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Identifying early diffusion imaging biomarkers of regional white matter injury as indicators of executive function decline following brain radiotherapy: A prospective clinical trial in primary brain tumor patients

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Abstract

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: All authors.

Statistical analysis: KRT, NB, CRM, TN

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POTENTIAL CONFLICTS OF INTEREST

JAH-G has research funding from Varian Medical Systems (Palo Alto, CA), unrelated to the current study. There are no other conflicts of interest to disclose.

Background and Purpose: Executive function (EF) decline is common after radiation therapy (RT), yet the etiology is unclear. We analyzed the association between longitudinal changes in frontal lobe white matter microstructure and decline in EF following RT in brain tumor patients on a prospective clinical trial.

Materials and Methods: Diffusion tensor imaging was obtained on 22 patients with brain tumors prior to RT, as well as 3- and 6-months post-RT, in a prospective, observational trial. Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) were calculated within the superficial white matter (SWM) of the anterior cingulate (AC) and dorsolateral prefrontal cortex. Measures of cognitive flexibility, verbal fluency, and verbal set-shifting were obtained pre- and post-RT. Reliable change indices were calculated to determine significant baseline to 6-month EF changes.

Results: Decreases in FA and increases in MD were observed in the caudal AC (CAC) at 3-months post-RT. CAC changes were characterized by increased RD bilaterally. From baseline to 6-months post-RT, decreased FA and increased MD and RD of the CAC was associated with decline in verbal set-shifting ability, whereas increased MD in the CAC was associated with a decline in cognitive flexibility.

Conclusion: White matter underlying the AC may be particularly vulnerable to radiation effects. Early microstructural loss within AC SWM represents an important biomarker for EF decline, and dose reduction in this region may represent a possibility for cognitive preservation for patients receiving radiotherapy.

Keywords

brain tumors; radiation therapy; neurocognition; executive function; neuroimaging

INTRODUCTION

Radiation therapy (RT) is fundamental for brain tumor management, yet most brain tumor patients will live long enough to experience some capacity of RT-induced neurocognitive decline[1]. The majority of research in this area has focused on effects of RT on hippocampal networks and subsequent memory decline[2,3]. However, it is increasingly recognized that RT-induced brain injury is not limited to the hippocampus and memory. Damage to prefrontal white matter may have important consequences, notably a decline in executive functioning (EF), abilities including multi-tasking, planning, fluency, and flexibility in thinking (i.e., cognitive flexibility)[4]. Indeed, evidence suggests EF decline may be more pronounced than memory decline following RT[5,6].

Given the importance of EF to occupational status and quality of life[7,8], identifying early imaging biomarkers of EF decline could have important implications for RT planning and clinical trial development. Micro structural damage from RT has been demonstrated on diffusion tensor imaging (DTI) weeks to months following treatment[2,3,9–11]. These early microstructural changes appear to progress over time and may portend progressive and irreversible cognitive decline[2,3]. The underlying biological mechanisms which mediate cognitive decline are not entirely clear, and a deeper understanding could inform therapeutic changes that could mitigate this decline.

We investigated whether early microstructural changes to prefrontal white matter are associated with later decline in EF in patients with brain tumors undergoing fractionated RT on a prospective trial. The white matter beneath the anterior cingulate (AC) and dorsolateral prefrontal cortex (DLPFC) was analyzed given the established importance of these regions to EF[12]. Furthermore, we focused on the white matter directly beneath these regions (i.e., superficial white matter; SWM) because the SWM enables communication across neighboring gyri (i.e., cortico-cortical connectivity) in the form of U-fibers and has been shown to play a critical role in cognition[13–15]. The AC white matter (i.e., dorsal cingulum) was of particular interest due to its vulnerability to RT-injury[16]. We hypothesized that compromise to SWM in these regions within 3 months post-RT would predict EF decline 6 months post-RT.

MATERIALS AND METHODS

Standard protocol approvals, registrations, and patient consents:

This prospective, longitudinal study was approved by our institutional review board. All participants provided written informed consent.

