threshold for high distress and 35 (27.8%) meeting criteria for probable depression. In multivariable analyses, worse perceived cognitive function was independently predicted by greater distress ($\beta = +0.55$, $p < 0.001$), higher fatigue ($\beta = +0.57$, $p < 0.001$), and shorter ET duration ($\beta = -1.84$/year, $p = 0.002$). Emotional distress was primarily driven by fatigue ($\beta = +0.76$, $p < 0.001$) and modestly by cognitive complaints ($\beta = +0.11$, $p = 0.02$). No significant associations were found for age or ET type (tamoxifen vs aromatase inhibitor), indicating that therapy-specific hormonal mechanisms were less relevant than global symptom burden.

Discussion:

The observed prevalence and pattern of cognitive complaints mirror findings from prior endocrine and chemotherapy-related cognitive studies. However, the inverse relationship between ET duration and cognitive complaints suggests possible neuropsychological adaptation or selective persistence among long-term adherent patients rather than progressive cognitive decline. The strong correlations between

fatigue, distress, and cognitive perception support a multidimensional model in which psychological and physiological mechanisms, such as inflammatory and neuroendocrine dysregulation, jointly shape symptom burden. These findings emphasize the clinical importance of routine screening and targeted management of fatigue and distress in survivorship care, as they are modifiable determinants of perceived cognitive function and overall wellbeing.

Conclusion:

Fatigue and emotional distress are key, interrelated drivers of perceived cognitive impairment in women undergoing adjuvant ET for early luminal breast cancer. Routine screening for these symptoms and integration of evidence-based supportive interventions should be central to survivorship care to sustain adherence, function, and quality of life.

Categories: Breast Cancer; Supportive and Survivorship Care; Neurocognitive Effects of Cancer Therapy; Psycho-oncology; Translational Research / Biomarker and Mechanism of Toxicity

Introduction

Breast cancer remains the most commonly diagnosed malignancy in women worldwide [1]. According to the International Agency for Research on Cancer, breast cancer accounted for 11.7% of all new malignant tumors in 2020 [2]. Approximately 70% of breast cancers are estrogen-receptor positive, falling into the luminal subtype. Adjuvant endocrine therapy (ET), either tamoxifen or an aromatase inhibitor, is a cornerstone for this population: the standard of care is 5–10 years of treatment, which substantially reduces recurrence risk and improves long-term survival [1–4]. The success of ET is reflected in survival statistics. At the present time, five-year survival for early-stage breast cancer exceeds 90% [4–7]. Consequently, attention has shifted towards adherence and survivors' long-term quality of life.

Estrogen modulates hippocampal and prefrontal networks that support learning, memory and executive function [8–12]. ET works by suppressing estrogen signaling or blocking estrogen receptors; while beneficial for tumor control, these pharmacologic effects have the potential to disrupt neural processing. Data from animal and human imaging studies suggest that tamoxifen and aromatase inhibitors can alter brain glucose metabolism and connectivity [13–16]. Clinical evidence is, however, mixed. The largest prospective longitudinal study to date found that survivors receiving ET for 5–10 years reported worse cognitive complaints than those not taking ET, although objective neuropsychological tests showed only modest changes [17]. Comprehensive reviews note that global cognition often remains intact, but deficits appear in specific domains, particularly verbal memory, processing speed and fluency, whereas attention, executive function and visuospatial abilities are generally preserved [18–21]. Moreover, self-reported cognitive function often correlates poorly with objective test performance but is closely linked to anxiety, depression and fatigue [18, 22–24]. This distinction emphasizes the importance of assessing both subjective and objective cognitive outcomes in survivorship research.

Longer exposure to ET may exacerbate cognitive symptoms. In a recent Chinese cohort study using propensity score matching, duration of ET emerged as an independent risk factor for cognitive impairment: every additional year of therapy increased the odds of cognitive decline (OR 1.30, 95% CI 1.01–1.67) [25]. The investigators concluded that prolonged ET, although essential for disease control, could increase the risk of cognitive impairment. Population-based surveys corroborate this finding: in a cohort of more than 2,200 women with early breast cancer, ET alone was associated with a 1.6-fold increased odds of neurocognitive symptoms compared with no systemic therapy. These data suggest that the potential neurocognitive cost of extended therapy should be balanced against its survival benefit, especially as guidelines increasingly favor extended regimens beyond five years.

Survivors often experience fatigue, sleep disturbance, emotional distress and depressive symptoms; these symptoms can directly affect attention, working memory and processing speed. Strong correlations between self-reported cognitive impairment and negative emotional states such as anxiety, depression and fatigue have been observed [18, 22, 23, 26]. For example, the National Cancer Institute's Psychosocial Distress guidelines note that subjective cognitive complaints commonly coexist with anxiety and depression and are associated with reduced participation in daily activities [27]. Furthermore, fatigue itself is both a direct symptom of systemic therapy and a contributor to cognitive inefficiency. Recognition of these interrelations is essential, because addressing fatigue and mood may ameliorate cognitive complaints even in the absence of measurable neuropsychological impairment [28, 29].

Survivorship, now the norm for early-stage luminal breast cancer, must encompass care more than recurrence surveillance. Persistent cognitive complaints can impair work ability, social participation and adherence to therapy [17, 19, 24]. Yet cognitive deficits are often under-recognized; many women underreport difficulties or attribute them to ageing or stress. Moreover, self-reported impairments may not align with objective test results, underscoring the need for formal cognitive assessments alongside patient-reported outcomes [18, 30, 31]. The scarcity of long-term prospective studies and the heterogeneity of assessment tools complicate understanding of the true prevalence and trajectory of ET-related cognitive changes. Recent guidelines therefore encourage routine screening for cognitive and emotional symptoms in breast cancer survivors and advocate supportive interventions such as cognitive rehabilitation, mindfulness-based stress reduction and tailored physical activity [27].

The existing literature demonstrates that ET can affect cognition, particularly in domains sensitive to estrogen withdrawal, and that cognitive complaints are intertwined with fatigue and emotional distress. However, most studies have focused on objective neuropsychological tests or global quality-of-life measures, often neglecting the patient's perceived cognitive abilities and the contextual factors driving these perceptions [32]. Moreover, data on survivors in real-world clinical settings, particularly those on long-term ET in early-stage luminal breast cancer, remain sparse. By using validated instruments, our study seeks to elucidate how cognitive and emotional dimensions interact during long-term ET, identify modifiable predictors of perceived cognitive decline and inform targeted survivorship strategies [28, 33, 34]. Ultimately, understanding this hormone-brain-emotion axis may help clinicians balance the benefits

of extended ET against neurocognitive risks and tailor supportive care to improve adherence and quality of life.

