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Relationships between reading performance and regional spontaneous brain activity following surgical removal of primary left-hemisphere tumors: A resting-state fMRI study

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ABSTRACT

Left-hemisphere intraparenchymal primary brain tumor patients are at risk of developing reading difficulties that may be stable, improve or deteriorate after surgery. Previous studies examining language organization in brain tumor patients have provided insights into neural plasticity supporting recovery. Only a single study, however, has examined the role of white matter tracts in preserving reading ability post-surgery and none have examined the functional reading network. The current study aimed to investigate the regional spontaneous brain activity associated with reading performance in a group of 36 adult patients 6–24 months following left-hemisphere tumor resection. Spontaneous brain activity was assessed using resting-state fMRI (rs-fMRI) regional homogeneity (ReHo) and fractional amplitude low frequency fluctuation (fALFF) metrics, which measure local functional connectivity and activity, respectively. ReHo in the left occipito-temporal and right superior parietal regions was negatively correlated with reading performance. fALFF in the putamen bilaterally and the left cerebellum was negatively correlated with reading performance, and positively correlated in the right superior parietal gyrus. These findings are broadly consistent with reading networks reported in healthy participants, indicating that reading ability following brain tumor surgery might not involve substantial functional re-organization.

1. Introduction

Therapeutic advances in the treatment of primary brain tumors have improved the 5-year survival rate to 20–40% (Allemani et al., 2018), however surviving patients may still experience neurological, functional, and psychosocial impairments that impact their daily activities and overall quality of life (Huang and Sliwa, 2011; Teng et al., 2021). Left-hemisphere intraparenchymal primary brain tumor patients in particular are at risk of developing reading difficulties that can persist following surgery (Brownsett et al., 2019; Cargnelutti et al., 2020b; Guarracino et al., 2021; Tomasino et al., 2020). The focus of this paper is on *oral reading*, where difficulties may be characterized by issues in decoding real and/or pseudo words. Reading is an important skill that enables participation in a range of activities across work, family, social,

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and leisure domains. As a result of reading difficulties, people with aphasia can experience loss, frustration and disappointment, as well as limitations in their ability to fully participate in their communities including returning to work (Hinckley, 2002; Kjellén et al., 2017).

In the week following brain tumor removal, estimates of reading impairment are as high as 58–79% but, in the 3–6 months that follow, the majority of patients recover their reading ability (Cargnelutti et al., 2020b; Tomasino et al., 2020). This recovery may be indicative of neural plasticity and reorganization of the language system that compensates for changes related to the tumor, surrounding edema, resection, and peri-resection treatment effects. Several studies have used multi-modal neuroimaging to examine language reorganization in brain tumor patients, providing evidence for plasticity in both peritumoral and contra-tumoral regions and in structural and functional connectivity (see Cargnelutti et al., 2020a for a review; Deverdun et al., 2020). However, to our knowledge, only a single study to date has focused specifically on reorganization of the reading network in brain tumor patients. In that study, Cargnelutti et al. (2020b) used diffusion tensor imaging to evaluate the role of white matter in preserving reading ability four months after surgery. They found that the length of streamlines of the left uncinate fasciculus and the bilateral arcuate fasciculus increased in patients with improved reading performance. These findings provide another reason for the sparing of these tracts during neurosurgery. While this study sheds light on the structural connectivity changes that support reading in brain tumor patients after surgery, further studies are needed to understand the functional network changes that also occur.

Resting-state functional connectivity associated with reading has been investigated in healthy participants using region-of-interest (ROI) based approaches (e.g., Hampson et al., 2006; Koyama et al., 2010). The resting-state functional connectivity method typically involves an a priori selection of ROIs derived from task-based fMRI results in healthy participants or from lesion-symptom mapping in stroke patients to identify patterns of network activity. However, selecting ROIs based on these criteria is not appropriate for brain tumor patients whose functional networks are likely to have undergone substantial functional re-organization both prior to and following surgical resection and adjuvant treatments (Cargnelutti et al., 2020a).