Participants and procedure:

Fifty-four adults with primary brain tumors who were eligible for fractionated partial-brain RT with either protons or photons (1.8-2.0 Gy per fraction, 50.4-60Gy total dose) were enrolled in this prospective, observational study from 2014-2016. Eligibility criteria included age >18 years, Karnofsky performance status >70, estimated life expectancy >1 year, and ability to undergo neurocognitive testing in English. Patients who had received prior brain RT were excluded. Patients underwent brain MRI and neurocognitive testing before RT (pre-RT) and at 3 and 6-months post-RT. Participants included in the current analysis all had MRIs at two time points: pre-RT and 3 months post-RT, as well as neuropsychological data pre-RT and 6-months post-RT. Six months post-RT was selected as our time point for evaluating EF decline because this time point is long enough post-RT to capture the onset of “late-delayed” cognitive effects that may be irreversible and often progressive[17]. Twenty-two patients met the above inclusion criteria to form the final study cohort.

Image acquisition:

MRI scans for all patients at each time point were acquired on a 3.0T 750 GE system (GE Healthcare, Milwaukee, Wisconsin) equipped with an 8-channel head coil. The imaging protocol included a 3D volumetric T1-weighted inversion recovery spoiled gradient echo sequence (echo time [TE]/repetition time [TR] = 2.8/6.5 ms; inversion time [TI] = 450 ms; flip angle = 8 degrees; field of view [FOV] = 24 cm; 1 mm isotropic resolution) and a 3D FLAIR sequence (TE/TR = 125/6000 ms, TI = 1868 ms, FOV = 24 cm, slice thickness = 1 mm). Diffusion data were acquired with a single-shot pulsed-field gradient spin EPI sequence (TE/TR = 96 ms/17 s; FOV = 24 cm, matrix = 128 × 128 × 48; 1.87 × 1.875 in-plane resolution; slice thickness = 2.5 mm; 48 slices) with b = 0, 500, 1500, and 4000 s/mm^2, with 1, 6, 6, and 15 unique gradient directions for each b-value respectively, and one

average for each non-zero b-value. For use in nonlinear B_0 distortion correction, two additional b=0 volumes were acquired with either forward or reverse phase-encode polarity.

Image processing:

All imaging data were preprocessed using in-house algorithms developed in MATLAB. Anatomical scans were corrected for distortions due to gradient nonlinearities[18]. Diffusion scans were corrected for spatial distortions associated with gradient nonlinearities, susceptibility, and eddy currents[19,20]. Diffusion data were resampled to 1mm isotropic resolution using a linear interpolation method and registered to anatomic scans using a joint probability distribution objective function [21]. The diffusion tensor at each time point was calculated using mono-exponential fitting from b=0, 500, and 1500 s/mm^2. Four main diffusion metrics were extracted at each time point. Fractional anisotropy (FA) is an expression of the degree of directional bias and hence is considered a marker of microstructural integrity. Mean diffusivity (MD) represents the average mobility of water within a voxel and may be most sensitive to edema; axial diffusivity (AD) has been shown to be sensitive to axonal injury, and radial diffusivity (RD) to demyelination[22].

Weighted averages of T1 and T2 FLAIR images were calculated to account for edema during registration of diffusion images. Tumor, tumor beds, surgical cavities/scars, and regions of edema were manually contoured, slice by slice, and censored for each patient and at each unique time point on the resampled, co-registered volumes in atlas space prior to analysis. Voxels in the censoring mask were excluded from the final ROI [9]. Successful image registration and censoring was confirmed via visual inspection by two users, including a radiation oncologist.

Superficial white matter (SWM): Volumetric MRIs were used to reconstruct the cortical surface using *FreeSurfer, 5.3.0* and to parcellate the surface into 34 gyral-based regions of interest (ROIs)[23]. Estimates of FA, MD, RD, and AD were calculated from the co-registered DTI maps by sampling up to 5 mm below the white matter surface normal at each vertex and then averaging within each ROI volume (see Figure 1).

For this study, ROIs included SWM within the right and left AC, as well as the SWM beneath the DLPFC (Figure 1). White matter beneath the AC includes the dorsal part of the cingulum bundle and is frequently implicated in cognitive set-shifting[24], whereas the DLPFC has been implicated in both set-shifting and verbal fluency[25]. Furthermore, AC was divided into the rostral AC (RAC) and caudal AC (CAC) given their proposed differential roles in cognitive processing. Specifically, the RAC has been implicated in attentional control and error detection, while the CAC may be critical when tasks demand high levels of cognitive control, including cognitive flexibility and set-shifting[26].

