Title
Characteristics Associated with Inter-Individual Differences in the Trajectories of Self-Reported Attentional Function in Oncology Outpatients Receiving Chemotherapy

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Characteristics Associated with Inter-Individual Differences in the Trajectories of Self-Reported Attentional Function in Oncology Outpatients Receiving Chemotherapy

by

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ABSTRACT

Purpose/Objectives: Between 14% and 85% of patients report noticeable changes in cognitive function during chemotherapy (CTX). These cognitive changes include alterations in memory, psychomotor speed, and executive functioning. Executive function encompasses a person's ability to direct attention towards planning, decision-making, and abstract thinking. The purposes of this study were to determine which demographic, clinical, and symptom characteristics were associated with inter-individual variability in initial levels of attentional function as well as with changes in the trajectories of attentional function in a sample of oncology patients who underwent two cycles of CTX.

Methods/Settings: Oncology outpatients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. The Attentional Function Index (AFI) was used to assess perceived effectiveness in completing daily tasks that required working memory and attention. Hierarchical linear modeling (HLM) was used to evaluate inter-individual variability in initial levels and the trajectories of attentional function.

Sample: Patients were receiving CTX for breast, gastrointestinal, gynecological, or lung cancer (n = 1,329).

Findings: The demographic, clinical, and symptom characteristics that were associated with inter-individual differences of attentional function at enrollment (i.e., intercept) were: employment status, functional status, trait anxiety, depressive symptoms, sleep disturbance, evening fatigue, and morning energy. Gender was the only characteristic associated with inter-individual differences in the trajectories of attentional function. Morning fatigue was the only

characteristic associated with both initial levels as well as the trajectories of attentional function. **Conclusions:** On average, prior to the next dose of CTX, patients reported moderate levels of attentional function that persisted over two cycles of CTX. Many of the clinical and symptom characteristics are amenable to interventions. Clinicians need to assess patients for changes in attentional function and associated characteristics and recommend evidence-based interventions.

Key Words: attentional function; chemotherapy; cognitive function; hierarchical linear modeling; executive function

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INTRODUCTION

Between 14% and 85% of patients report noticeable changes in cognitive function during chemotherapy (CTX).[32] These cognitive changes include alterations in memory, psychomotor speed, and executive functioning.[27] Executive function encompasses a person's ability to direct attention towards planning, decision-making, and abstract thinking.[27] While memory and psychomotor speed are important mental processes, changes in executive function during CTX are particularly important to evaluate because lower levels of executive function are associated with increases in anxiety, depression, and fatigue.[4, 51]

One self-report measure that has been used to evaluate changes in executive function in oncology patients is the Attentional Function Index (AFI). The AFI was developed by Cimprich and colleagues to evaluate changes in executive function in women undergoing breast cancer surgery.[13] More recently, changes in attentional function were evaluated in patients with breast and prostate cancer undergoing radiation therapy;[49, 50] in patients who were followed for 6 months after breast cancer surgery;[47] and in cancer survivors.[30, 60] However, no studies were found that evaluated for changes in self-reported attentional function in patients receiving multiple cycles of CTX.

Of note, no recommendations are available on the optimal method to use to evaluate changes in executive function in patients undergoing CTX.[27] However, both patients and clinicians need information about how CTX may impact patients' cognitive abilities. Therefore, the AFI which is relatively short and easy to complete, may provide important information on how executive function changes over time in oncology patients receiving CTX. In addition, given the paucity of longitudinal studies on self-reported changes in attentional function during CTX, additional research is warranted at this time. Therefore, the purposes of this study were to determine which demographic, clinical, and symptom characteristics were associated with inter-individual variability in initial levels of, as well as with changes in the trajectories of attentional function in a sample of oncology patients who underwent two cycles of CTX.

METHODS

Patients and Settings

This study is part of a larger, longitudinal study of the symptom experience of oncology outpatients receiving CTX.[37, 52, 63, 74, 75] Eligible patients were ≥18 years of age; had a diagnosis of breast, gastrointestinal (GI), gynecologic (GYN), or lung cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs.

Instruments

A demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income.

Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well established validity and reliability.[34] Patients rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms).[33, 34]

Self-Administered Comorbidity Questionnaire (SCQ) consists of 13 common medical conditions simplified into language that can be understood without prior medical knowledge.[67] Patients indicated if they had the condition; if they received treatment for it (proxy for disease severity) and if it limited their activities (indication of functional limitations). For each condition, the patient can receive a maximum of 3 points. The total SCQ score ranges from 0 to 39. The SCQ has well established validity and reliability.[9, 12]

Alcohol Use Disorders Identification Test (AUDIT) is a 10-item questionnaire that assesses alcohol consumption, alcohol dependence, and the consequences of alcohol abuse in the last 12 months. The AUDIT gives a total score that ranges between 0 and 40. Scores of ≥8 are defined as hazardous use and scores of ≥16 are defined as use of alcohol that is likely to be

harmful to health.[2, 3] The AUDIT has well established validity and reliability.[5, 6, 66] In this study, its Cronbach's alpha was 0.63.