An alternative to ROI-based approaches is to use regional measures of resting-state fMRI (rs-fMRI), such as regional homogeneity (ReHo) and fractional amplitude of low-frequency fluctuation (fALFF). These measures have been shown to predict reading performance in both alphabetic and non-alphabetic script languages, such as English and Chinese, respectively (Koyama et al., 2020; Xu et al., 2015). The measures use a data-driven approach to provide complementary information about local functional properties in the brain. Specifically, ReHo is a measure of the synchronization of time series among neighboring voxels (Liu et al., 2010; Zang et al., 2004) that provides an estimate of *short-distance functional connectivity*, while fALFF is a measure of the low-frequency signal fluctuation in a time series (Yang et al., 2007, 2007, 2007; Zou et al., 2008) that provides an estimate of frequency-specific *local neural activity*. ReHo can be assessed using either Kendall's coefficient of concordance (KCC-ReHo; Kendall and Gibbons, 1990) or coherence in the frequency domain (Cohe-ReHo; Sun et al., 2004). Cohe-ReHo has been proposed to be less sensitive to random noise induced by phase differences in time series than KCC-ReHo (Liu et al., 2010). Physiological noise due to neurovascular uncoupling may introduce phase delay in time series, hence it is possible that Cohe-ReHo is a more sensitive measure of ReHo in tumor patients. Both ReHo and fALFF have been used successfully to evaluate spontaneous brain function in patients with brain tumors (e.g., Agarwal et al., 2017; Boyer et al., 2016) but relationships between these measures and reading performance have yet to be examined in this population.

1.1. Current study objective

The current study aimed to investigate the spontaneous neural activity associated with the organization of reading performance in patients following surgical resection of a left-hemisphere intraparenchymal primary brain tumor. Rs-fMRI data, together with structural MRI and behavioral data, were collected from 36 patients 6–24 months post-surgery. The rs-fMRI data were indexed using three measures of spontaneous regional activity: (1) KCC-ReHo; (2) Cohe-ReHo; (3) and fALFF. Language performance was evaluated using a standardized formal language battery, the Comprehensive Aphasia Test (CAT; Swinburn et al., 2004). We focused on the reading tasks from the CAT for our current analyses, and examined relationships between the rs-fMRI measures and reading performance at the whole-brain level using linear regression analyses.

2. Methods

2.1. Participants

Forty-seven participants who underwent surgery to remove a primary intraparenchymal left hemisphere brain tumor between 6 and 24 months earlier were recruited as part of a larger study examining long-term language outcomes (Brownsett et al., 2019; Kearney et al., 2022). Their surgery was conducted at the Princess Alexandra, Royal Brisbane and Women's, and Royal Melbourne and Melbourne Private Hospitals by SO, RLJ, and KD, respectively. All patients were right-handed and native speakers of English. Exclusion criteria included non-primary and non-intraparenchymal tumors, history of uncorrected hearing or visual impairment, other neurological or psychiatric condition, substance abuse, head injury, or metal implants. All provided written informed consent in accordance with the protocols approved by the Human Research Ethics Committees at their respective Hospitals (HREC/14/QPAH/367; HREC/15/MH/58). From this sample, a subset of 36 patients (17 female) were selected who had both structural and rs-fMRI datasets. Table 1 summarizes the patients' demographic and clinical data. Table 2 provides information about the surgical technique employed for 24/36 patients; this information was not available for the remaining 12 participants. We also do not have information regarding the clinical course or long-term survival of this cohort.

2.2. Reading assessment

All patients were assessed in a single session at their respective hospitals using the CAT (Swinburn et al., 2004), with sessions usually taking place on the same day as image acquisition (median = 0 days, IQR = 0). For the present study, we used the CAT's Total Reading score, which aggregates performance across subtests of reading aloud of words, complex words, function words, and nonwords and provides a reasonably detailed clinical characterization of reading performance.

Table 1
Patients' demographic and clinical data.

Variables		N	Mean ± SD	Range
Age (years)		36	45.2 ± 14.2	19–74
Education (years)		36	12.9 ± 2.4	10–18
Time post-surgery (days)		36	304 ± 136	168–710
WHO grade	2	22	n/a	2–4
	3	1		
	4	13		
Resection + lesion volume (ml)		36	48 ± 52.7	3.25–272

SD: standard deviation, WHO: World Health Organization 2016 Classification of Central Nervous System Tumors (Diamandis and Aldape, 2018), Resection+: Lesion comprising the primary resection plus voxels with hyperintense FLAIR and gadolinium-enhanced signal from residual tumor, edema, and peri-treatment effect.

Table 2
Surgical technique employed for 24/36 participants.

Variables		N (%)
Awake surgery		12 (50)
Intraoperative DES language map		11 (45.8)
Intraoperative MRI		3 (12.5)
Gliolan		3 (12.5)
Resection	Partial	22 (91.7)
	Total	2 (8.3)

DES = direct electrical stimulation, MRI: magnetic resonance imaging.