Co-registration of planning CTs and dose maps: The precontrast T_1-weighted MR images were co-registered to the CT simulation images that were used in the patient's original radiation treatment plan using custom software in Matlab (MathWorks, Natick MA) [21,27]. After careful visual confirmation of accurate registration, the transformation matrix from this registration was used to resample the delivered radiation dose distribution from the treatment plan to the MRI volume space, to ensure voxel-to-voxel correspondence.

Neuropsychological testing:

Neuropsychological tests of EF included measures of cognitive flexibility (Wisconsin Card Sorting Test; WCST)[28], verbal fluency and verbal set-shifting [Delis-Kaplan Executive Function System (D-KEFS)[29] Verbal Fluency Test]. All tests were conducted by a trained research assistant or a postdoctoral fellow and were supervised by a board-certified neuropsychologist. Outcome measures of interest included WCST Perseverative Errors (WCST-PE), D-KEFS Letter Fluency (LF), and D-KEFS Category Switching Accuracy (CSA). Raw scores were converted to standardized scaled or T-scores, adjusting for age and sex, and in some cases, ethnicity and years of education[30]. *Reliable change indices* (RCIs) were used to calculate neuropsychological change from baseline to 6 months post-RT, accounting for practice effects [31]. RCIs are commonly used when neuropsychological batteries are repeated because they provide a robust measure of whether the change in an individual's score over time is within or beyond that which might be accounted for by measurement variability, as well as practice effects, alone [32].

Statistics:

Diffusion changes were calculated as a percentage change from pre-RT to 3-months post-RT. Changes in EF were determined using the RCIs described above, with individual decline defined as RCI ≤ −1.0. One-sample t-test (H_0=0) was used to determine significant group decline in RCIs. Paired t-tests were used to evaluate changes in diffusion parameters. Spearman correlations were used to investigate associations between region-specific mean dose and diffusion parameter change from baseline to 3 months post-RT. Univariate and multivariate analyses were used to determine whether changes in RCIs for each of the three tests (WCST-PE, D-KEFS-LF, and D-KEFS-CSA) were associated with any of the following clinical variables: type of tumor (i.e., glioma versus non-glioma), concurrent chemotherapy, adjuvant chemotherapy, tumor location, proton therapy, antiepileptic drug use or steroid use. Linear regression analyses were used to determine whether diffusion changes were associated with changes in EF RCIs, while controlling for age, gender, and any significant univariate clinical predictors.

RESULTS

Clinical characteristics.

Clinical characteristics of the patient cohort are presented in Table 1.

Diffusion changes.

From pre-RT to 3 months post-RT, FA decreased in the right CAC [mean paired difference = −0.021 ± 0.034, t (19) = 2.38, p = .029], whereas MD increased in both the right [mean paired difference = $2.82\times10^{-5} \pm 4.93\times10^{-5}$, t (19) = −2.43, p = .026] and left [mean paired difference = $2.83\times10^{-5} \pm 5.34\times10^{-5}$, t (19) = −2.24, p = .038] CAC. Post-hoc analyses revealed that increases in MD were driven by increased RD in the right [mean paired difference = $3.49\times10^{-5} \pm 5.21\times10^{-5}$, t (19) = −2.84, p = .011] and left [mean paired difference = $2.35\times10^{-5} \pm 4.14\times10^{-5}$, t (19) = −2.42, p = .028] CAC, whereas no significant changes in AD were found during this time-period (see Figure 2). No changes were

observed in the right or left RAC or in the DLPFC during the pre-RT to 3 months post-RT (p-values >.05) (see Supplemental eFigures 1 and 2).

Neuropsychological changes.

Baseline neuropsychological scores, as well as group and individual change scores are presented in Table 2. At baseline, 5% of patients were impaired on the D-KEFS-CSA, 9% of patients were impaired on the WCST-PE, and 36% were impaired on D-KEFS-LF (i.e., > 1.0 standard deviation below the normative mean[30]). Group means revealed that the patients were largely intact in EF at baseline, with a minimal number of patients impaired. At 6-month follow-up, there was a significant decline in performance on the WCST at the group level [t (20) = −3.19, p = .005], but no significant changes were observed on the D-KEFS-LF [t(20) =.131, p > .05] or D-KEFS-CSA [t(20) = −.55, p >.05]. The absence of a group effect for the two DKEFS measures may be due to the high variability in individual change scores for these two measures (i.e., 14-19% declined, but 14-24% improved).

Association between early DTI changes and EF changes.