Attentional Function Index (AFI) consists of 16 items designed to measure attentional function.[17] A higher total mean score on a 0 to 10 numeric rating scale (NRS) indicates greater capacity to direct attention.[17] Total scores are grouped into categories of attentional function (i.e., <5.0 low function, 5.0 to 7.5 moderate function, >7.5 high function).[16] The AFI has well established reliability and validity.[17] In this study, the Cronbach's alpha for the AFI total score was 0.93.

Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) each have 20 items that are rated from 1 to 4. The summed scores for each scale can range from 20 to 80. The STAI-T measures a person's predisposition to anxiety as part of one's personality. The STAI-S measures a person's temporary anxiety response to a specific situation or how anxious or tense a person is "right now" in a specific situation. Cutoff scores of $\geq$31.8 and $\geq$32.2 indicate high levels of trait and state anxiety, respectively. The STAI-S and STAI-T inventories have well established validity and reliability.[7, 35, 69] In the current study, the Cronbach's alphas for the STAI-T and STAI-S were 0.92 and 0.96, respectively.

Center for Epidemiological Studies-Depression scale (CES-D) consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. A total score can range from 0 to 60, with scores of $\geq$16 indicating the need for individuals to seek clinical evaluation for major depression. The CES-D has well established validity and reliability.[10, 64, 68] In the current study, the Cronbach's alpha for the CES-D total score was 0.89.

Lee Fatigue Scale (LFS) consists of 18 items designed to assess physical fatigue and energy.[41] Each item was rated on a 0 to 10 NRS. Total fatigue and energy scores are calculated as the mean of the 13 fatigue items and the 5 energy items, respectively. Higher scores indicate greater fatigue severity and higher levels of energy. Using separate LFS questionnaries, patients were asked to rate each item based on how they felt within 30 minutes

of awakening (i.e., morning fatigue, morning energy) and prior to going to bed (i.e., evening fatigue, evening energy). The LFS has established cut-off scores for clinically meaningful levels of fatigue (i.e., ≥3.2 for morning fatigue, ≥5.6 for evening fatigue) [24] and energy (i.e., ≥6.2 for morning energy, ≥3.5 for evening energy).[24] It was chosen for this study because it is relatively short, easy to administer, and has well established validity and reliability.[25, 41, 42, 53, 54, 56] In the current study, the Cronbach's alphas were 0.96 for morning and 0.93 for evening fatigue and 0.95 for morning and 0.93 for evening energy.

General Sleep Disturbance Scale (GSDS) consists of 21-items designed to assess the quality of sleep in the past week. Each item was rated on a 0 (never) to 7 (everyday) NRS. The GSDS total score is the sum of the seven subscale scores that can range from 0 (no disturbance) to 147 (extreme sleep disturbance). Each mean subscale score can range from 0 to 7. Higher total and subscale scores indicate higher levels of sleep disturbance. Subscales scores of $\geq$3 and a GSDS total score of $\geq$43 indicate a significant level of sleep disturbance.[24] The GSDS has well established validity and reliability.[39, 40, 54] In the current study, the Cronbach's alpha for the GSDS total score was 0.83.

Occurrence of pain was evaluated using the Brief Pain Inventory.[18] Patients who responded yes to the question about having pain were asked to indicate if their pain was or was not related to their cancer treatment. Patients were categorized into one of four groups (i.e., no pain, only noncancer pain, only cancer pain, both cancer and noncancer pain).

Study Procedures

The study was approved by the Institutional Review Board at each of the study sites. Eligible patients were approached in the infusion unit by a member of the research team to discuss participation in the study. Written informed consent was obtained from all patients. Depending on the length of their CTX cycles (i.e., 14-day, 21-day, or 28-day), patients completed study questionnaires in their homes, a total of six times over two cycles of CTX (prior to CTX administration (i.e., recovery from previous CTX cycle at assessments 1 and 4),

approximately 1 week after CTX administration (i.e., acute symptoms at assessments 2 and 5) and approximately 2 weeks after CTX administration (i.e., potential nadir at assessments 3 and 6).

Data Analyses

Descriptive statistics and frequency distributions were generated on the sample characteristics and symptom severity scores at enrollment using the Statistical Package for the Social Sciences (SPSS) version 22.[29]

HLM based on full maximum likelihood estimation was performed in two stages using software developed by Raudenbush and Bryk.[65] The HLM methods are described in detail elsewhere.[1, 19, 38, 55, 56] In brief, during stage 1, intra-individual variability in attentional function over time was examined. A piecewise model strategy was employed to evaluate the pattern of change in AFI scores over time because the six assessments encompassed two cycles of CTX. The six assessments were coded into two pieces. Assessments 1, 2, and 3 comprised the first piece (PW1) that was used to model changes over time during the first CTX cycle. Assessments 4, 5, and 6 comprised the second piece (PW2) that was used to model changes over time during the second CTX cycle. A piecewise model can be more sensitive to the timing and sequencing of changes in a dependent variable than conventional HLM models that would have assessed linear, quadratic, or cubic changes over the six assessments and would not have paid attention to the two different CTX cycles.[61]

The second stage of the HLM analysis examined inter-individual differences in the piecewise trajectories of attentional function by modeling the individual change parameters (i.e., intercept and slope parameters) as a function of proposed predictors at level 2. Supplementary Table 1 lists the potential predictors that were developed based on a review of the literature on attentional function in oncology patients undergoing CTX.