Raw scores were converted to T-scores (lower scores denote poorer performance) and compared to the cut-off for impairment, defined as being below the fifth percentile of a sample of neurologically healthy controls (Swinburn et al., 2004). Using this criterion, 4/36 (11%) of patients had a reading impairment. Fig. 1 shows the distribution of the patients' T-Scores. Reading impairment was not explained by concomitant hemianopia; performance on a line-bisection subtest of the CAT was within normal range for 35/36 participants, and the remaining participant scored highly on the reading subtests.

Table 3 shows Spearman's rank order correlations between demographic and clinical data and the T-scores. Only years of education significantly correlated with reading scores; more years of education was associated with better reading performance.

2.3. MRI procedure

All patients underwent a 45-min MRI session comprising structural, diffusion and rs-fMRI acquisitions at their respective hospital sites. For the rs-fMRI scan, participants were instructed to remain still with their eyes open and to avoid going to sleep.

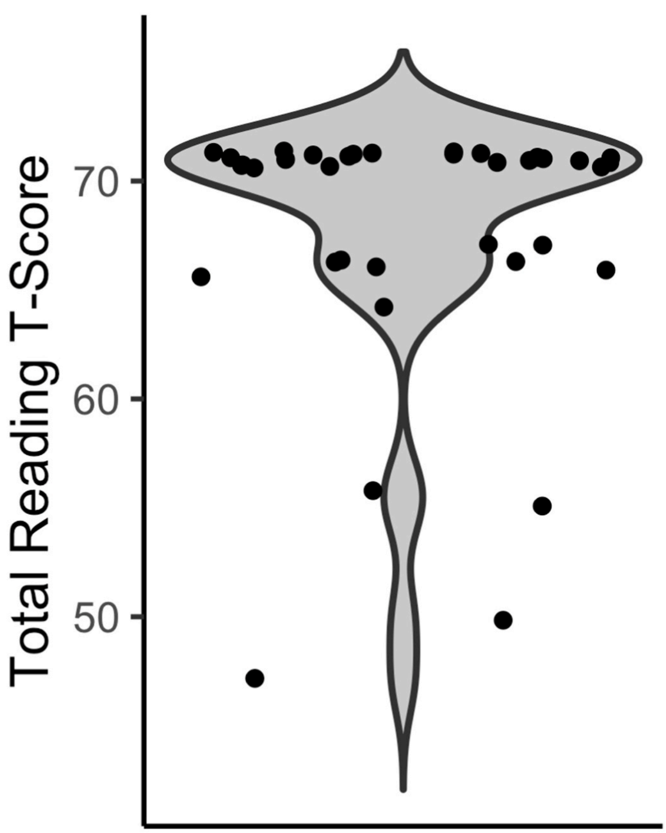

Fig. 1. Violin plot showing the distribution of T-Scores on the Total Reading measure from the CAT (Swinburn et al., 2004). Lower scores indicate poorer performance.

Table 3
Demographic and clinical correlations with reading t-scores.

Variable	*Rho*	*p*
Age (years)	−.18	.306
Education (years)	.59	<.001
Time post-surgery (days)	−.10	.575
WHO grade	−.26	.132
Resection + lesion volume (ml)	−.14	.41

WHO: World Health Organization, Resection+: Lesion comprising the primary resection plus voxels with hyperintense FLAIR and gadolinium-enhanced signal from residual tumor, edema, and peri-treatment effect.