There were no associations between baseline clinical characteristics and changes in performance on measures of EF (p-values > .05). Therefore, only age and gender were included as co-variates in the models. Decreases in FA (r = −.57, p = .034) and increases in MD (r = .56, p = .035) and RD (r = .70, p = .005) of the left CAC were associated with decreases in D-KEFS-CSA performance (see Figure 3). In addition, increase in MD of the right CAC was associated with poorer performance on the WCST-PE (r = .56, p = .035). No other associations were found between change in diffusion parameters and change in RCIs.

Association between regional dose distribution, DTI, and EF changes.

Mean dose to each ROI is shown in Table 3. Higher mean dose to the right DLPFC was associated with greater increases in AD and RD at 3-months post-RT (r = .457, p = .049; r = .475, p = .040, respectively). In addition, the association between higher mean dose to the left CAC and reductions in FA at 3-months post-RT approached significance (r = −.447, p = .055).

DISCUSSION

In this study, we demonstrate the vulnerability of white matter beneath the cingulate cortex (i.e., cingulum bundle) to radiation-induced microstructural injury, and support findings that this region, as well as neighboring regions within the DLPFC, are sensitive to RT-dose[2,3,9,16]. In our prospective cohort of primary brain tumor patients, we also demonstrate a direct association between early post-RT injury to the dorsal cingulum and later decline in EF—a novel finding that has not been previously reported in patients undergoing fractionated brain RT. Furthermore, we demonstrate that white matter directly beneath the cortex (i.e., SWM) has the potential to be used as a biomarker of EF. The SWM connects adjacent gyri in the form of U-fibers and/or longer intralobar fibers[33] and may play a critical role in cognition by facilitating communication across neighboring cortex[15]. We introduce the use of SWM as a valuable imaging biomarker for RT-induced damage and

associated neurocognitive decline – an increasingly relevant clinical outcome in brain tumor research and RT toxicity.

Our findings of significant associations between early DTI changes and subsequent EF decline have important clinical implications for both prognostication and early intervention. Specifically, increasing RD is thought to primarily reflect demyelination[22], a process typically reversible via oligodendrocyte progenitor cells (OPCs) to avoid permanent axonal injury otherwise seen in rodents and humans[34]. Although these OPCs may be rendered dysfunctional by RT[35], promising in vivo mouse and rat studies have investigated the implantation of exogenous, functioning OPCs, which can generate oligodendrocytes and remyelinate radiated lesions[36,37]. Early identification of radiosensitivity harbingering later EF deficits, as shown here, could introduce the opportunity for such remyelination, as well as medical intervention (e.g., psychostimulants)[38] during a critical period and before permanent injury has occurred[39]. Establishing neurocognitive correlates with radiosensitive regions could also serve to dictate more elegant dose constraints for treatment planning with increasingly conformal RT techniques[40,41], or may support further investigation of heavy particle therapy (i.e., protons) to minimize dose to these clinically important, yet radiosensitive, regions [42,43].

The SWM within the dorsal cingulum demonstrated both significant post-RT changes in FA and MD, as well as an association with RT-dose and EF decline. These findings are consistent with previous studies of regional radiosensitivity, which found significant dose-dependent white matter diffusion changes in the cingulum[2,16,44,45]. However, prior work associating post-RT diffusion biomarkers with cognitive decline have focused on the ventral (i.e., parahippocampal) portion of the cingulum and associations with memory or verbal fluency[2,3]. Here, we focus on the SWM of the dorsal cingulum given the importance of this region and the overlying AC cortex to EF, and particularly to cognitive set-shifting[24,46]. Despite our prediction, we did not find significant associations between SWM changes in DLPFC and set-shifting or verbal fluency. Given the relatively large DLPFC ROI, it is possible that underlying white matter changes were present in subregions of the DLPFC that were not captured with our omnibus ROI. Furthermore, previous studies actually showed verbal fluency improvement[3], which may reflect region-specific (or skill-specific) benefits of tumor control or effects of the dynamic use of other medical interventions known to impact neurocognition (i.e., chemotherapy, antiepileptic drugs) [47,48].

EF appears particularly vulnerable to CNS-directed RT[5,6], which is concerning given the significant impact that EF deficits can have on patient QOL[7,8]. Our findings that executive dysfunction may be the result of region-specific microstructural changes suggest further research could lead to better informed RT dose constraints. Among cooperative group trials, cognitive-sparing brain radiotherapy protocols have focused on hippocampal avoidance in whole brain RT, primarily aimed at memory protection[49]. We propose that equal attention should be paid to minimizing executive dysfunction from the early stages of treatment planning, and that mitigating dose to the dorsal cingulum may be particularly important for EF preservation.