Materials And Methods

Study design and participants

This was a cross-sectional, single-center, online survey study conducted at a single-center Portuguese Oncology Unit. Eligible participants were women aged ≥ 18 years with histologically confirmed early-stage, hormone receptor–positive (luminal) breast cancer who were receiving adjuvant ET (either tamoxifen or an aromatase inhibitor [AI]) after definitive surgery. Exclusion criteria included history of metastatic disease, neurologic or severe psychiatric disorders, and inability to complete online questionnaires in Portuguese. Between January and June 2023, all patients actively collecting medication from the hospital pharmacy were screened for eligibility. Patients meeting inclusion criteria were approached by their treating physician during follow-up or prescription renewal visits and subsequently contacted by e-mail. Each patient received a unique link to complete a one-time online survey designed using a secure institutional REDCap-based platform. Responses were collected anonymously, and no financial compensation was provided. A total of 271 patients contacted, 126 patients completed the survey and were included in the final analysis. Clinical variables, including age, ET type and duration, prior chemotherapy, and menopausal status, were self-reported and cross-checked against medical records when available. The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional ethics committee. All participants provided informed consent prior to participation. Data were anonymized and handled in compliance with applicable data protection regulations. All instruments were used under academic or open-access license for non-commercial research. FACT-Cog v3 is distributed by FACIT.org under a no-fee academic license. The PDQ-BC and PDI are freely available for academic use and require no special license.

Patient-reported outcome measures

Cognitive function was assessed using the Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog v3)[35], a validated 37-item instrument comprising four subdomains: *Perceived Cognitive Impairments*, *Perceived Cognitive Abilities*, *Comments from Others*, and *Impact on Quality of Life*. Items are scored on a 5-point Likert scale (from *never* to *several times per day*). Higher *Perceived Cognitive Impairment* and *Impact* scores indicate worse cognition, whereas higher *Perceived Abilities* scores indicate better cognitive function. Emotional distress was evaluated using the Psychosocial Distress Questionnaire-Breast Cancer (PDQ-BC) [36], which includes items from the Psychological Distress Inventory (PDI) assessing fatigue, tension, sadness, irritability, and loss of energy. Total distress scores range from 0 to 60, with higher scores denoting greater psychological burden. Fatigue was measured using the fatigue subdomain of the Psychosocial Distress Questionnaire-Breast Cancer (PDQ-

BC)[36], scored on a 0–48 scale; depressive symptoms and fatigue interference were also extracted from PDQ-BC subdomains.

Data processing and Statistical analysis

Data were exported into IBM SPSS Statistics v27 for analysis; figures and graphics were generated using Microsoft Excel v365. Descriptive analyses were performed for demographic, clinical, and questionnaire data (mean ± standard deviation or median [range] for continuous variables; n [%] for categorical variables). Associations between FACT-Cog, PDQ-BC, and clinical parameters were explored using Pearson correlation coefficients (r), with 95% confidence intervals and two-tailed significance testing. Subgroup analyses compared results by ET type (tamoxifen vs AI), duration (≤ 3 vs > 3 years), and presence of depressive symptoms using t-tests, Mann–Whitney U, or χ^2 tests, as appropriate. To identify independent predictors of cognitive and emotional outcomes, multivariable linear regression models were built. Predictors included distress, fatigue, ET duration, and age for cognitive outcomes, and fatigue and cognitive complaints for distress. All continuous predictors were standardized (β coefficients reported). All tests were two-tailed; $p < 0.05$ considered significant. Model assumptions were verified (linearity, homoscedasticity, absence of multicollinearity; variance inflation factors < 2). Statistical significance was set at $p < 0.05$.

Results

Participant Characteristics

A total of 126 women responded to the online survey and were included in the analysis. The median age was 55.5 years (range 34–81), and all participants were receiving adjuvant ET for early-stage luminal breast cancer. Treatment duration at the time of the survey was 37 months (range 6–140), with 53 (42.1%) taking tamoxifen and 73 (57.9%) taking an aromatase inhibitor (AI) (letrozole, anastrozole or exemestane). 14 (11.1%) premenopausal women received concurrent ovarian suppression. 82 (65.1%) had received prior chemotherapy, and 98 (77.8%) had received radiotherapy. Baseline demographics and treatment characteristics did not differ significantly between the tamoxifen and AI groups, as summarized in Table 1 (baseline characteristics). The cohort was predominantly Caucasian (97. %) and entirely female; no significant gender differences were present because no men were enrolled. Age distribution and therapy duration were comparable between ET types, supporting combined analyses for subsequent outcomes.

Table 1

Baseline demographic and clinical characteristics *Baseline demographic and clinical characteristics of the study population (n = 126), stratified by endocrine therapy type (Tamoxifen vs Aromatase Inhibitors). Continuous variables are presented as median (range), and categorical variables as number (%). No significant differences were observed between groups.*

Variable	**All**	**Tamoxifen**	**Aromatase-Inhibitors**
	n = 126	**n = 53(42%)**	**n = 73(58%)**
Sex - n(%)			
female	126(100)	53(100)	73(100)
male	0(0)	0(0)	0(0)
Age - years			
median	55.5	54	57
min-max	34–81	34–73	36–81
Ethnicity - n(%)			
Caucasian	123(97.6)	52(98)	71(97)
Black	1(0.8)	0(0)	1(1)
Asian	1(0.8)	0(0)	1(1)
Other	1(0.8)	1(2)	0(0)
Time under ET - months			
median	37	34	39
min-max	6-140	6-120	7-140
Ovarian function suppression - n,(%)			
Yes	14(11)	0(0)	14(19)
No	112(89)	53(100)	59(81)
Prior chemotherapy - n,(%)			
Yes	82(65)	35(66)	47(64)
No	44(35)	18(34)	26(36)
Prior radiotherapy - n,(%)			
Yes	98(78)	40(75)	58(79)
No	28(22)	13(25)	15(21)