2.4. Image acquisition

The imaging sessions were conducted on Siemens Skyra, Trio, or Prisma 3 T MRI systems (Erlangen, Germany). At all sites, rs-fMRI was acquired with whole-brain coverage using an echo-planar imaging sequence with the following parameters: Skyra (TE = 30 ms; TR = 2000 ms; flip angle = 90°; FOV = 94 × 94; voxel-size = 2.23 × 2.23 × 5.5 mm; 21 axial slices; 198 vol; N = 7); Prisma 1 (TE = 30 ms; TR = 2700 ms; flip angle = 80°; FOV = 72 × 72; voxel-size = 2.64 × 2.64 × 2.6 mm; 50 axial slices; 160 vol; N = 11); Prisma 2 (TE = 30 ms; TR = 2050 ms; flip angle = 80°; FOV = 72 × 72; voxel-size = 2.64 × 2.64 × 2.6 mm; 50 axial slices; 210 vol; N = 16); and Trio (TE = 30 ms; TR = 2700 ms; flip angle = 90°; voxel-size = 3.44 × 3.44 × 3.3 mm; 36 axial slices; FOV = 64 × 64; 190 vol; N = 2). At all sites, high resolution FLAIR and post-gadolinium contrast MPRAGE T_1-weighted images were also acquired with the following parameters: Prisma (FLAIR; TR = 5000ms, TE = 332ms, TI, 1800ms, FOV 256x256 × 176mm, 1 mm^3 voxels; MPRAGE: TR = 2100ms, TE = 3.03ms, TI 1100ms, FOV 256x240 × 192mm, 1 mm^3 voxels), Skyra (FLAIR; TR = 7000ms, TE = 381ms, TI, 2050ms, FOV 250x250 × 160mm, 0.98 mm^3 voxels; MPRAGE; TR = 2020ms, TE = 2.35ms, TI 1020ms, FOV 256x256 × 176mm, 1 mm^3 voxels), and Trio (FLAIR; TR = 6000 ms TE = 390ms, TI 2100ms, FOV 250x250 × 160mm, 0.98 mm^3 voxels; MPRAGE: TR = 2150ms, TE = 3.03ms, TI 1100ms, FOV: 256x240 × 160mm, 1 mm^3 voxels).

2.5. Preprocessing

Lesions were drawn manually on the T1-weighted and FLAIR images using MRIcroGL software (v6; https://www.nitrc.org/projects/mricrogl/) in axial orientation. Two lesion maps were drawn per participant: one representing the primary *resection* and one comprising of the resected area plus voxels with FLAIR hyperintense and gadolinium-enhanced signal from residual tumor, edema and/or peri-treatment effects (*resection*+). The FLAIR images were coregistered to the T1-weighted images, and these parameters were used to reslice the lesion maps into the native T1 space. The T1-weighted images and lesion maps were then normalized into MNI standard space via the Clinical Toolbox (Rorden et al., 2012) in Statistical Parametric Mapping (SPM12; Wellcome Department of Cognitive Neurology, London, UK) using enantiomorphic normalization (Nachev et al., 2008) and a lesion-mask cost function (Brett et al., 2001).

The rs-fMRI preprocessing steps were performed using the RESTplus toolkit (v1.25; Jia et al., 2019). The initial five volumes from all series were discarded, and slice timing correction performed for the different acquisitions per site. Next, each time series was realigned to the first image of the initial series and a mean image generated and used to coregister the realigned series to the T1-weighted image. The realigned and coregistered volumes were then normalized into MNI standard space in SPM12 using the transformations for each patient derived from the Clinical Toolbox (Rorden et al., 2012). Detrending was applied to remove linear trends in the normalized time series, and nuisance covariates were next removed via linear regression: Head motion effects were removed using the Friston 24-parameter model (Friston et al., 1996), followed by white matter and cerebrospinal signals. Global signal regression was not performed. Finally, temporal bandpass filtering (0.01–0.08 Hz) was performed prior to calculating ReHo measures but not for fALFF.

2.6. ReHo and fALFF calculations

All ReHo and fALFF calculations were performed in RESTplus (v1.25; Jia et al., 2019). The first measure of ReHo was calculated based on Kendall's rank-based coefficient of concordance (KCC-ReHo; Zang et al., 2004) that assesses the synchronization between a given voxel's signal time course and those of its 26 nearest neighboring voxels. The second method of calculating ReHo assessed coherence in the frequency domain (Cohe-ReHo; Liu et al., 2010; Sun et al., 2004). fALFF (Zou et al., 2008) was calculated as the ratio of the power spectrum of low-frequency signal fluctuations (0.01–0.08 Hz) to that of the entire frequency range (0–0.25 Hz). ReHo and fALFF maps were Z-standardized and then smoothed with a 6 mm FWHM isotropic Gaussian kernel.

2.7. Data analysis

We performed separate linear regressions in SPM12 with the ReHo and fALFF voxel values as dependent variables, CAT Total Reading T-scores as the independent variable, and age, gender, education in years, time post-surgery (TPS), WHO grade, scanner acquisition and resection + lesion volume as nuisance covariates. For all analyses, a height threshold of $p < .001$ was adopted with a spatial cluster extent threshold of $p < .05$ (FWE corrected via the Bonferroni procedure across the whole brain). Suprathreshold results were localized using the Automated Anatomical Labelling atlas (AAL3v1; Rolls et al., 2020).