Strengths of this study include our prospective, longitudinal trial design and our use of RCIs to account for practice effects. In particular, practice effects represent a common confounding variable in prior studies that are highly problematic when measuring cognitive changes over brief time intervals (i.e., months), as is often the case in RT studies. These practice effects have not frequently been accounted for in previous studies but can be important[3,50]. In addition, we evaluated multiple components of EF in our study, including verbal and nonverbal cognitive flexibility/set-shifting as well as verbal fluency. Given that EF is a very multifaceted domain, use of only a single measure may not be sufficient for capturing complex microstructural-function relationships. It is noteworthy that, despite the heterogeneity of our patient sample, we were able to detect reliable changes in white matter microstructure and EF in the months following RT that support additional efforts.

This study has several limitations. A small number of patients with high grade malignant brain tumors had tumor progression (N = 3, 13%) during the 6-month study period. These patients were still included in the study since we only analyzed regions that were remote from the tumor and edema, and meticulously censored slice-by-slice any area near tumor, edema, or surgical scars, as in previous studies[16,27]. Although chemotherapy was not a significant predictor of EF decline in our analysis, chemotherapy has been shown previously to impair neurocognition[47] with total brain volume loss[51] and impairment of OPC function[34], which can further exacerbate white matter changes. Specifically, studies investigating the microstructural effects of chemotherapy using DTI have demonstrated reduced white matter integrity within fronto-temporal association tracts (i.e., superior longitudinal fasciculus) and decreased structural connectivity across the entire brain[52]. Future studies with larger sample sizes should model these and other potential confounding factors that were not accounted for in our analyses. We did not evaluate all white matter regions that have been shown to contribute to EF, nor did we perform a comprehensive analysis of all EFs. Rather, we targeted two regions most frequently implicated in EF and components that have been shown to impact vocational status and QOL (i.e., cognitive set-shifting and verbal fluency)[7,8]. While a 6-month post-RT time frame in this study likely captured the *onset* of late-delayed cognitive effects, longer followup periods are needed to confirm the chronicity of these EF deficits, as well as SWM changes. Our prospective trial is positioned to measure these later effects in the future. Finally, it is important to note that studies such as this have made conclusions based on group trajectories, but ultimately, understanding how to predict individual trajectories post-RT will enable physicians to engage in more personalized treatment planning.

Our study investigates the mechanisms behind post-RT neurocognitive decline and is the first to consider SWM within the prefrontal and AC regions as a biomarker of RT-induced EF decline. This work confirms the vulnerability of the dorsal cingulum to early demyelination following RT, which may suggest a window for neuroprotective interventions and/or could be used to help to inform dose-sparing protocols to preserve EF. These findings could have broad implications for all patients, from pediatric to adult, receiving RT for brain tumors or even other neurological disorders (e.g., arteriovenous malformations).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- We measured executive function (EF) decline 6 months after brain radiotherapy (RT)
- Anterior cingulate (AC) superficial white matter (SWM) is important to EF and sensitive to RT
- Diffusion imaging markers of AC SWM damage occurred 3-months post-RT
- Prospectively, superficial AC SWM damage was associated with 6-month EF decline
- SWM under the AC may be particularly vulnerable to RT effects

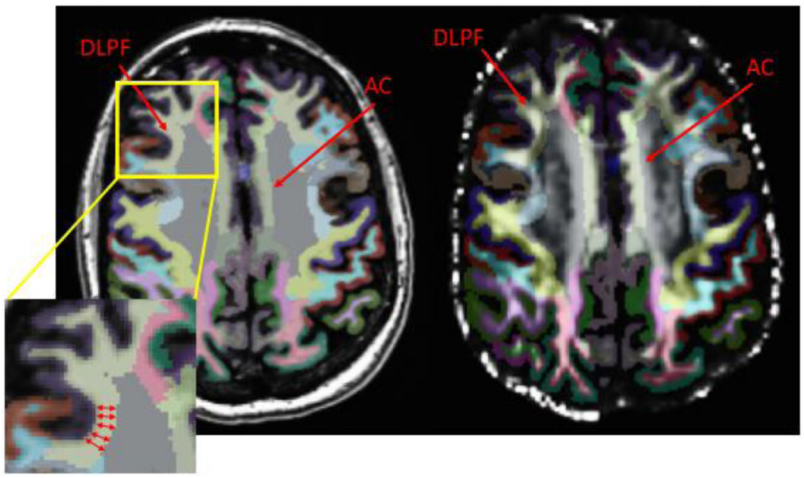

Figure 1.