Patient-reported cognitive outcomes

The Functional Assessment of Cancer Therapy Cognitive Function (FACT-Cog v3) revealed a broad spectrum of perceived cognitive function. The mean FACT-Cog total score on the 0-148 scale (higher scores = better cognitive function) was 100.4 ± 21.4, corresponding to a cognitive complaint index of 47.6 ± 21.4 when reverse coded for ease of interpretation (higher values indicate greater perceived impairment). 91 (72.2%) reported at least occasional difficulty, and 27 (21.4%) reported frequent or very frequent interference. The most commonly endorsed problem was difficulty remembering new information, with 52 (41.3%) experienced this several times per week or more, followed by slowed thinking, trouble concentrating, and difficulty finding words (Fig. 2 shows the full distribution of cognitive complaints by item). Conversely, some positive items (e.g. “My mind is as sharp as it has always been”) were less frequently endorsed, suggesting a shift toward self-perceived cognitive inefficiency during ET. Scores on the Perceived Cognitive Impairments subscale were higher than those on the Impact on Quality of Life and Comments from Others subscales (Fig. 3), underscoring that patients recognized their own cognitive difficulties more than receiving external feedback about them.

Patient-reported emotional and fatigue outcomes

Emotional distress, measured with the Psychosocial Distress Questionnaire–Breast Cancer (PDQ-BC), was common but heterogeneous. The mean distress score (0–60) was 20.5 ± 13.2. Up to 34 (27.0%) of respondents scored ≥ 29, a threshold suggesting clinically relevant distress. Within the distress components, fatigue/energy and cognitive/concentration domains were most prominent (Fig. 3). The fatigue scale (0–48) had a mean of 21.0 ± 12.2; 76 (60.3%) of patients reported feeling a lack of energy or being exhausted at least “occasionally,” and 57 (45.2%) felt fatigued “frequently” or “very frequently.” Feelings of sadness or loss of pleasure were present but less prevalent: About 32 (25.4%) respondents experienced depressed mood often, and 9 (7.1%) very often. Probable depression, defined by frequent sadness or anhedonia, affected 35 (27.8%) of the cohort. In addition, 38 (30.2%) of respondents had taken medical leave from work since diagnosis, 28 (22.2%) reported reduced work performance, and 25 (19.8%) reported financial strain. 24 (19.0%) reported sexual distress (FSDS-R ≥ 26), but the average FSDS-R score was modest (mean 12.6 ± 14.4), reflecting the varied importance of sexual activity across ages and life stages. Together, these data highlight fatigue and emotional distress as central issues for patients on ET (Table 2 and Fig. 1 provide descriptive comparisons by therapy type and item-level emotional distributions).

Table 2
Cognitive, emotional and quality-of-life outcomes according to endocrine therapy type

Variable	All	Tamoxifen	Aromatase-Inhibitors
	n = 126	n = 53(42%)	n = 73(58%)
Cognitive function (FACT-Cog v3)			
Mean (0–148*)	47.6 ± 21.4	47.6 ± 22.1	47.4 ± 21.0
Any cognitive interference – n (%)	91 (72)	39 (74)	52 (71)
Frequent/very frequent interference – n (%)	27 (21)	12 (23)	15 (21)
Emotional distress (PDQ-BC / PDI)			
Mean (0–60**)	20.5 ± 13.2	21.8 ± 13.7	19.8 ± 12.9
Above clinical cutoff (≥ 29) – n (%)	34 (27)	14 (26)	20 (27)
Fatigue score (0–48**)	21.0 ± 12.2	22.1 ± 12.5	20.2 ± 12.0
Probable depression – n (%) †	36 (28)	15 (28)	21 (29)
High interference with daily life – n (%)	27 (21)	12 (23)	15 (21)
Sexual distress (FSDS-R, 0–52)	12.6 ± 14.4	11.8 ± 13.9	13.2 ± 14.8
FSDS-R ≥ 26 – n (%)	24 (19)	8 (15)	16 (22)
Work impact – n (%)			
On medical leave since diagnosis	38 (30)	17 (32)	21 (29)
Reporting reduced work performance	28 (22)	11 (21)	17 (23)
Financial strain – n (%)	25 (20)	10 (19)	15 (21)

Higher FACT-Cog scores indicate worse perceived cognitive impairment (reverse-coded).

** Higher the value, the higher the distress.

† Defined as reporting frequent sadness or anhedonia on the distress questionnaire (symptom-based).

Patient-reported outcomes assessing perceived cognitive function (FACT-Cog v3), emotional distress (PDQ-BC/PDI), fatigue (0–48 scale), sexual distress (FSDS-R), and work or financial impact, stratified by endocrine therapy type. Data are presented as mean ± SD or n (%). Higher scores indicate greater symptom burden unless otherwise specified.

Correlation analyses

We examined the relationships among cognitive complaints, emotional distress, fatigue and clinical variables. Pearson correlations showed that fatigue and emotional distress were strongly correlated ($r = 0.81$, $p < 0.001$), indicating that women who felt more exhausted also reported greater psychological burden. Cognitive complaints correlated moderately with both fatigue ($r = 0.58$, $p < 0.001$) and emotional distress ($r = 0.58$, $p < 0.001$). Thus, patients with higher fatigue and higher distress were more likely to perceive cognitive deficits. Duration of ET correlated negatively with cognitive complaints ($r = -0.34$, $p = 0.004$), suggesting that longer therapy was associated with fewer perceived cognitive problems. Age correlated weakly and nonsignificant with cognitive complaints ($r = -0.12$, $p = 0.21$) and emotional distress ($r = -0.15$, $p = 0.08$). The type of ET (tamoxifen versus AI) had no meaningful correlation with cognitive or emotional scores ($r \approx 0.06$, $p > 0.40$). These correlations are illustrated in Fig. 4, where the forest plot shows point estimates and 95% confidence intervals for each association; a negative correlation denotes that longer therapy was associated with better cognition, whereas positive correlations denote worse outcomes.

Subgroup comparisons

To explore potential modifiers, we compared outcomes across key subgroups. Age group (< 55 vs ≥ 55 years): younger women (< 55 years) tended to have slightly higher distress scores (mean 22.9 vs 18.4), but the difference did not reach statistical significance ($p = 0.055$); cognitive complaints were similar between age groups. Therapy type: mean cognitive (47.6 vs 47.4) and emotional (21.8 vs 19.8) scores were nearly identical between tamoxifen and AI groups, and no significant differences were observed in fatigue, depression prevalence, sexual distress or work interference (all $p > 0.30$). Therapy duration: patients on ET > 3 years reported significantly fewer cognitive complaints (mean 42.1 vs 49.9, $p = 0.005$) and slightly lower interference with daily life, whereas emotional distress was similar by duration. This pattern suggests possible adaptation or selective persistence over time. Presence of depression: patients meeting criteria for probable depression (28%) had markedly worse outcomes; their cognitive impairment scores were on average 17 points higher ($p < 0.001$) and distress scores 21 points higher ($p < 0.001$) than those without depression. They were more likely to report work interference, financial strain and sexual distress, underscoring the intertwined nature of mood and cognitive perception. These subgroup results are summarized graphically in Table 2 and Fig. 5.

Multivariable predictors of cognitive and emotional outcomes

Multivariable linear regression models were constructed to identify factors independently associated with cognitive impairment and emotional distress. For cognitive outcomes, predictors included distress score, fatigue score, duration of therapy, therapy type and age. The model explained 41% of the variance in cognitive complaints. Higher distress and greater fatigue were significant independent predictors of worse perceived cognition ($\beta = +0.55$ and $+0.57$ per point increase, both $p < 0.001$). Therapy duration remained an independent protective factor; each additional year of ET was associated with a -1.84 point

decrease in cognitive complaints (p = 0.002). Therapy type and age were not independent predictors. These findings are visualized in the left panel of Fig. 5. The results support that cognitive perceptions are driven by psychological and physical symptom burden rather than demographic factors or type of endocrine agent. In the emotional distress model, predictors included fatigue, cognitive complaint score, therapy type, duration and age. The model explained 69% of the variance in distress scores. Fatigue emerged as the dominant predictor (β = +0.76 per point, p < 0.001), consistent with its strong bivariate correlation with distress. Cognitive complaints contributed modestly but significantly (β = +0.11 per point, p = 0.02), while therapy type, duration and age did not have significant effects. The right panel of Fig. 5 depicts these results. Taken together, the models highlight that symptom burden, fatigue and emotional state, are closely linked to subjective cognitive function, and that longer therapy duration may confer adaptation or selection benefits.

Additional observations

The survey also assessed the impact of cognitive and emotional symptoms on work and daily functioning. 38 (30.2%) had been on medical since their cancer diagnosis, and 28 (22.2%) reported reduced work performance. Financial strain attributable to treatment effects was reported by 25 (19.8%), and 24 (19.0%)experienced significant sexual distress. These figures illustrate the broader survivorship challenges faced by women on long-term ET. Although these domains were not the primary focus of multivariable analyses, they provide context for the clinical relevance of cognitive and emotional outcomes.

Discussion

This cross-sectional survey of 126 women with early-stage luminal breast cancer receiving adjuvant ET provides a comprehensive snapshot of cognitive and emotional outcomes during survivorship. Several key patterns emerged. First, perceived cognitive impairment was both frequent and multifaceted. More than 70% of participants reported some degree of cognitive interference and over one fifth reported frequent or very frequent interference, despite a mean reversed FACT-Cog score of 47.6 ± 21.4, which is comparable to prior cohorts of endocrine-treated survivors [20]. The most commonly endorsed complaints involved memory lapses, slowed thinking, difficulty concentrating and word-finding problems, echoing previous observations that ET may disproportionately affect verbal memory and processing speed[19]. Emotional distress was also common: the mean PDQ-BC total was 20.5 ± 13.2 (of 60), and 27% of respondents exceeded the clinical cut-off for clinically significant distress, consistent with reported distress prevalence in early breast cancer[19]. Fatigue was pervasive (mean 21.0/48), and 28% of women met criteria for probable depression. Importantly, the correlations among these domains were striking. Fatigue correlated strongly with distress (r = 0.81) and moderately with cognitive complaints (r = 0.58); distress was also moderately correlated with cognitive complaints (r = 0.55). These associations confirm prior reports that subjective cognitive difficulties are tightly linked to anxiety, depression and fatigue and support a symptom-cluster model of “cancer-related cognitive impairment” [17, 19, 25, 26].

Notably, therapy duration demonstrated a negative correlation with cognitive complaints: women exposed to ET for more than three years reported fewer cognitive problems and less distress compared with those on therapy for a shorter period, despite similar fatigue levels. This pattern may also reflect the diminishing contribution of prior chemotherapy to cognitive complaints over time, neurotoxic and inflammatory effects tend to attenuate beyond the early survivorship years, with psychological and endocrine factors progressively assuming greater influence on perceived cognition [37]. This finding contrasts with a recent Chinese cohort study, which identified ET duration as a risk factor for cognitive impairment (odds ratio 1.30 per year), and with early reports that longer therapy exacerbates cognitive risk [25]. Several factors might explain this paradox. Importantly, neither age nor ET type (tamoxifen vs. aromatase inhibitors) influenced cognitive or emotional outcomes, and those treated with tamoxifen versus AI exhibited remarkably similar symptom profiles. Women reporting depressive symptoms, however, exhibited markedly higher cognitive and emotional burden, highlighting depression as a key modifier of survivorship experience.

Cognitive complaints and therapy type

Our observations align with the growing body of evidence that cognitive complaints are common among breast cancer survivors on ET but do not consistently differ between tamoxifen and aromatase inhibitor users [18, 38, 39]. In several prospective and cross-sectional studies, tamoxifen has been linked to decrements in verbal memory, executive function or fluency relative to controls; however, other reports found no significant differences between tamoxifen and AIs or between ET and no ET [18, 25, 40–42]. Effect sizes are generally small and confounded by concurrent chemotherapy, menopausal status and psychosocial factors. Our finding of no difference may thus reflect that cognitive complaints are driven more by symptom burden, such as fatigue, emotional distress, sleep disruption, than by the specific pharmacologic mechanism of ET. In addition, individual variability in estrogen sensitivity, cognitive reserve and psychological resilience could mask subtle pharmacologic differences.

Duration of therapy and cognitive adaptation

The inverse association between ET duration and cognitive complaints was unexpected. Most observational studies report either neutral or deleterious effects of longer therapy. Several hypotheses may account for our finding. Adaptation over time, patients may experience an initial spike in cognitive complaints after initiating ET, which attenuates as they adjust physiologically and psychologically. Longitudinal studies have noted stabilization or improvement in cognitive performance within the first year of therapy, suggesting neuroplastic or compensatory mechanisms [20, 43, 44]. Selective discontinuation may also play a role: patients with severe cognitive symptoms might stop therapy prematurely or decline participation in surveys, leaving a healthier cohort in the longer-duration group (survivor bias). Third, psychological adjustment may occur; patients may learn to accommodate mild cognitive lapses, develop coping strategies and report less interference over time [44–46]. Finally, the cross-sectional design precludes inference about causality; a longitudinal study is required to

disentangle adaptation, selection and true improvement. Nonetheless, our data suggest that cognitive complaints are not inevitably progressive and may decrease with continued therapy.

Comparison with chemotherapy-related cognitive impairment

Chemotherapy ("*chemobrain*") has long been recognized as a contributor to cognitive decline in breast cancer, particularly affecting memory and executive function [19]. However, ET-related effects appear subtler and more variable. Our findings support this: although a high proportion of women reported cognitive complaints, the mean FACT-Cog scores fell within ranges typical for community controls, and domain-specific deficits were not severe. Objective neuropsychological tests often show small to negligible effects of ET. Moreover, the strong associations with fatigue and distress suggest that perceived cognitive deficits in ET may reflect the psychological milieu rather than direct neurotoxicity [47]. The absence of differences by therapy type also contrasts with some chemotherapy regimens where agents like taxanes have pronounced neurotoxic profiles [18, 19, 25]. Thus, our results reinforce the concept that endocrine-related cognitive symptoms constitute part of a broader symptom cluster with significant psychological and behavioral components.

Mechanistic considerations

The linkage between fatigue, emotional distress and cognitive complaints likely reflects converging biological and psychological pathways. Cancer and its treatments elicit systemic inflammation and dysregulation of cytokines (e.g., IL-6, TNF-α) that can cross the blood-brain barrier and induce "*sickness behavior*", manifesting as fatigue, mood changes and cognitive sluggishness [48–50]. Neuroendocrine disruption, particularly of the hypothalamic-pituitary-adrenal axis, may alter cortisol rhythms and stress responsivity, contributing to depression, anxiety and cognitive inefficiency [50–52]. Estrogen deprivation via ET may accentuate these processes, as estrogen has neuroprotective roles in synaptic plasticity and energy metabolism [53–55]. Psychologically, fatigue and distress tax attentional resources and working memory, increasing cognitive load and the likelihood of perceived lapses. Sleep disturbances, common with ET due to hot flashes and night sweats, further exacerbate cognitive and emotional dysregulation [21, 52, 56]. These intertwined mechanisms support the observed strong correlations between fatigue and distress and their shared impact on cognition.

An alternative explanation is that ET's neurocognitive effects are largely indirect, mediated through vasomotor symptoms, sleep problems and mood disturbances rather than direct neurotoxicity [10]. Randomized trials have found minimal differences in objective cognitive performance between tamoxifen and AI, and observational studies have shown that the severity of hot flashes and depressive symptoms predicts cognitive complaints [57]. Thus, interventions targeting sleep, mood and fatigue may be more effective than switching endocrine agents for alleviating cognitive complaints.

Clinical and survivorship implications

These findings have important implications for survivorship care. Routine screening for fatigue, emotional distress and cognitive complaints should be integrated into long-term follow-up of patients on ET. Simple, validated patient-reported outcomes (e.g., FACT-Cog, PDQ-BC, Distress Thermometer) can identify those at risk and prompt timely referral for supportive care. Because fatigue and distress strongly drive perceived cognitive impairment, interventions that reduce these symptoms exercise programs, cognitive-behavioral therapy, mindfulness-based stress reduction, pharmacologic management of sleep or vasomotor symptoms, could yield meaningful cognitive benefits [27, 56, 58]. Evidence demonstrates that exercise improves fatigue and mood, enhances neuroplasticity and may indirectly mitigate cognitive complaints. Psychological therapies can reduce distress and improve self-efficacy, addressing the cognitive-emotional feedback loop. Cognitive rehabilitation and compensatory strategy training could further empower patients to manage cognitive lapses [29, 59–61].

Multidimensional survivorship care is critical. Approximately 30% of participants in our study were on medical leave since diagnosis, 22% reported reduced work performance and 20% experienced financial strain. These functional impairments underscore the need for occupational therapy and vocational rehabilitation to support return to work. Sexual distress, reported by 19% of women, necessitates attention to sexual health and intimacy counselling [62]. A coordinated, multidisciplinary approach involving oncologists, psycho-oncologists, neurologists, physiotherapists and social workers should address not only cancer control but also physical, cognitive, emotional and socioeconomic well-being. Shared decision-making regarding ET continuation should incorporate patient preferences, symptom burden and quality of life alongside recurrence risk.

Study Limitations

Our study has several limitations that warrant consideration. Cross-sectional design prevents causal inference. The observed negative association between ET duration and cognitive complaints could reflect adaptation or selection bias rather than true improvement; longitudinal assessment is needed to confirm trajectories. Self-report measures may over- or under-estimate actual cognitive impairment; subjective complaints often correlate more with mood and fatigue than with objective deficits. We did not administer neuropsychological tests or gather biomarkers (e.g., hormone levels, inflammatory markers), limiting mechanistic insight. Selection bias is possible; participants were predominantly Caucasian and well-educated, responded to an online survey and may not represent the broader breast cancer population. Patients with severe cognitive problems may have been less likely to complete an online questionnaire, potentially underestimating symptom prevalence. We lacked detailed information on pre-existing mental health conditions, menopause status or prior chemotherapy, which could influence outcomes. Finally, the modest sample size limited power to detect subtle differences by ET type or other covariates.

Directions for future research

Several avenues merit exploration. First, prospective longitudinal studies should track cognitive and emotional trajectories throughout ET to determine whether cognitive complaints improve, worsen or

stabilize over time, and to identify critical periods for intervention. Incorporating both objective neuropsychological testing and subjective measures will clarify the relationship between perceived and actual deficits. Second, integration of biomarkers-serum estrogen, inflammatory cytokines, cortisol rhythms and neuroimaging (e.g., MRI, PET) could elucidate biological mechanisms underlying the symptom cluster and identify high-risk phenotypes [63–65]. Third, larger samples would allow examination of effect modifiers such as menopausal status, prior chemotherapy, comorbidities and sociodemographic factors. Investigating whether younger women, those with depression or those still working experience different trajectories could inform tailored interventions [14]. Fourth, interventional studies are needed to evaluate whether targeted approaches, fatigue management, exercise programs, cognitive rehabilitation, psychotherapeutic interventions or pharmacologic agents, can alleviate cognitive complaints and distress and improve adherence to ET. Finally, research should develop and evaluate multidisciplinary survivorship frameworks that embed cognitive and emotional monitoring, patient education and coordinated care into routine follow-up [66–68].

Conclusions

Perceived cognitive difficulties are highly prevalent among women receiving adjuvant endocrine therapy for early luminal breast cancer, driven primarily by fatigue and emotional distress rather than therapy type. While objective cognitive decline appears limited, the persistence of self-reported impairment underscores the clinical relevance of the hormone-brain-emotion axis in survivorship. Oncology care must evolve beyond tumor surveillance to proactively address these interrelated symptoms. Early psychosocial screening and structured supportive interventions should become standard components of endocrine therapy follow-up. Strengthening collaboration between oncology and primary care is critical to ensure longitudinal, proximity-based management that promotes adherence, functional recovery, and sustained quality of life for breast cancer survivors.

Declarations

Additional Information

Aknowledgments: The authors thank all participating patients for their time and contribution to this research. We also acknowledge the clinical teams involved in patient recruitment and the Unidade Local de Saúde Lisboa Ocidental for logistical support.

Funding Statement: The authors received no specific funding for this work.

Competing interest: The authors declare that no competing interests exist.

Data Avilability Statement: All relevant data are contained within the manuscript and its Supporting Information files. De-identified datasets used in the analyses are available from the corresponding author on reasonable request.

Ethics Statement: This study was approved by the Unidade Local de Saúde Lisboa Ocidental Ethics Committee (Approval No. 2017070005). All participants provided written informed consent prior to participation. The study was conducted in accordance with the Declaration of Helsinki and all applicable national regulations.

Concent for publication: Not Aplicable

Author Contributions: Authors reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Figures

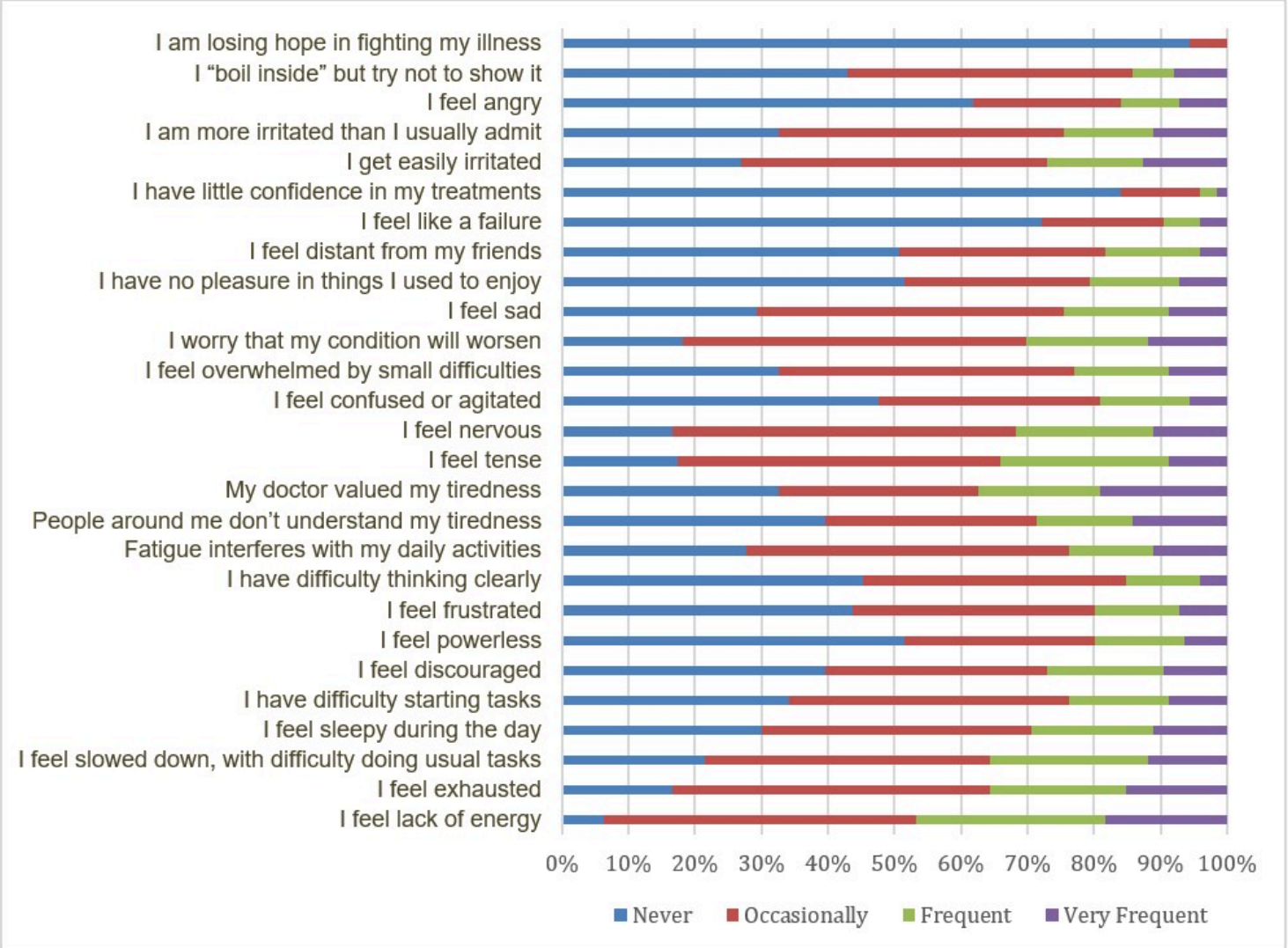


Figure 1

Frequency distribution of emotional distress symptoms

Stacked bar chart showing the distribution of responses to all items of the PDQ-BC/PDI emotional distress section (n = 126). Most patients reported at least occasional emotional symptoms, with fatigue- and energy-related complaints ("I feel lack of energy," "I feel exhausted") being most frequent, followed by frustration, irritability, and anxiety. A smaller subset endorsed feelings of sadness, discouragement, or social withdrawal. Higher frequency categories ("frequent," "very frequent") indicate greater emotional burden.

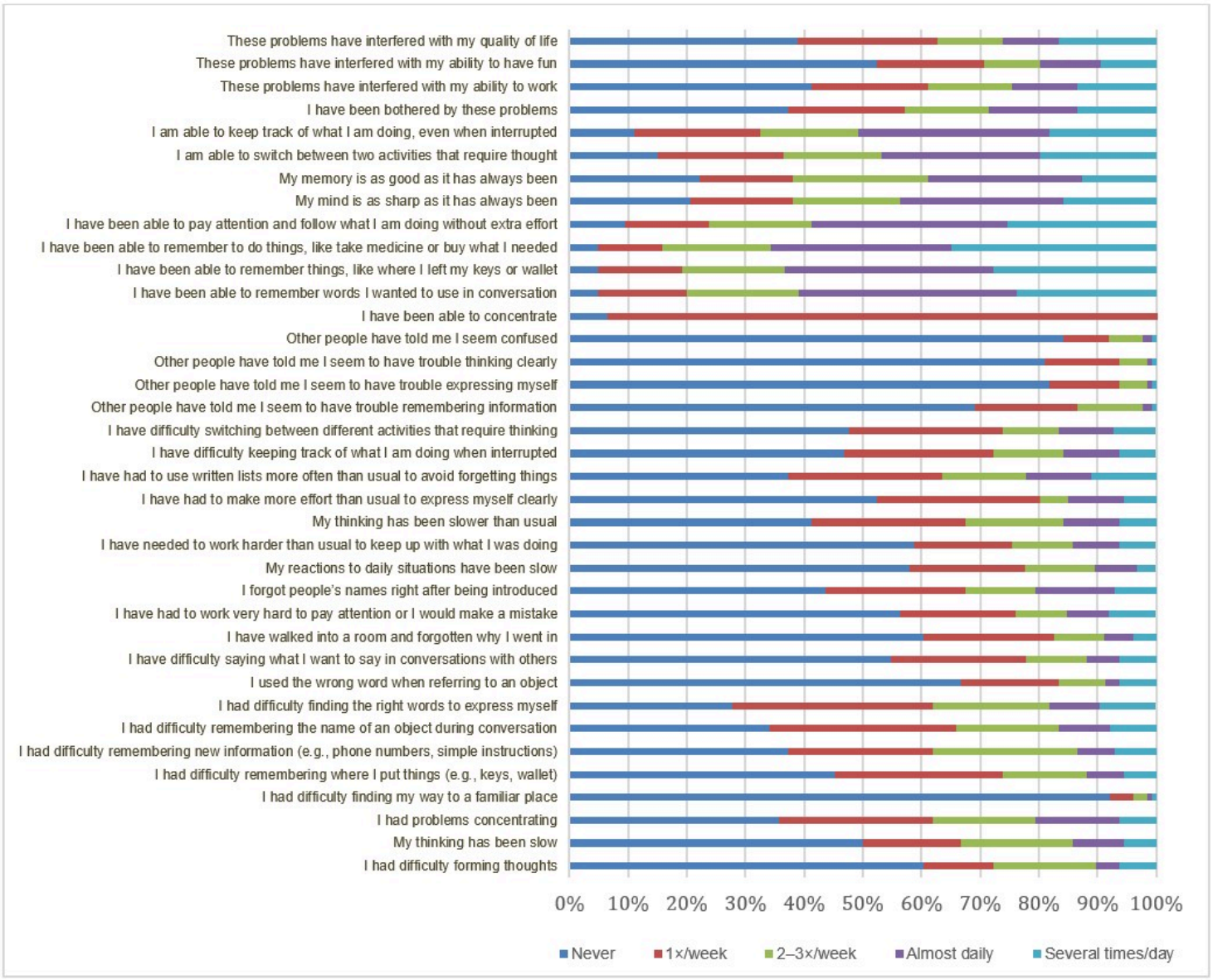


Figure 2

Frequency distribution of cognitive complaints (FACT-Cog v3).

Stacked bar chart showing the frequency of responses to all items of the FACT-Cog v3 questionnaire (n = 126). The majority of patients reported at least occasional cognitive difficulties, particularly in domains related to attention, memory, and word finding. Complaints were most frequent for "difficulty remembering new information" and "slowed thinking," whereas positive items (e.g., "My mind is as sharp as it has always been") showed lower endorsement. Higher frequency categories ("almost daily," "several times per day") indicate greater perceived cognitive impairment.