To improve estimation efficiency and construct a parsimonious model, exploratory level 2 analyses were completed in which each potential predictor was assessed to determine

whether it would result in a better fitting model if it alone were added as a level 2 predictor. Predictors with a *t* value of <2.0 were excluded from subsequent model testing. All potential significant predictors from the exploratory analyses were entered into the model to predict each individual change parameter. Only predictors that maintained a statistically significant contribution in conjunction with other predictors were retained in the final model. A *p*-value of <.05 indicated statistical significance.

Table 1. Demographic, clinical, and symptom characteristics of patients (n=1329)

Demographic Characteristics	
Age (years; mean (SD))	57.13 (12.39)
Gender (% female (n))	78.0 (1036)
Ethnicity (% (n))	
White	69.5 (923)
Black	9.9 (132)
Asian/Pacific Islander	9.6 (128)
Hispanic/Mixed/Other	11.0 (146)
Education (years; mean (SD))	16.20 (2.97)
Married or partnered (% yes (n))	65.0 (864)
Lives alone (% yes (n))	21.2 (282)
Currently employed (% yes (n))	34.8 (462)
Child care responsibilities (% yes (n))	21.7 (289)
Income (% yes (n))	
Less than $30,000	18.3 (217)
$30,000 to <$70,000	21.2 (252)
$70,000 to < $100,000	17.0 (202)
More than $100,000	43.6 (518)
Clinical Characteristics	
Number of comorbidities (mean (SD))	2.40 (1.43)
Self-administered Comorbidity Questionnaire score (mean (SD))	5.47 (3.20)
Body mass index (kg/m^2; mean (SD))	26.16 (5.62)
Hemoglobin (gm/dL; mean (SD))	11.54 (1.43)
Karnofsky Performance Status score (mean (SD))	79.98 (12.38)
Have you ever considered yourself a smoker (% yes (n)	34.8 (462)
Exercise on a regular basis (% yes (n))	71.6 (951)
Specific comorbidities reported (% yes (n))	
High blood pressure	30.0 (399)
Back pain	25.7 (342)
Depression	19.3 (256)
Osteoarthritis	12.0 (160)
Anemia or blood disease	12.3 (164)
Lung disease	11.3 (150)
Diabetes	9.0 (119)
Liver disease	6.4 (85)
Heart disease	5.6 (75)
Rheumatoid arthritis	3.1 (41)
Ulcer or stomach disease	4.9 (65)
Kidney disease	1.4 (19)
Cancer diagnosis (% yes (n))	
Breast	40.4 (537)
Gastrointestinal	30.4 (404)
Gynecological	17.5 (232)
Lung	11.7 (156)
Time since cancer diagnosis (years; mean (SD))	1.97 (3.87)
Time since cancer diagnosis (years; median)	0.42
Any prior cancer treatments (% yes (n))	75.7 (1006)
Number prior cancer treatments (mean (SD))	1.59 (1.50)
Chemotherapy cycle length (% (n))	
14 days	41.7 (438)
21 days	51.0 (678)
28 days	7.3 (97)
Presence of metastatic disease (% yes (n))	67.0 (891)

Demographic Characteristics	
Number of metastatic sites including lymph node involvement (mean (SD))	1.24 (1.23)
Number of metastatic sites excluding lymph node involvement (mean (SD))	0.78 (1.05)
Symptom Characteristics at Enrollment	
Attentional Function Index score (mean (SD))	6.38 (1.82)
Lee Fatigue Scale: evening fatigue score (mean (SD))	5.33 (2.15)
Lee Fatigue Scale: morning fatigue score (mean (SD))	3.13 (2.25)
Lee Fatigue Scale: evening energy score (mean (SD))	3.54 (2.04)
Lee Fatigue Scale: morning energy score (mean (SD))	4.40 (2.25)
Center for Epidemiological Studies-Depression Scale score (mean (SD))	13.0 (9.77)
General Sleep Disturbance Scale score (mean (SD))	52.6 (20.21)
Trait Anxiety score (mean (SD))	35.15 (10.40)
State Anxiety score (mean (SD))	33.97 (12.34)
Pain present (% yes (n))	72.8 (968)

Abbreviations: gm/dL = grams per deciliter; kg/m^2 = kilograms per meters squared; SD = standard deviation; RT = radiation therapy.

RESULTS

Sample Characteristics

The demographic, clinical, and symptom characteristics of the sample (n=1,329) are presented in Table 1. The sample was predominately female (78%) with a mean age of 57 years, was well educated (16 years), currently not employed (65%), partnered (65%), and did not have child care responsibilities (78%). On average, the patients were two years from their cancer diagnosis (median = 0.42 years), primarily being treated with 21-day CTX cycles (51%), and had one metastatic site. At enrollment, the mean scores on the GSDS, the STAI-T, and STAI-S were above the cut-off scores for clinically meaningful levels of sleep disturbance, trait anxiety, and state anxiety, respectively. In addition, morning energy scores were below the clinically meaningful cutoff score. The mean AFI score at enrollment (6.38 $\pm$ 1.82) was in a range that indicated a moderate level of function.

Changes in Attentional Function Over Time

The first HLM analysis examined how AFI scores changed within the two cycles of CTX. The estimates for the initial piecewise model are presented in Table 2. Since the model was unconditional (i.e., no covariates), the intercept represents the average AFI score at enrollment (i.e., 6.385 on a scale of 0 to 10). The estimated linear piecewise rates of change were -0.605 and -0.425 (both $p<.0001$) for piecewise linear 1 and piecewise linear 2, respectively. The estimated quadratic piecewise rates of change were 0.385 and 0.137 (both $p<.0001$) for piecewise quadratic 1 and piecewise quadratic 2, respectively. The combination of each coefficient determines the curves for the two piecewise components' changes in attentional function scores over time.

Figure 1A displays the mean AFI scores over the two cycles of CTX. From assessment 1 to 2, AFI scores declined over time and recovered by assessment 3. Over the second CTX cycle, while a similar pattern was observed, the decline in scores was less steep. The results indicate a sample-wide change in AFI scores over time. However, they do not indicate that all of

the patients' AFI scores changed at the same rate over time. The variance components (Table 2) suggest that considerable inter-individual variability existed in the trajectories of attentional function. A spaghetti plot of a random sample of 50 patients demonstrates the inter-individual variability in AFI scores (Figure 1B). These results supported additional analyses of predictors of inter-individual differences in initial levels as well as in the trajectories of attentional function.

Table 2. Hierarchical Linear Model for Attentional Function

Attentional Function	Coefficient (SE)	
	Unconditional Model	Final Model
Fixed effects		
Intercept	6.385 (.050)$^{+}$	6.38 (.039)$^{+}$
Piecewise 1 – linear rate of change	-0.605 (.067)$^{+}$	-0.602 (.067)$^{+}$
Piecewise 1 – quadratic rate of change	0.385 (.032)$^{+}$	0.384 (.032)$^{+}$
Piecewise 2 – linear rate of change	-0.425 (.044)$^{+}$	-0.423 (.044)$^{+}$
Piecewise 2 – quadratic rate of change	0.137 (.014)$^{+}$	0.136 (.014)$^{+}$
Time invariant covariates		
Intercept		
Working		0.201 (.067)*
Karnofsky Performance Status		0.014 (.003)$^{+}$
Trait anxiety		-0.037 (.005)$^{+}$
Depressive symptoms		-0.023 (.006)$^{+}$
Sleep disturbance		-0.008 (.002)$^{+}$
Morning fatigue		-0.181 (.023)$^{+}$
Evening fatigue		-0.099 (.017)$^{+}$
Morning energy		0.093 (.015)$^{+}$
Piecewise 1 – linear rate of change		
Female		-0.388 (.151)*
Morning fatigue		0.124 (.030)$^{+}$
Piecewise 1 – quadratic rate of change		
Female		0.209 (.076)*
Morning fatigue		-0.044 (.014)*
Piecewise 2 – linear rate of change		
Female		-0.263 (.106)*
Piecewise 2 – quadratic rate of change		
Female		0.073 (.034)*
Variance components		
In intercept	1.582^{+}	1.049^{+}
Goodness-of-fit deviance (parameters estimated)	22222.406 (7)$^{+}$	21197.420 (21)
Model comparison χ^2 (df)		1024.986 (14)**