Overlay of the superficial white matter (SWM) segmentation on a T1 (left) and FA (right) map. DLPF = dorsolateral prefrontal SWM and AC = anterior cingulate SWM. The dorsolateral prefrontal ROI was comprised of pars opercularis, pars triangularis, pars orbitalis caudal middle frontal gyrus, rostral middle frontal gyrus superficial white matter (SWM) of the Desikan-Killiany atlas within Freesurfer. SWM diffusion parameters were calculated by sampling up to 5 mm below the white matter surface normal at each vertex and then averaged within each ROI.

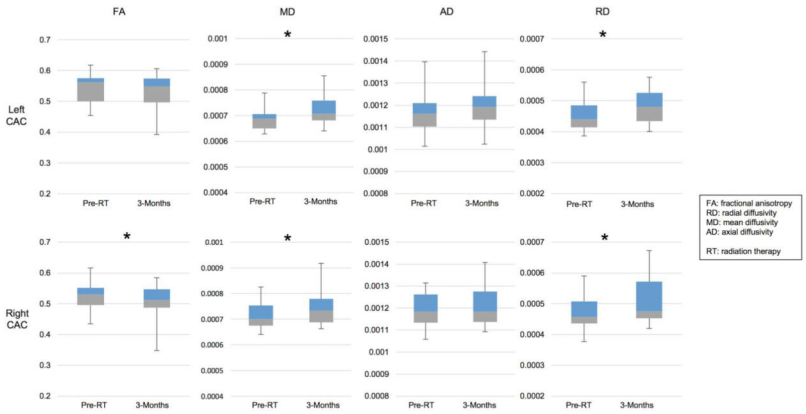

Figure 2.

Pre-radiation therapy (RT) to 3-months post-RT changes in left and right caudal anterior cingulate (CAC) SWM diffusion parameters

*Significant differences on paired t-test at $p<.05$.

Abbreviations: CAC, caudal anterior cingulate; SWM, superficial white matter.

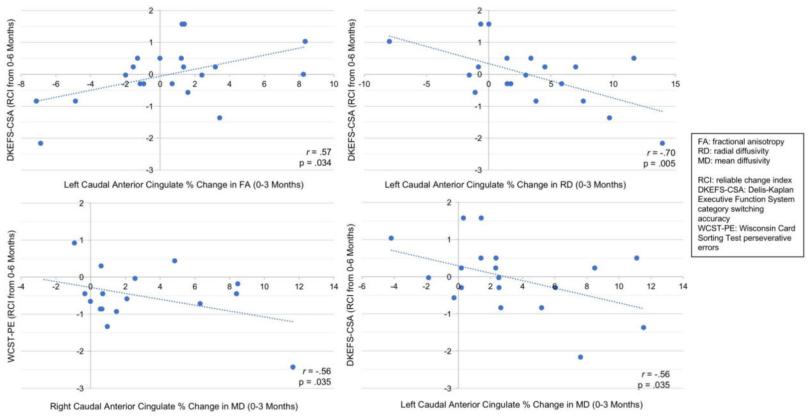

Figure 3.

Scatter plots demonstrating correlation between early percent change in left and right caudal anterior cingulate superficial white matter and executive function decline. Of note, the directionality for WCST-PE has been flipped for easier interpretation of the figure (i.e., higher values shown here indicate improved performance vs lower values indicate lower performance to be consistent for more intuitive comparison to the DKEFS tests shown).

Table 1.