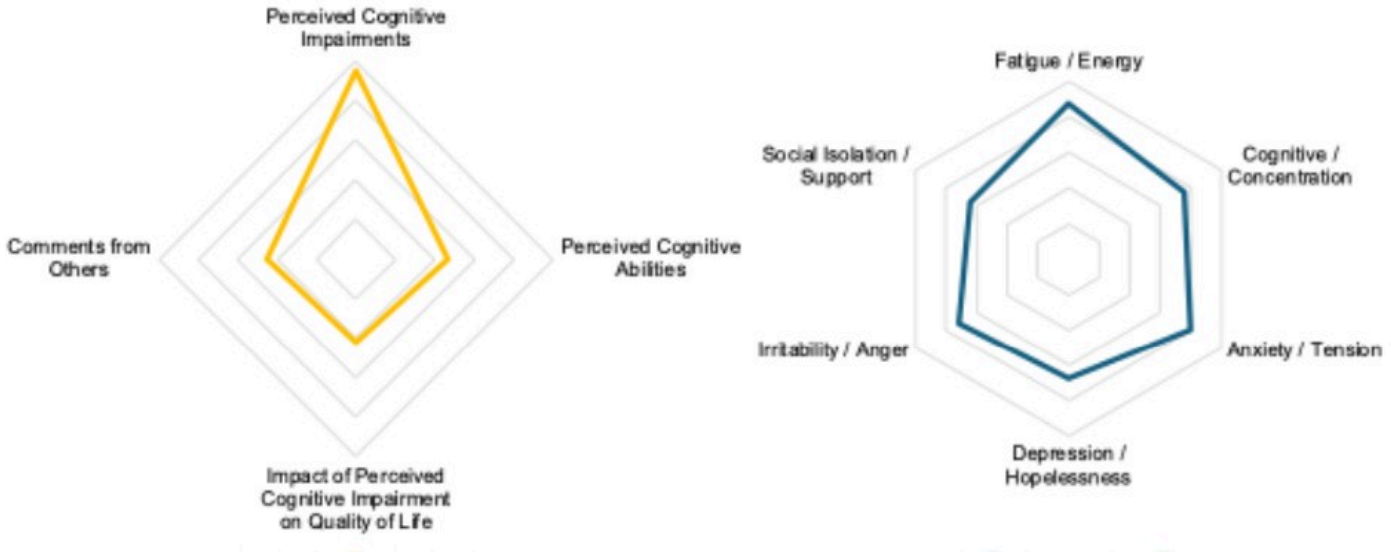
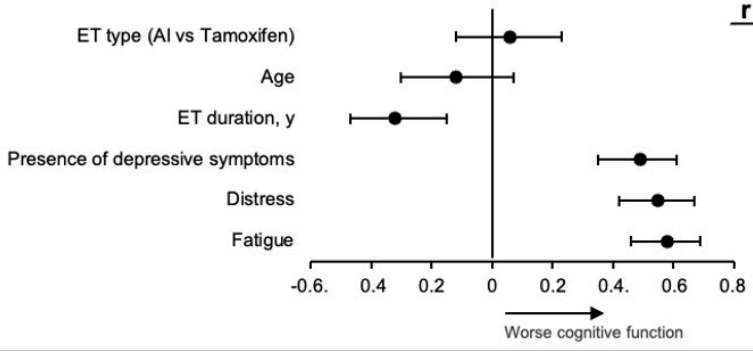


Figure 3

Profiles of Cognitive and Emotional Burden During Adjuvant Endocrine Therapy.

Radar charts illustrating mean standardized scores across cognitive (FACT-Cog v3) and emotional distress (PDQ-BC/PDI) subdomains in women receiving adjuvant endocrine therapy (n = 126). Higher values reflect greater symptom burden. Patients reported the greatest impairment in Perceived Cognitive Impairments *and* Fatigue/Energy, *followed by* Cognitive/Concentration *and* Anxiety/Tension *domains.* Impact on Quality of Life *and* Depression/Hopelessness *remained clinically relevant but less pronounced. Together, these profiles depict fatigue- and cognition-centered distress as the predominant features of the hormone–brain–emotion axis in endocrine therapy users.*



	r (Pearson)	Lower 95% CI	Upper 95% CI	p-value
ET type (AI vs Tamoxifen)	0.06	-0.12	0.23	0.41
Age	-0.12	-0.3	0.07	0.27
ET duration, y	-0.32	-0.47	-0.15	0.008
Presence of depressive symptoms	0.49	0.35	0.61	< 0.001
Distress	0.55	0.42	0.67	< 0.001
Fatigue	0.58	0.46	0.69	< 0.001

Figure 4

Forest plot of correlations between cognitive function and clinical or psychosocial variables.

Forest plot displaying Pearson correlation coefficients (r) with 95% confidence intervals for associations between global cognitive function (FACT-Cog total) and selected clinical and psychosocial variables. Higher fatigue, distress, and depressive symptoms were moderately associated with worse perceived cognitive function, whereas longer endocrine therapy (ET) duration correlated with fewer cognitive complaints. Age and ET type showed no significant association.

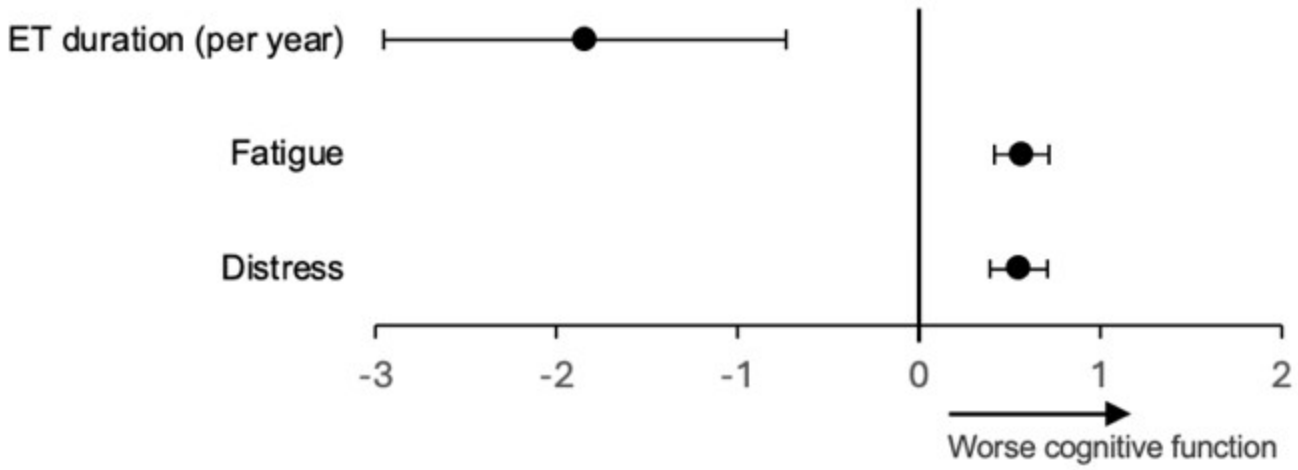


Figure 5

Forest plots of independent predictors of cognitive and emotional outcomes in multivariable analysis.

Forest plot showing Pearson correlation coefficients (r) with 95% confidence intervals for associations between global cognitive function (FACT-Cog total score) and key clinical and psychosocial variables. Positive values indicate worse perceived cognitive function (higher impairment). Fatigue, distress, and depressive symptoms were moderately correlated with poorer cognitive outcomes, whereas longer endocrine therapy duration correlated with fewer complaints ($r = -0.34$, $p < 0.01$).