*p<.05, **p<.001, +p<.0001

Abbreviations: df = degrees of freedom; SE = standard error

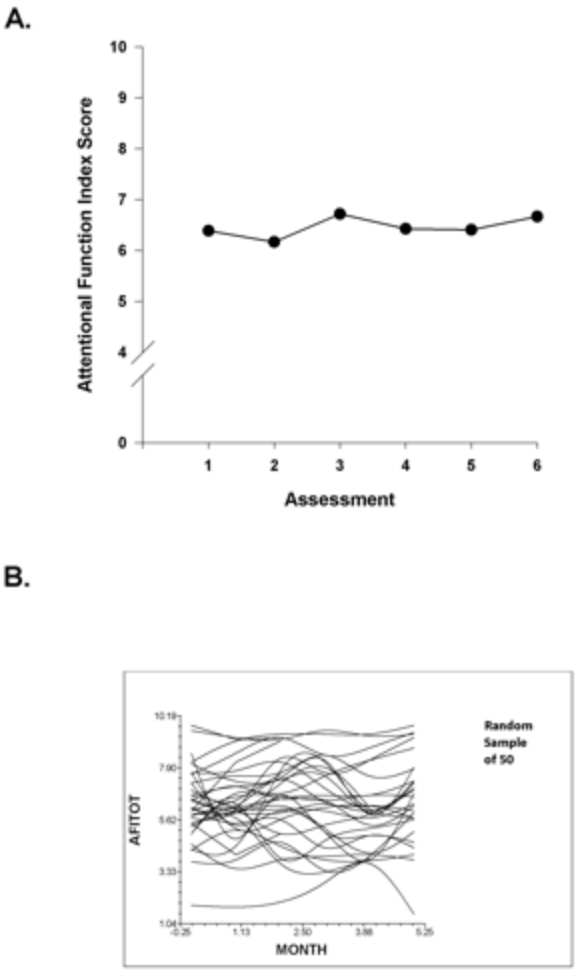

Figure 1. Piecewise model of mean Attentional Function Index scores for six assessment points over two cycles of chemotherapy (CTX; A). Spaghetti plots of individual attentional function trajectories for a random sample of 50 patients over two cycles of CTX (B). Abbreviation: AFITOT = Attentional Function Index score.

Predictors of Initial Levels of Attentional Function

As shown in the final model (Table 2), the demographic, clinical, and symptom characteristics that predicted inter-individual differences in initial levels of attentional function (i.e. intercept) were: employment status and KPS score, as well as enrollment levels of trait anxiety, depressive symptoms, sleep disturbance, evening fatigue, and morning energy. To illustrate the effects of the demographic and clinical characteristics, Figures 2A-B display the adjusted change curves for AFI scores that were estimated based on differences in employment status (i.e., employed or not employed) and functional status (i.e., lower/higher calculated as one SD above and below the mean KPS score). To illustrate the effects of the symptom characteristics, Figures 3A-E display the adjusted change curves for AFI scores that were estimated based on differences in trait anxiety (i.e., lower/higher calculated as one SD above and below the mean STAI-T score), depressive symptoms (i.e., lower/higher calculated as one SD above and below the mean CES-D score), sleep disturbance (i.e., lower/higher calculated as one SD above and below the mean GSDS score), evening fatigue (i.e., lower/higher calculated as one SD above and below the mean LFS evening fatigue score), and morning energy (i.e., lower/higher calculated as one SD above and below the mean LFS morning energy score).

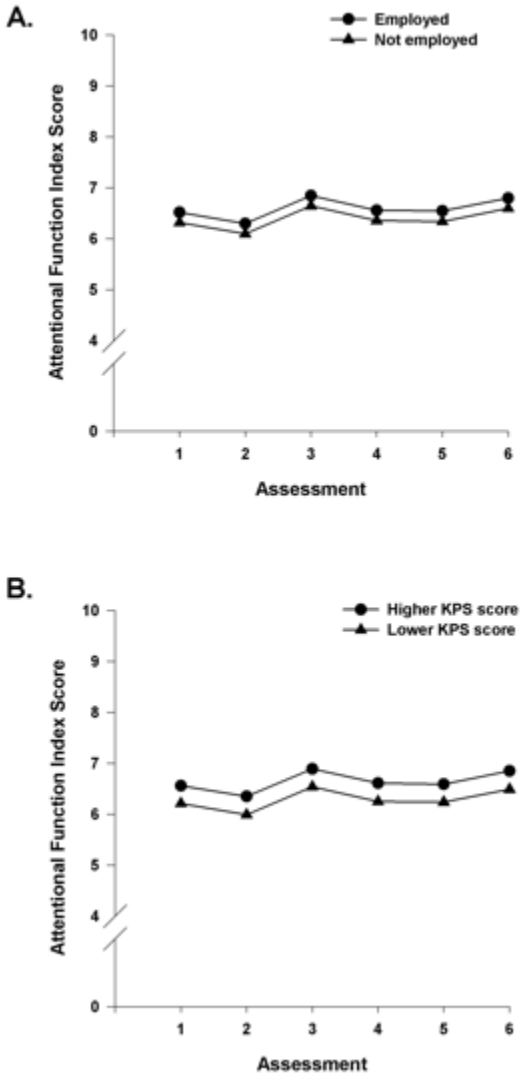

Figure 2. Influence of employment status (A) and Karnofsky Performance Status (KPS) score at enrollment (B) on inter-individual differences in the intercept for attentional function.

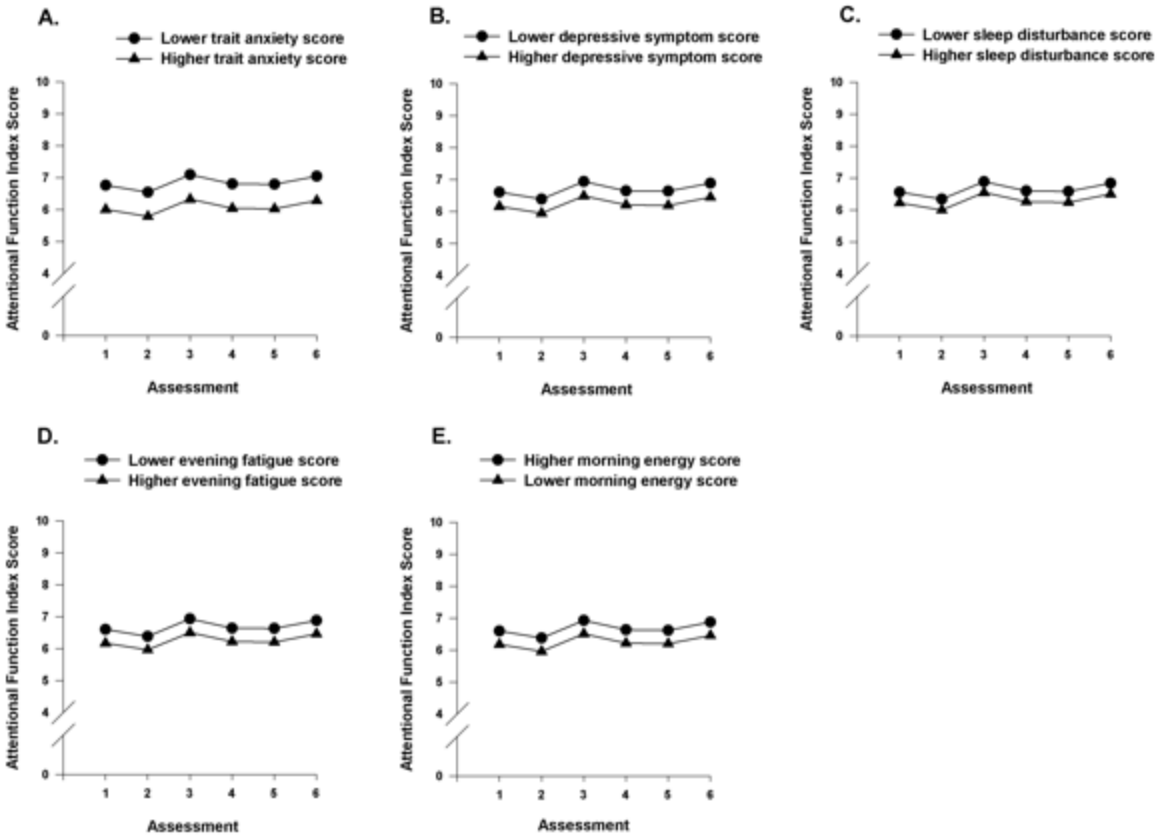

Figure 3. Influence of enrollment scores for trait anxiety (A), depressive symptoms (B), sleep disturbance (C), evening fatigue (D), and morning energy (E) on inter-individual differences in the intercept for attentional function.

Predictor of the Trajectories of Attentional Function

The only characteristic that predicted inter-individual differences in the trajectories of attentional function was gender. Figure 4A displays the adjusted change curves for AFI score for the male and female patients.

Predictor of Both Initial Levels of and the Trajectories of Attentional Function

The only characteristic that predicted inter-individual differences in initial levels and in the trajectories of attentional function was morning fatigue. Figure 4B displays the adjusted change curves for AFI scores that were estimated based on differences in morning fatigue (i.e. lower/higher calculated as one SD above and below the mean LFS morning fatigue score).

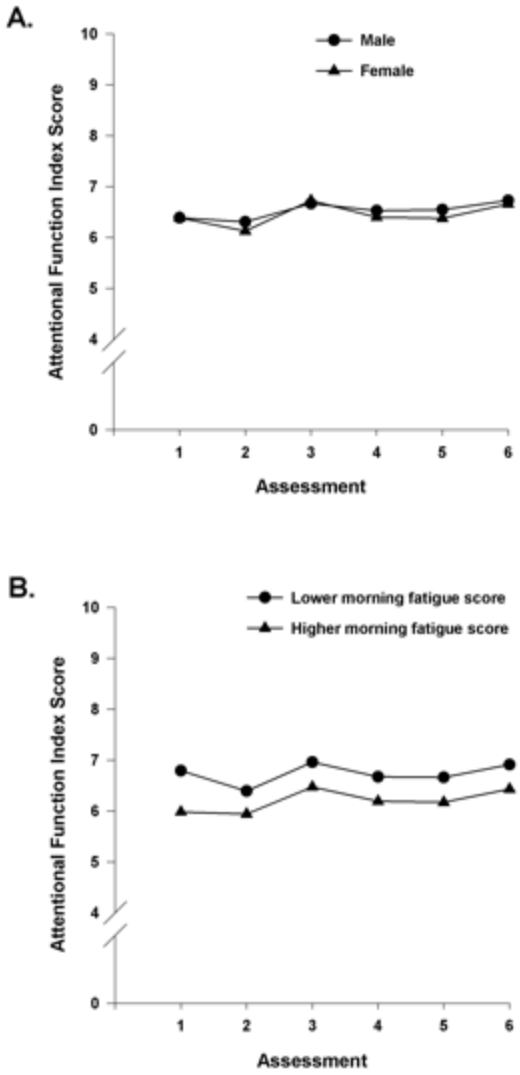

Figure 4. Influence of gender (A) on inter-individual differences in the slope parameters for attentional function and influence of enrollment scores for morning fatigue on inter-individual differences in the intercept and slope parameters for attentional fatigue (B).

DISCUSSION

To the best of our knowledge, this study is the first to examine changes in self-reported attentional function over the course of two cycles of CTX and the first to use HLM to determine demographic, symptom, and clinical characteristics associated with inter-individual differences in initial levels and in the trajectories of attentional function during CTX. Of note, the initial AFI scores in the current study were in the moderate range (i.e., 6.385). This score is somewhat lower than the AFI score reported by women prior to the initiation of radiation therapy for breast cancer (i.e., 6.56)[49] and similar to the score reported by women prior to breast cancer surgery (i.e., 6.32).[47]. While the HLM analyses determined that a piecewise model fit the data best, the changes in AFI scores over the two cycles of CTX were relatively stable over time. Taken together, these findings suggest that regardless of treatment, oncology patients experience decrements in various aspects of executive function. Additional research is warranted to determine how long these decrements persist following the completion of CTX.

As part of the HLM analysis, a number of non-modifiable and modifiable characteristics were identified that were associated with decrements in initial levels and/or the trajectories of attentional function during CTX. The remainder of the discussion focuses on these non-modifiable and modifiable characteristics.

Non-modifiable Characteristics

Two non-modifiable characteristics (i.e., gender, employment status) were associated with decrements in attentional function. While no gender differences in initial levels of attentional function were found in the current study, females had slightly worse attentional function scores over the two cycles of CTX (Figure 4A). While the majority of the studies that used the AFI evaluated patients with breast cancer,[11, 15, 59, 60] findings regarding gender differences in attentional function during and following cancer treatment are inconclusive.(3-4) For example, in one study, [48] no gender differences in AFI scores were reported. In contrast, in another study, compared to men with prostate cancer,[49] women with breast cancer reported lower AFI

scores. Additional research is warranted on gender differences in self-reported attentional function because several lines of evidence suggest that the impact of gender on cognitive function is complex. For example, in the general population, gender differences in cognitive function are noted in a number of domains.[28, 45, 57] In addition, sex steroid hormones are known to modulate cognitive function.[22]

Employment status was the second non-modifiable characteristic identified. Consistent with a previous report of women undergoing radiation therapy for breast cancer,[50] patients who were employed at the time of enrollment into the current study reported higher levels of attentional function (Figure 2A). However, in other studies,[14, 48] no association was found between employment status and AFI scores. As noted by Williams and colleagues, [72] being employed may condition the mechanisms involved in directing attention to function more efficiently. Therefore, when patients are not working, they do not experience this routine conditioning. This deficit may contribute to the perception of decreases in attentional function.

Modifiable Characteristics

A number of modifiable characteristics were associated with lower AFI scores (i.e., poorer functional status, higher trait anxiety, higher depression, higher sleep disturbance, higher evening fatigue, higher morning fatigue, lower morning energy). First, poorer functional status at enrollment was associated with lower levels of attentional function at enrollment (Figure 2B). This association is not surprising given that a growing body of evidence in the gerontology literature suggests that cognition and mobility are intertwined (for reviews see [23, 58]). For example, attention is a necessary cognitive resource for maintaining one's ability to walk. In addition, attentional deficits are independently associated with postural instability, impairments in the performance of activities of daily living, and future falls.[73] These findings suggest that oncology patients undergoing CTX may need referrals to physical therapy for exercise interventions to improve both cognition and physical function.

While the current study is the first to evaluate the impact of a number of common symptoms on initial levels as well as changes in attentional function at multiple points over two cycles of CTX, our findings are consistent with a number of cross-sectional studies that reported associations between these symptoms and cognitive function. For example, higher levels of trait anxiety and depression were associated with lower levels of attentional function in women newly diagnosed with breast cancer.[14, 16, 43] In addition, in a study of patients with breast and prostate cancer,[49] higher levels of sleep disturbance were associated with lower levels of attentional function.

Morning fatigue was the only modifiable symptom characteristic that was associated with both initial levels of as well as the trajectories of attentional function over the two cycles of CTX (Figure 4B). Our findings are consistent with data from several studies,[8, 21, 71] and a systematic review,[26] that found that increases in physical fatigue in oncology patients were associated with decrements in cognitive function. This association may be explained by the fact that recent evidence suggests that cancer and its treatments trigger inflammatory processes that contribute to increased levels of physical fatigue and cognitive dysfunction in oncology patients.[8]

In terms of these modifiable symptom characteristics, it should be noted that at the time of enrollment into the current study, patients had levels of trait anxiety and sleep disturbance that were above the clinically meaningful cutoff scores. In addition, levels of depression, morning and evening fatigue, and decrements in morning and evening energy were in the moderate range. Therefore, for patients whose symptom scores were one standard deviation about the mean score for the entire sample, their symptoms were at clinically meaningful levels. Our findings suggest that oncology patients undergoing CTX warrant a comprehensive symptom assessment and management plan. The exact relationships among these symptoms and decrements in cognitive function are undoubtedly complex and warrant investigation in future studies.

Limitations

Several limitations warrant consideration. First, our evaluation of cognitive function was limited to a self-report measure that primarily evaluated changes in executive function.[17] Therefore, our findings regarding changes in attentional function over time, as well as the characteristics associated with decrements in attentional function warrant confirmation using objective measures of various components of cognitive function.

Another limitation was the inability to test interaction effects between and among each individual demographic, clinical, or symptom characteristic. Although our findings suggest that a number of non-modifiable and modifiable characteristics are associated with decrements in attentional function, future studies need to consider the impact of multiple co-occurring symptoms or symptoms clusters on attentional function.[20, 21, 36]

Some of the studies on cognitive changes during cancer treatment compare patients undergoing cancer treatment with healthy controls.[17, 31, 44, 62]. In some of these studies,[17] levels of cognitive function in patients beginning cancer treatment are lower than those of the healthy controls. In the current study, AFI scores at enrollment were in the moderate range and the majority of the patients had received previous treatment for their cancer. Future studies should evaluate patients prior to the initiation of CTX and compare findings to healthy controls.

Clinical Implications and Directions for Future Research

Findings from this study suggest that all of the modifiable characteristics associated with decrements in attentional function are amenable to clinical interventions. Clinicians need to assess patients for decrements in attentional function and associated risk factors and prescribe evidenced-based interventions to improve cognitive function and/or reduce co-occurring symptoms. A number of studies are demonstrating that increased physical activity has beneficial effects on both physical and cognitive function.[23, 58] In addition, increased physical activity may reduce sleep disturbance and fatigue and improve mood in these patients.[46, 70]

Additional research is warranted on changes in cognitive function from prior to through and following the completion of CTX. Findings from longitudinal studies with both subjective and objective measures of cognitive function and associated demographic, clinical, and symptom characteristics will provide important information to educate patients about changes in cognitive function during and following treatment. Studies are needed that evaluate the efficacy of multimodal interventions to reduce symptom burden and enhance cognitive function.

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APPENDIX

Supplementary Table 1. Potential Predictors of Intercept, and Piecewise 1 and Piecewise 2 Linear and Quadratic Components for Attentional Function

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
Demographic Characteristics					
Age	◆			◆	◆
Sex	◆		◆	◆	◆
Ethnicity (White versus Non-White)					
Education	◆	◆			
Marital status	◆				
Live alones	◆				
Employment status	◆				
Child care responsibilities					
Clinical Characteristics					
Body mass index (kg/m^2)					
Past or current history of smoking	◆				
Hemoglobin (gm/dL)	◆				
Karnofsky Performance Status Scale score	◆			◆	◆
Self-administered Comorbidity Questionnaire score	◆				
Exercise on a regular basis	◆				
Time since cancer diagnosis					
Any prior cancer treatments					
Number prior cancer treatments	◆		◆	◆	◆
Type of prior cancer treatments					
Presence of metastatic disease				◆	◆
Number of metastatic sites including lymph node involvement				◆	◆
Number of metastatic sites excluding lymph node involvement		◆	◆	◆	◆
Symptom Characteristics					
Attentional Function Index score at enrollment		◆	◆		
Lee Fatigue Scale: Evening fatigue score at enrollment	◆			◆	◆

APPENDIX (CONTINUED)

Potential Predictors	Intercept	Piecewise 1 Linear Component	Piecewise 1 Quadratic Component	Piecewise 2 Linear Component	Piecewise 2 Quadratic Component
Lee Fatigue Scale: Morning fatigue score at enrollment	◆	◆		◆	◆
Lee Fatigue Scale: Evening energy score at enrollment	◆			◆	◆
Lee Fatigue Scale: Morning energy score at enrollment	◆			◆	◆
Center for Epidemiological Studies-Depression Scale score at enrollment	◆			◆	◆
General Sleep Disturbance Scale score at enrollment	◆			◆	◆
Trait Anxiety score at enrollment	◆			◆	◆
State Anxiety score at enrollment	◆			◆	◆
Pain present at enrollment	◆				

◆= From exploratory analysis had a *t*-value of ≥2.0.

Abbreviations: gm/dL = grams per deciliter; kg/m^2 = kilogram per meters squared.

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