Demographic and Clinical Characteristics of the Patient Sample

Demographic	**Patients, No. (%)**
Gender	
Men	11 (50.0)
Women	11 (50.0)
Age (mean, SD)	47.5 (14.8)
Education, years (mean, SD)	14.7 (2.9)
Cancer or Treatment Characteristic	**Patients, No. (%)**
Tumor Pathology *	
Meningioma	4 (18.2)
Vestibular schwannoma	2 (9.1)
Craniopharyngioma	2 (9.1)
Pituitary adenoma	1 (4.5)
Gliomas	
Pilocytic astrocytoma	1 (4.5)
Diffuse astrocytoma, IDH wild type, grade II	1 (4.5)
Diffuse astrocytoma, IDH mutated, grade II	1 (4.5)
Oligodendroglioma, IDH mutated, 1p19q co-deleted, grade II	1 (4.5)
Ependymoma, grade II	1 (4.5)
Anaplastic astrocytoma, IDH wild type, grade III	1 (4.5)
Anaplastic gemistocytic astrocytoma, IDH mutated, grade III	1 (4.5)
Glioblastoma, IDH mutated	6 (27.3)
Proton Beam Therapy	7 (31.8)
Prescription dose	
Median	5400 cGy
Range	(5040-6000 cGy)
Chemotherapy	
Concurrent	11 (50.0)
Adjuvant	13 (59.0)
Steroids	12 (54.5)
Seizures	10 (45.5)
Tumor location	
Temporal	7 (31.2)
Frontal	2 (9.1)
Parietal	3 (13.6)
Cerebellar	3 (13.6)
Suprasellar	5 (22.7)
Sphenoid Wing	1 (4.5)
Base of Skull	1 (4.5)
Surgery type	
Gross-total resection	3 (13.6)

Demographic	Patients, No. (%)
Sub-total resection/biopsy	17 (77.3)
None	2 (9.1)

* Based on the 2016 World Health Organization (WHO) classification of tumors of the central nervous system

Table 2.

Neuropsychological results at baseline and 6-months post-RT

	WCST-PE	D-KEFS-LF	D-KEFS-CSA
Pre-RT (T-score)	50.9 (11.6)	49.1 (15.7)	55.6 (13.1)
No. impaired * (%)	2/22 (9%)	8/22 (36%)	1/22 (5%)
6 Months Post-RT			
RCI (pre – 6 month)	−.55 (.752) ††	+.04 (1.52)	−.11 (.926)
No. declined † (%)	3/19 (16%)	4/21 (19%)	3/21 (14%)
No. improved (%)	0/19 (0%)	5/21 (24%)	3/21 (14%)

Abbreviations: RT, radiation therapy; RCI, reliable change index (with practice effects); WCST-PE, Wisconsin Card Sorting Test Perseverative Errors; D-KEFS-LF, Delis-Kaplan Executive Function System Letter Fluency; D-KEFS-CSA, Delis-Kaplan Executive Function System Category Switching Accuracy

* Patients were considered ‘impaired’ if they scored at least one standard deviation below the normative mean.

† Patients were considered to have ‘declined’ if they declined by > 1 RCI.

†† Significant decline at 6-month follow-up at the group level on one-sample t-test [t (20) = −3.19, p = .005].

Three patients were missing WCST-PE scores at the 6-month testing; one patient was missing D-KEFS-LF; and one patient was missing D-KEFS-CSA.

Table 3.

Regional mean dose and correlation with diffusion parameter changes from baseline to 3 months post-RT

Structure	Mean Dose (mean Gy, [SD])	FA *r*(P)	MD *r*(P)	AD *r*(P)	RD *r* (P)
Left SWM					
RAC	20.0 (16.0)	−.480 (.032)	.184 (.450)	−.077 (.753)	−.072 (.770)
CAC	18.9 (17.2)	**−.447 (.055)** *	−.053 (.836)	−.263 (.291)	.005 (.984)
DLPFC	11.6 (10.9)	−.119 (.618)	.035 (.887)	.044 (.858)	−.005 (.983)
Right SWM					
RAC	23.3 (17.0)	−.066 (.782)	−.125 (.611)	−.032 (.898)	−.130 (.596)
CAC	21.3 (17.6)	−.162 (.494)	.202 (.408)	.132 (.591)	.077 (.753)
DLPFC	14.3 (13.7)	.189 (.425)	.441 (.058)	**.457 (.049)** †	**.475 (.040)** †

*Approached significance near P<.05

†Significant at P<.05

Spearman correlation (*r*) between mean dose to SWM structure and percent change in diffusion parameters from baseline to 3 months post-RT (i.e. a negative value represents a higher dose associated with decreased percent change over time). Two patients were missing one or more diffusion values at the 3-month time point. No patients were removed from the cohort due to due poor image registration or image quality. Abbreviations: SWM, superficial white matter; Gy, Gray; SD, standard deviation; RCI, reliable change index; FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity