Longitudinal Analysis of Depression and Anxiety Symptoms as Independent Predictors of Neurocognitive Function in Primary Brain Tumor Patients

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Abstract

Purpose: Primary brain tumor patients are vulnerable to depression and anxiety symptoms, which may affect their neurocognitive functioning. We performed a prospective longitudinal analysis to examine the association between depression and anxiety symptoms and domain-specific neurocognitive functioning in primary brain tumor patients receiving radiation therapy (RT).

Methods and Materials: On a prospective trial, 54 primary brain tumor patients receiving RT underwent comprehensive neurocognitive evaluation at baseline (pre-RT), and 3, 6, and 12 months post-RT. Neurocognitive assessments measured attention/processing speed, verbal and visuospatial memory, and executive functioning, including Delis-Kaplan Executive Function System Trail-Making Test (DKEFS-TMT), DKEFS Verbal Fluency, and Brief Visuospatial Memory Test-Revised. Depression and anxiety symptoms were also assessed at each time point with Beck Depression and Anxiety Inventories (BDI-II and BAI), respectively. Higher scores reflect more numerous or severe depression or anxiety symptoms. Univariable and multivariable linear mixed-effects models assessed associations between BDI-II and BAI scores and domain-specific

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neurocognitive scores over time, controlling for pre-existing depression or anxiety disorders and other patient, tumor, and treatment characteristics.

Results: Higher BAI scores were associated with worse attention and processing speed in univariable analyses: DKEFS-TMT visual scanning ($P= .003$), number sequencing ($P= .011$), and letter sequencing ($P<.001$). On multivariable analyses, these associations remained significant (all P .01). Higher BDI-II scores were also associated with poorer attention/processing speed (DKEFS-TMT Letter Sequencing) in univariable ($P= .002$) and multivariable ($P= .013$) models. Higher BAI scores were associated with worse visuospatial memory (Brief Visuospatial Memory Test-Revised Delayed Recall) on univariable ($P= .012$) but not multivariable analyses ($P= .383$). Similarly, higher BDI-II scores were associated with poorer executive functioning (DKEFS Verbal Fluency Category Switching) on univariable ($P= .031$) but not multivariable analyses ($P= .198$).

Conclusions: Among primary brain tumor patients receiving RT, increased depression and anxiety were independently associated with worsened neurocognition, particularly in attention/ processing speed. Depression and anxiety symptoms should be controlled for in prospective clinical trials and managed in the clinical setting to optimize neurocognitive functioning.

Introduction

Symptoms of depression and anxiety can affect up to 40% to 90% of patients with brain tumors.[1,2] Brain tumor patients are at risk of developing the downstream effects of depression and anxiety symptoms, including emotional distress, decreased quality of life,[3] decreased treatment adherence,[4] poorer immune and hormonal responses to cancer,[5] and independently worse survival outcomes.[6,7]

Neurocognitive functioning is a critical clinical outcome for primary brain tumor patients, and is now prioritized in clinical trials as an integrated endpoint alongside patient survival, tumor response, and quality of life.[8] Within the neuropsychologic literature, depression and anxiety are often investigated as possible confounders of neurocognitive functioning.[9,10] Indeed, evidence from Huntington disease,[11] Parkinson disease,[12] multiple sclerosis,[13] and studies of older adults[14,15] show that greater symptoms of depression and anxiety are associated with poorer neurocognitive and physical functioning. Among patients with cancer, there are longitudinal studies investigating patients with breast,[16,17] prostate,[18] and colorectal[19] cancer, with findings showing mixed results that obscure clear associations. Primary brain tumor patients present a unique and complicated scenario; neurocognition can be affected by the tumor itself (location, growth, grade),[20] tumor treatments, including chemotherapy,[21] radiation therapy (RT),[22] surgery,[23] and medications (antiepileptic therapy and corticosteroid use[24,25]).

To our knowledge, no study has investigated the relationship between depression and anxiety symptoms and neurocognitive functioning longitudinally in primary brain tumor patients. A thorough understanding of this relationship is crucial within the brain tumor population, as clinical trials investigating novel brain tumor treatments are increasingly including neurocognition as the primary outcome in metastatic,[26,27] pediatric,[28] and adult primary brain tumor populations.[29] We hypothesized that higher symptoms of depression and anxiety

are associated with poorer neurocognitive performance within the domains of attention and processing speed, executive functioning, and visuospatial and verbal memory.

Methods

Protocol approval and consent

This study was approved by our institutional review board. All enrolled patients provided written informed consent.

Study design and participants

As part of an ongoing single institution prospective, longitudinal trial, we evaluated 54 patients with primary brain tumors treated with fractionated partial-brain RT (1.8-2.0 Gy per fraction, 50.4-60 Gy total dose). Eligibility criteria included: age >18 years, Karnofsky performance status (KPS) >70, ability to complete neurocognitive evaluation in English, and life expectancy >1 year. Patients with prior brain RT were excluded. Subjects were examined before RT, and 3, 6, and 12 months post-RT. At each time point, depression and anxiety symptoms were assessed, along with a battery of well-validated neurocognitive tests.

Depression and anxiety assessments

The Beck Depression Inventory-II[30] (BDI-II) and Beck Anxiety Inventory[31] (BAI) are well-validated, self-report questionnaires quantifying the number and severity of depression and anxiety symptoms experienced within the past 1 to 2 weeks. Greater number and severity of symptoms of depression and anxiety are reflected in an increased BDI-II and BAI score, respectively. These assessments are robust and have been used in other oncology studies.[6,32]

Neurocognitive assessments

The neurocognitive battery consisted of 12 validated tests, categorized into 3 domains. Attention and processing speed was measured by: Delis-Kaplan Executive Function System[33] Trail Making Test (DKEFS-TMT) (visual scanning, number sequencing, and letter sequencing conditions) and Wechsler Adult Intelligence Scale-IV[34] (digit span and coding subtests). Executive functioning included: DKEFS Verbal Fluency (letter fluency and category switching conditions) and the Wisconsin Card Sort Test[35] (perseverative errors). The memory domain, assessing verbal and visuospatial memory, included: Hopkins Verbal Learning Test-Revised[36] (total recall and delayed recall) and the Brief Visuospatial Memory Test[37] (total recall and delayed recall). These domains were chosen because they tend to demonstrate the greatest impairment in brain tumor patients after radiation.[38] These specific tests are also ideal for repeat testing (at each time point), as alternate but psychometrically equivalent forms were available. Raw neurocognitive test scores were converted to age-, sex-, and education-adjusted T-scores.[38]

Statistical analysis

Baseline differences in BAI and BDI-II scores based on demographic groups were tested using 2-sample *t* tests, one-way analysis of variance (ANOVA), and Pearson's correlation as appropriate, whereas post hoc pairwise *t* tests (Holm correction) were conducted after

significant associations identified via one-way ANOVA. Longitudinal BDI-II and BAI scores were fitted using linear mixed-effects models,[39] with time and demographic variables as predictors and random subject intercept.

Separate univariable linear mixed-effects models were fitted using longitudinal T-scores from each of the 12 neurocognitive assessments as the outcome, and either depression or anxiety symptoms at the same time point as the predictor, again with random subject intercepts. In total, 24 univariable models explored continuous, time-varying BDI-II or BAI symptom scores as a predictor of neurocognitive performance.

Finally, stepwise procedure was used to adjust for demographic, tumor, and treatment characteristics in the association between time-varying BDI-II or BAI symptom scores and neurocognitive performance. We assessed the following variables for inclusion in each of the models: sex, age, race or ethnicity, time point, RT type (intensity modulated RT/volumetric arc therapy vs proton therapy), concurrent treatment with chemotherapy, history of seizures, antiepileptic drug use, highest education level (categorized as up to high school (12 years), college (12<x 16 years), or graduate school (>16 years), baseline KPS, tumor histology (benign tumor versus glioma), and prior history of clinical anxiety or depression. Each of the variables was first assessed as a predictor of neurocognition in univariable linear mixed-effects models including random subject intercept. Those with a P value of <.20 were then included in a multivariable stepwise backward selection procedure, using P value <.10 as the criterion for remaining in the model, while keeping either time-varying BAI or BDI-II as the main predictor in the model. This stepwise procedure was repeated for all combinations of BDI-II or BAI symptom scores and neurocognitive performance. All statistical analyses were performed in R.[40]

Results

Patient cohort

Of the 60 patients currently enrolled in the clinical trial, this analysis includes 54 patients with baseline neurocognitive and anxiety and depression symptom data (Fig. E1). Patient characteristics are shown in Table 1. This cohort was 60% male, predominantly non-Hispanic white race (78%), and highly educated (49% college educated, 30% graduate level education). Notably, 9 patients had been diagnosed with an anxiety disorder before their brain tumor diagnosis and 8 patients had a prior diagnosis of clinical depression.

At baseline the median patient BDI-II score was higher than the median BAI score, at 8.5 and 5.5, respectively (Table 1). Although patients tended to report higher baseline depression symptoms than anxiety symptoms, moderate-severe BAI scores were more common (n = 8, 17%) than moderate-severe BDI-II scores (n = 4, 7%). The minimal range of symptoms was most common at baseline, comprising 75% of BDI-II responses and 58% of BAI responses.

Twelve tests among 3 cognitive domains (attention and processing speed, executive functioning, and memory) were examined, as described earlier. Changes in these neurocognitive outcomes over time have been assessed and reported previously.[41,42]

Depression and anxiety symptoms

BDI-II and BAI scores for the cohort over time are shown in Figure 1. There was no statistically significant change in BDI-II scores over time (Figure. 1a and b). BAI scores, however, did decrease significantly over time (linear mixed-effects, $P = .003$; Figure. 1c and d).

Analyses of the associations between patient characteristics and baseline BDI-II and BAI scores are shown in Table 2. History of depression was the only significant predictor of higher BDI-II at baseline ($P = .011$). Female sex was associated with significantly higher BAI scores at baseline ($P = .048$). High school education level was also significantly associated with a higher BAI score at baseline compared with groups with higher education levels ($P = .028$ in post hoc pairwise *t* test, Holm adjusted). Patients treated with protons had a lower BAI score at baseline ($P = .026$) compared with patients treated with intensity modulated RT and volumetric arc therapy.

Linear mixed-effects analysis of longitudinal BDI-II and BAI scores with univariable demographic predictors are shown in Table 3. A prior history of seizures ($P = .043$), anxiety ($P = .020$), and depression ($P = .041$) each predicted for increased BDI-II scores over the course of the study. History of anxiety predicted for increased BAI scores over time ($P = .015$).

Neurocognitive function as predicted by anxiety symptoms

Figure 2 shows the results of analyzing longitudinal BAI score as a predictor for each independent neurocognitive assessment, assessed at the same time as the BAI score. Univariable models (Figure. 2a) show that an increase in symptoms of anxiety significantly predicted for a decreased T-score in 3 of the 5 assessments of attention and processing speed. These assessments include DKEFS-TMT visual scanning ($\beta = -0.388$, $P = .003$), number sequencing ($\beta = -0.292$, $P = .011$), and letter sequencing ($\beta = -0.393$, $P < .001$). After controlling for covariates in multivariable models (Figure. 2b), BAI remained a significant independent predictor of all 3 assessments of DKEFS-TMT visual scanning ($\beta = -0.425$, $P < .001$), number sequencing ($\beta = -0.261$, $P = .011$), and letter sequencing ($\beta = -0.327$, $P = .003$). Inclusion of covariates in final multivariable models are shown in Table E1 and Table E2.

An increase in BAI score was associated with a decrease in the Brief Visuospatial Memory Test-Revised Delayed Recall score ($P = .012$) in univariable analysis. In the multivariable model, which controlled for sex, time point, highest education achieved, baseline KPS, and benign versus glioma tumor histology, the relationship became nonsignificant ($P = .383$). In univariable analysis, BAI score approached significance for predicting the Coding Total score ($\beta = -0.230$, $P = .071$), but after controlling for sex, highest education level, and history or ongoing seizure activity, this association was not significant ($P = .195$).

Neurocognitive function as predicted by depressive symptoms

Figure 3 shows results of longitudinal BDI-II score as a predictor of each independent neurocognitive test score in univariable (Figure. 3a) and multivariable (Figure. 3b) analyses.

Within the domain of attention and processing speed, BDI-II was a predictor of DKEFS-TMT letter sequencing in univariable ($\beta = -0.381$, $P = .002$) and multivariable analyses ($\beta = -0.303$, $P = .013$).

Higher BDI-II score was associated with poorer DKEFS verbal fluency category switching in univariable analysis ($\beta = -0.413$, $P = .031$), but not multivariable analysis ($P = .198$), which controlled for time point, highest education level, baseline KPS, chemotherapy treatment, and history or ongoing seizures. For HVLT total recall, BDI-II trended toward significance in univariable ($\beta = -0.339$, $P = .053$) but not multivariable ($P = .126$) models, which controlled for highest education level and antiepileptic drug treatment.

Discussion

In this study, we explore how longitudinal changes in depression and anxiety symptoms can independently affect neurocognitive functioning in a cohort of primary brain tumor patients receiving RT. To our knowledge, this relationship has not been investigated among primary brain tumor patients. We found that an increase in anxiety symptoms is an independent predictor of neurocognitive functioning, specifically within the domain of attention and processing speed. Thus, to optimize neurocognition within primary brain tumor patients, standard of care should include screening for and treatment of subclinical symptoms of depression and anxiety to improve outcomes. As brain tumor clinical trials are increasingly using neurocognitive functioning as a primary endpoint[26–29] commensurate with survival and quality of life, we recommend that symptoms of depression and anxiety should be quantified and controlled.

Brain tumor patients are known to be at risk of experiencing symptoms of anxiety and depression. Although our cohort had a greater median BDI-II score than BAI score at baseline, moderate-severe anxiety was more common than moderate-severe depression. We found a nonsignificant trend of depression symptoms over time, similar to previous descriptive studies of brain cancer[6,43,44] and breast cancer.[45] BAI scores significantly decreased over time within our cohort, also consistent with prior descriptive studies.[44] Most patients in this cohort completed their baseline assessment in the postsurgical period, a time often wrought with emotional distress. Anxiety about poor prognosis and an unpredictable future contribute to pretreatment worry, which has been shown to alter brain function and contribute to neurocognitive dysfunction independent of the actual upcoming treatments.[46] Ultimately these data support a high prevalence of subclinical depression and anxiety within primary brain tumor patients, and we argue for the early screening of depression and anxiety symptoms within this population.

We identified subsets of patients who may be at greater risk of experiencing symptoms of depression and anxiety. Consistent with previous studies,[2,47] our results support that women and patients with lower education levels have higher baseline anxiety symptoms. Our data also shows an association between proton RT and lower baseline BAI levels; this is likely due to a higher proportion of benign and low-grade tumors treated by protons versus photons. Unsurprisingly, prior history of clinical depression and anxiety are consistently associated with elevated symptoms of these conditions.[1,2] We also found that experiencing

ongoing seizures is a predictor of increased BDI scores, which is not explained by antiepileptic drug use in this study or previous studies.[24] Thus, seizures may present a unique neurologic risk for depressive symptoms independent of antiepileptic drug use or tumor diagnosis. We recommend universal screening of brain tumor patients for symptoms of depression and anxiety, but recognize that certain patient subsets have higher risk and may require closer follow-up.

Compared with data concerning symptoms of depression, there has been a dearth of literature regarding the relationship between anxiety symptoms and neurocognitive function. Here we investigate that relationship and find a significant correlation between the fluctuation of an individual's anxiety symptoms score and that patient's neurocognitive performance. The majority of the analyses within attention and processing speed show that BAI score is a significant predictor of test performance, with a greater number of symptoms associated with poorer performance. BAI score remains a significant, independent predictor after controlling for numerous characteristics, such as sex, educational attainment, tumor histology (benign versus glioma), surgical history, concurrent chemotherapy, and seizures. Anxiety manifests as a constellation of affective, cognitive, and physiologic symptoms that, beyond a certain threshold, can drain a person's attentional reserve. This loss may in turn exert a direct influence on attention and processing speed function that we find in this study and in other neurologic diseases.[48] Deficits in attention and processing speed are inextricably linked to intellectual function and a person's perception of their intellectual function. This can effect productivity at work, relationships with friends and family, and self-image.[19] We conclude that alleviating symptoms of anxiety may directly benefit patients with primary brain tumor from these cognitive and clinically important downstream effects.

We found that higher depression scores are associated with poorer performance on measures of attention and processing speed, executive functioning, and a trend within the memory domain. Although we maintain that the intrinsic nature of brain tumors causes a unique effect on neurocognition that should be investigated independently, these results are consistent with cohorts of different cancer subtypes. Among patients with breast cancer, both baseline anxiety and depression scores were significant longitudinal predictors of memory, attention, and executive functioning assessments.[17] Still, other studies of patients with colorectal[19] and prostate[18] cancer did not find associations between symptoms of anxiety or depression and neurocognitive functioning. However, those studies explored the relationship using binary cognitive outcomes (global deficit scores, cognitive impairment), which can obscure domain-specific associations. Our analysis capitalizes on a robust neurocognitive assessment with validated measures within each cognitive domain of interest as well as validated, selfreport measures of depression and anxiety symptoms. The studies that obtained the sensitivity to detect domain-specific neurocognitive effects did in fact find significant associations between anxiety and depression symptoms and functioning within certain neurocognitive domains.[17] These domain-specific effects of anxiety and depression symptoms are important to recognize, as they may have larger implications on prognosis[49] and survival,[6] especially within the brain tumor population.[47]

These results have strong implications for clinical care and ongoing clinical trial design. Due to the high prevalence of depression and anxiety symptoms within the primary brain tumor

population and the emerging evidence that these symptoms affect neurocognition, quality of life, and survival, we argue for the universal screening and treatment of symptoms early in the diagnosis. Implementation may be similar to the International Prostate Symptom Score, [50] in which ongoing screening becomes a major discussion point throughout treatment. Trials with neurocognitive functioning as a primary outcome should include screening and treatment protocols for depression and anxiety symptoms, as well as control for these symptoms in evaluation of cognitive assessment scores. These endpoints are not currently included in many ongoing trials.[29] These steps have the potential to improve patient outcomes without RT dose modifications or treatment changes.

There are limitations to this study. The overall sample size is relatively small, though similar in size to other prospective trials of this nature.[12,16,18] This cohort also underwent extensive, robust neurocognitive evaluation at each time point. As an exploratory analysis we make use of the richness of the data by exploring multiple neurocognitive domains, which provided granularity to detect important clinical correlations. Although all patients included were primary brain tumor patients receiving RT, heterogeneity existed with regard to treatment modality, tumor histology, and other characteristics. These differences were accounted for in the multivariable stepwise backward selection analysis, and thus the conclusions should be generalizable to any primary brain tumor patient presenting for treatment. Still, it is possible that there may be other unaccounted variables that could affect the relationship between mood and neurocognitive function. Although we cannot assume that the associations reported here are causative, our results suggest a clear independent association between symptoms of anxiety and depression and certain neurocognitive domains.

Conclusions

We have conducted the first prospective longitudinal analysis of the relationship between depression and anxiety symptoms and neurocognitive function among patients with primary brain tumors. Our study shows that depression and anxiety symptoms are independent predictors of neurocognitive functioning and may specifically influence attention and processing speed. These data support the evaluation and treatment of subclinical depression and anxiety symptoms throughout the disease course of primary brain tumor patients, as the relief of these symptoms may optimize cognition, quality of life, and overall survival. We urge ongoing and future clinical trials investigating neurocognitive functioning in brain tumor patients to include, treat, and control for symptoms of depression and anxiety.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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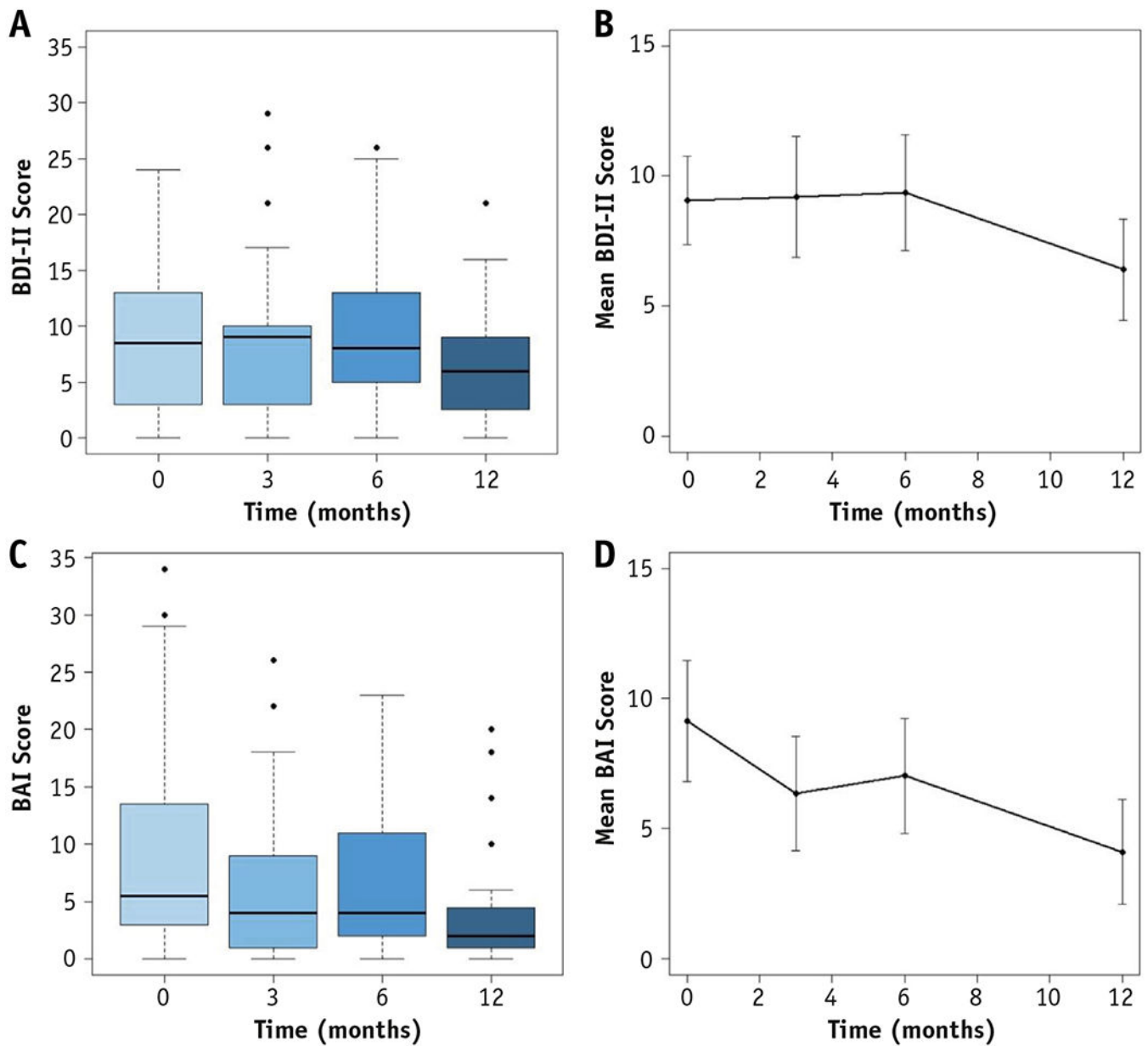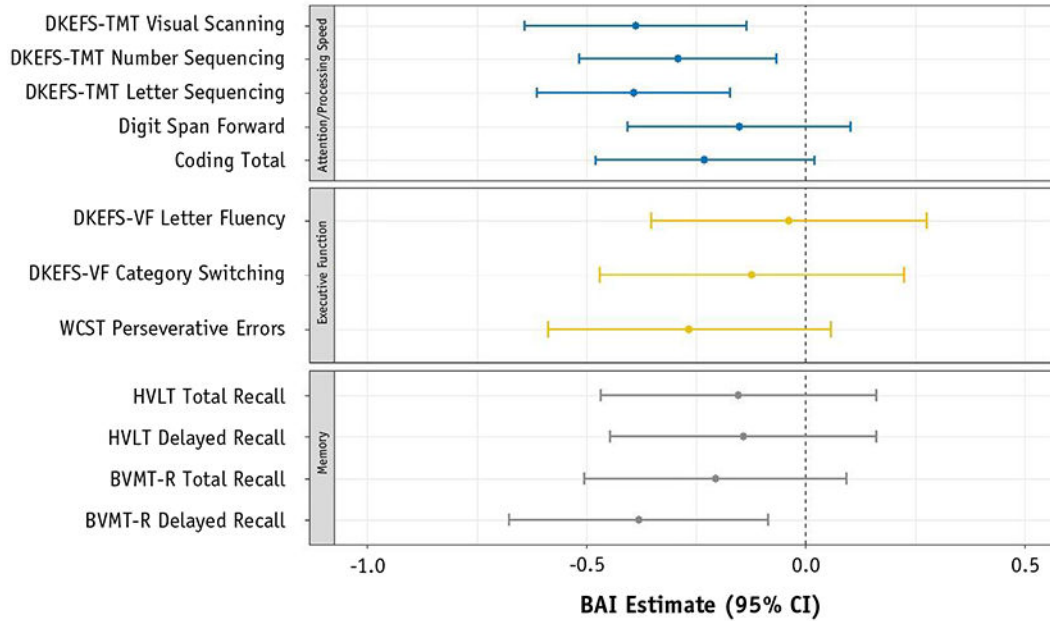
Fig. 1.
BDI and BAI scores over time. Boxplots and line plots for raw BDI and BAI scores over time. Line plots are mean scores over time with error bars representing the 95% confidence intervals. (a and b) BDI scores are not statistically different over time. (c and d) BAI scores significantly decrease over time ($P = .003$).

Fig. 2.
(a) Univariable linear mixed effects regression of anxiety symptoms on cognitive function.
(b) Multivariable linear mixed effects regression of anxiety symptoms on cognitive function.
Linear mixed effects analyses of BAI as a predictor of neurocognitive function. Assessments of attention or processing (5), executive functioning (3), and memory (4) are shown. Each assessment investigated with a unique model. β estimates are shown by dot. Whiskers reflect 95% confidence interval of the estimate. Significant associations are reflected by 95% confidence interval that do not cross the 0.0 reference line. (a) Shows univariable models. (b)

Shows multivariable models, controlled for appropriate covariates. *Abbreviations*: BVMT-R Brief Visuospatial Memory Test-Revised; CI = confidence interval; DKEFS-TMT = Delis-Kaplan Executive Function System Trail-Making Test; DKEFS-VF = DKEFS Verbal Fluency; HVLT = Hopkins Verbal Learning Test-Revised; WCST = Wisconsin Card Sort Test.

Fig. 3.
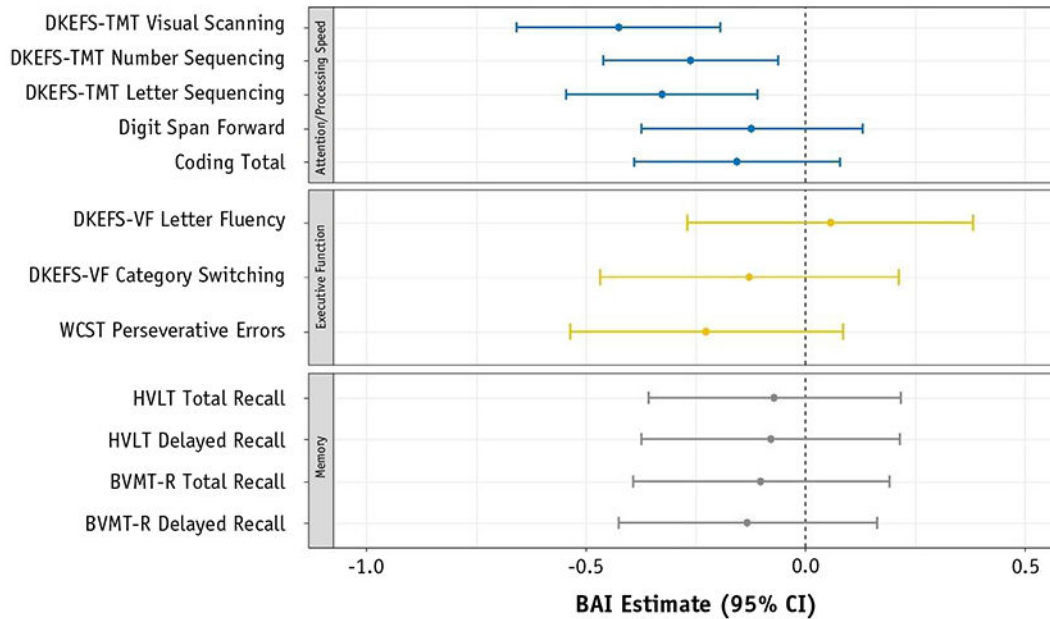(a) Univariable linear mixed effects regression of depression symptoms on cognitive function. (b) Multivariable linear mixed effects regression of depression symptoms on cognitive function. Linear mixed effects analyses of BDI as a predictor of neurocognitive function assessments of attention and processing (5), executive functioning (3), and memory (4) are shown. Each assessment investigated with a unique model. β estimates are shown by dot. Whiskers reflect 95% confidence interval of the estimate. Significant associations are reflected by 95% confidence interval that do not cross the 0.0 reference line. (a) Shows

univariable models. (b) Shows multivariable models, controlled for appropriate covariates. *Abbreviations*: BVMT-R Brief Visuospatial Memory Test-Revised; CI = confidence interval; DKEFS-TMT = Delis-Kaplan Executive Function System Trail-Making Test; DKEFS-VF = DKEFS Verbal Fluency; HVLT = Hopkins Verbal Learning Test-Revised; WCST = Wisconsin Card Sort Test.
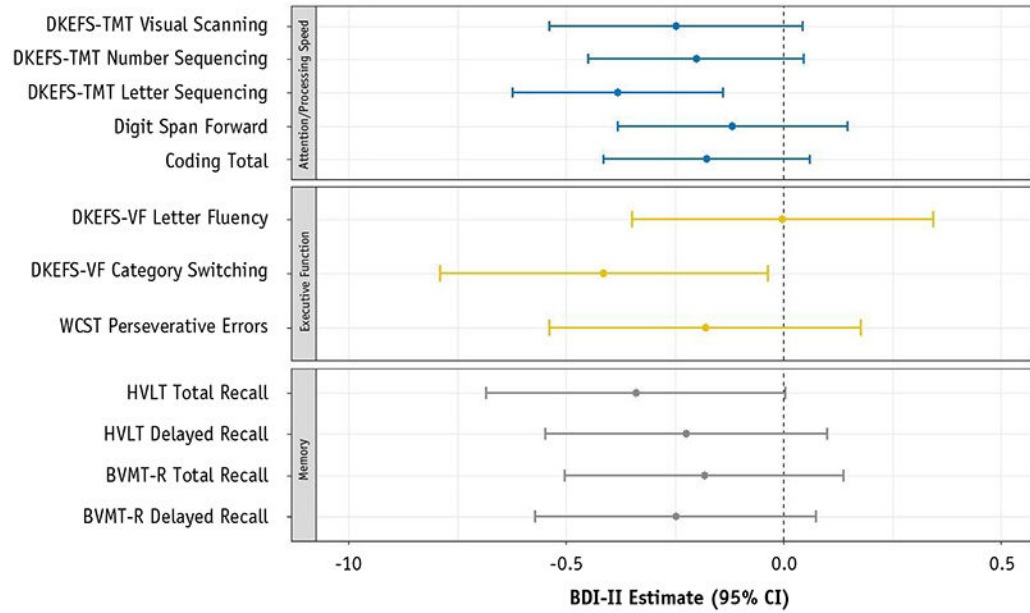
Table 1

Patient demographics and clinical characteristics

Characteristic of baseline population, n = 54	Frequency (%) or median (range)
Age, y	47 (20-75)
Sex	
Male	32 (60)
Female	22 (40)
Ethnicity	
Non-Hispanic	
Asian/Pacific Islander	3 (6)
Black	1 (2)
Middle Eastern	2 (4)
White	42 (78)
Hispanic	6 (11)
Highest education achieved, median (range)	16 (10-20)
High school	11 (21)
College	26 (49)
Graduate School	16 (30)
Tumor diagnosis	
Glioma	
Low-grade	9 (17)
High-grade	23 (43)
Meningioma	12 (22)
Pituitary adenoma	5 (9)
Schwannoma	2 (4)
Craniopharyngioma	2 (4)
Chondrosarcoma	1 (2)
Tumor side	
Left	27 (50)
Right	23 (42)
Central	4 (8)
Tumor region	
Frontal	16 (30)
Temporal	12 (22)
Suprasellar	9 (17)
Parietal	6 (11)
Base of skull	4 (7)
Cerebellar	3 (6)
Cavernous sinus	3 (6)
Sphenoid wing	1 (2)
RT type	
IMRT/VMAT	40 (74)

Characteristic of baseline population, n = 54	Frequency (%) or median (range)
Proton	14 (26)
Baseline KPS	
80	3 (6)
90	33 (61)
100	18 (33)
Surgery	
GTR	11 (20)
STR	33 (61)
Biopsy	3 (6)
None	7 (13)
Chemotherapy [*]	28 (52)
Seizures [†]	23 (43)
Antiepileptic drug use [‡]	28 (52)
Previously treated	
Anxiety	9 (17)
Depression	8 (15)
Baseline BDI-II, median (range) [§]	8.5 (0-24)
Minimal	41 (76)
Mild	9 (17)
Moderate	4 (7)
Severe	0
Baseline BAI, median (range) [§]	5.5 (0-34)
Minimal	29 (60)
Mild	11 (23)
Moderate	6 (13)
Severe	2 (4)

Abbreviations: GTR = gross total resection; IMRT/VMAT = intensity modulated RT/volumetric arc therapy; KPS = Karnofsky Performance Status; RT = radiation therapy; STR = subtotal resection.

[*] Received chemotherapy during or after RT.

[†] History of active seizures.

[‡] Taking antiepileptic drugs during study.

[§] Severity categories based on standard cutoffs.[30,31]

Table 2

Baseline BAI and BDI associations with patient characteristics

Characteristic	Baseline BAI score		Baseline BDI score	
	Mean (SD)	P value	Mean (SD)	P value
Sex *				
Male	6.92 (6.5)	.048	8.81 (5.4)	.739
Female	11.77 (9.4)		9.45 (7.8)	
Age †				
rho est:	0.017	.901	−0.115	.408
Highest education ‡				
High school	14.1 (10.9)	.028 §	11.91 (7.9)	.234
College	6.52 (5.7)		7.96 (5.7)	
Graduate school	11.17 (8.5)		9.25 (6.2)	
Ethnicity ‡				
Non-Hispanic		.739		.177
Asian	4.06 (2.8)		3.33 (4.1)	
Black	2.00 (NA)		1.00 (NA)	
Middle Eastern	9.50 (0.7)		15.5 (4.9)	
White	9.86 (8.2)		9.48 (6.1)	
Hispanic	7.50 (11.1)		8.33 (8.2)	
History of anxiety *				
Yes	16.50 (11.0)	.059	13.67 (7.2)	.055
No	7.68 (6.8)		8.16 (5.9)	
History of depression *				
Yes	15.14 (9.1)	.093	14.13 (4.9)	.011
No	8.12 (7.7)		8.20 (6.2)	
Baseline KPS ‡				
80	13.00 (NA)	.876	9.67 (8.1)	.987
90	9.27 (8.5)		9.03 (6.2)	
100	8.71 (8.0)		9.06 (6.9)	
RT type *				
IMRT/VMAT	10.62 (8.6)	.026	9.95 (6.6)	.056
Protons	5.57 (6.0)		6.57 (5.0)	
Glioma *				
Yes	9.85 (8.4)	.526	9.63 (6.0)	.464
No	8.32 (8.1)		8.27 (7.0)	
Seizures *				
Yes	10.61 (8.1)	.343	10.91 (4.9)	.055
No	8.27 (8.3)		7.71 (7.1)	

Characteristic	Baseline BAI score		Baseline BDI score	
	Mean (SD)	*P* value	Mean (SD)	*P* value
Antiepileptic drugs [*]				
Yes	9.22 (7.7)	.702	9.82 (5.3)	.218
No	9.08 (8.8)		8.27 (7.4)	
Chemotherapy [*]				
Yes	9.86 (7.5)	.578	9.54 (5.8)	.590
No	8.54 (8.8)		8.58 (7.1)	
Surgery [*]				
Yes	8.53 (7.9)	.375	8.91 (6.3)	.726
No	11.5 (9.4)		9.80 (7.3)	

Abbreviations: IMRT/VMAT = intensity modulated RT/volumetric arc therapy; KPS = Karnofsky Performance Status; RT = radiation therapy; SD = standard deviation.

[*] Two-sample t test.

[†] Pearson correlation.

[‡] One-way analysis of variance.

[§] Post hoc pairwise *t* test with Holm correction.

Table 3

Univariable longitudinal Analysis of BAI and BDI associations with patient characteristics

Characteristic	BAI score Estimate (95% CI)	LRT P value	BDI score Estimate (95% CI)	LRT P value
Sex				
Male	−3.06 (−6.97 to 0.85)	.128	−0.12 (−3.56 to 3.32)	.943
Age				
Continuous	0.02 (−0.18 to 0.22)	.771	−0.04 (−0.24 to 0.15)	.508
Highest education		.063		.420
High school	6.24 (1.14 to 11.3)		2.79 (−1.72 to 7.30)	
Graduate school	1.67 (−2.64 to 5.98)		−0.10 (−4.02 to 3.82)	
Ethnicity		.732		.326
Non-Hispanic				
Asian	−4.79 (−13.2 to 3.64)		−5.43 (−12.7 to 1.82)	
Black	−5.18 (−19.3 to 8.93)		−5.78 (−17.7 to 6.18)	
Middle Eastern	2.17 (−7.83 to 12.2)		5.34 (−3.09 to 13.8)	
Hispanic	−1.40 (−7.67 to 4.87)		−0.82 (−6.11 to 4.47)	
History of anxiety				
Yes	6.35 (1.45–11.3)	.015	5.27 (0.96–9.58)	.020
History of depression				
Yes	4.38 (−0.91 to 9.67)	.114	4.90 (0.39–9.41)	.041
Baseline KPS		.629		.855
80	−2.31 (−11.1 to 6.51)		0.32 (−7.32 to 7.96)	
90	1.33 (−2.79 to 5.45)		1.03 (−2.69 to 4.75)	
RT type				
Protons	−3.43 (−7.74 to 0.88)	.127	−2.41 (−6.13 to 1.31)	.217
Glioma				
Yes	1.13 (−2.79 to 5.05)	.579	1.93 (−1.40 to 5.26)	.271
Seizures				
Yes	1.80 (−2.12 to 5.72)	.375	3.47 (0.14–6.80)	.043
Antiepileptic drugs				

| Characteristic | BAI score | | BDI score | |
	Estimate (95% CI)	LRT P value	Estimate (95% CI)	LRT P value
Yes	0.44 (−3.42 to 4.36)	.825	1.97 (−0.38 to 4.32)	.251
Chemotherapy				
Yes	0.83 (−3.09 to 4.75)	.680	1.33 (−2.00 to 4.66)	.440
Surgery				
Yes	−3.78 (−8.68 to 1.12)	.137	−0.03 (−4.34 to 4.28)	.989

Abbreviations: CI = confidence interval; KPS = Karnofsky performance status; LRT = likelihood ratio test; RT = radiation therapy.