3. Results

3.1. Lesion data

Fig. 2 shows the lesion overlap maps based on the binarized lesion maps of all patients. All figures follow neurological convention with the left hemisphere of the brain appearing on the left side of the image. The maximum lesion overlap for the primary resection was found in the left superior middle frontal gyrus ($N = 6$). The maximum lesion overlap for the resection+ was found in the left middle frontal gyrus ($N = 8$).

3.2. Regression analyses

Table 4 and Fig. 3 show the results of the regression analyses predicting measures of ReHo and fALFF from reading performance.

Table 4
MNI coordinates of peak maxima showing significant relationships between reading performance and ReHo and fALFF.

Analysis	Peak MNI (x y z)			Z score	Cluster size (Voxels)
KCC-ReHo decreases					
Left Lingual Gyrus	−14	−88	−4	4.83	1084
Right Postcentral Gyrus	22	−44	64	4.40	394
Cohe-ReHo decreases					
Left Middle Occipital Gyrus	−38	−72	6	4.97	841
Right Precuneus	12	−52	58	4.06	213
fALFF increases					
Right Superior Parietal Gyrus	22	−62	62	3.96	257
fALFF decreases					
Left Putamen	−28	8	−6	4.18	525
Right Putamen	26	10	−8	4.12	814
Left Cerebellum Lobule IV/V	−8	−56	−22	3.78	203

p < .001 and p < .05 (FWE cluster-corrected).

3.2.1. ReHo

No regions showed significant positive correlations between either ReHo measure and reading performance. However, for KCC-ReHo, two clusters with peaks in the left lingual gyrus and right postcentral gyrus showed significant negative correlations, i.e., better reading performance was associated with reduced KCC-ReHo in these areas (see Table 3 and Fig. 3). Cohe-ReHo was also significantly negatively correlated with reading performance in the left middle occipital gyrus and the right precuneus.

3.2.2. fALFF

Significant positive and negative correlations were observed between fALFF and reading performance in several cortical and subcortical regions, respectively (Table 3, Fig. 3). The right superior parietal gyrus showed a significant positive correlation between fALFF and reading scores, while the bilateral putamen and cerebellum showed the opposite relationship, i.e., better reading performance was associated with reduced fALFF in these subcortical areas.

4. Discussion

The current study investigated the relationship between reading performance and measures of spontaneous regional brain activity derived from rs-fMRI 6–24 months following surgery for left-hemisphere primary tumors. We found that the majority of patients' reading performance was within normal limits, with only 11% showing impairment on the CAT (Swinburn et al., 2004). When associations with measures of

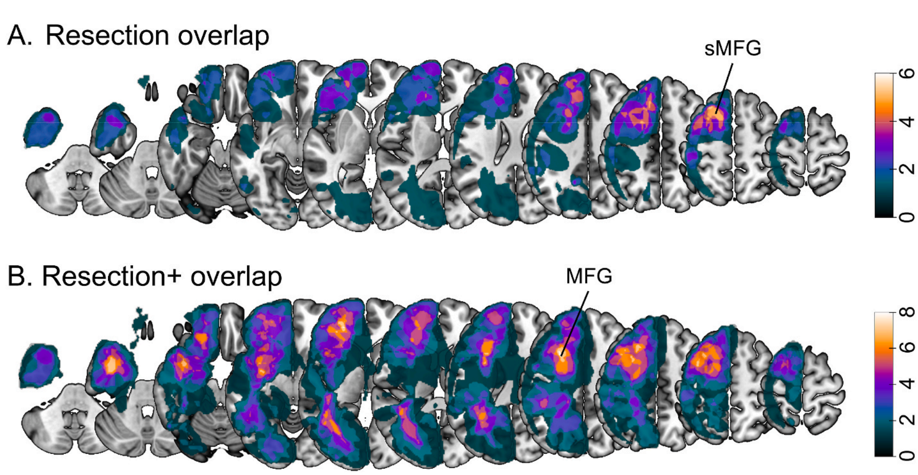

Fig. 2. Tumor lesion overlap maps. Lesions were delineated based on (A) the primary resection, and (B) the primary resection plus voxels with hyperintense FLAIR and gadolinium-enhanced signal from residual tumor, edema, and peri-treatment effect. The overlap maps are overlaid on axial slices of the MNI152 template provided with MRIcroGL software. Color bars indicate the number of participants with overlapping lesions in a given voxel. sMFG = superior middle frontal gyrus; MFG = middle frontal gyrus.

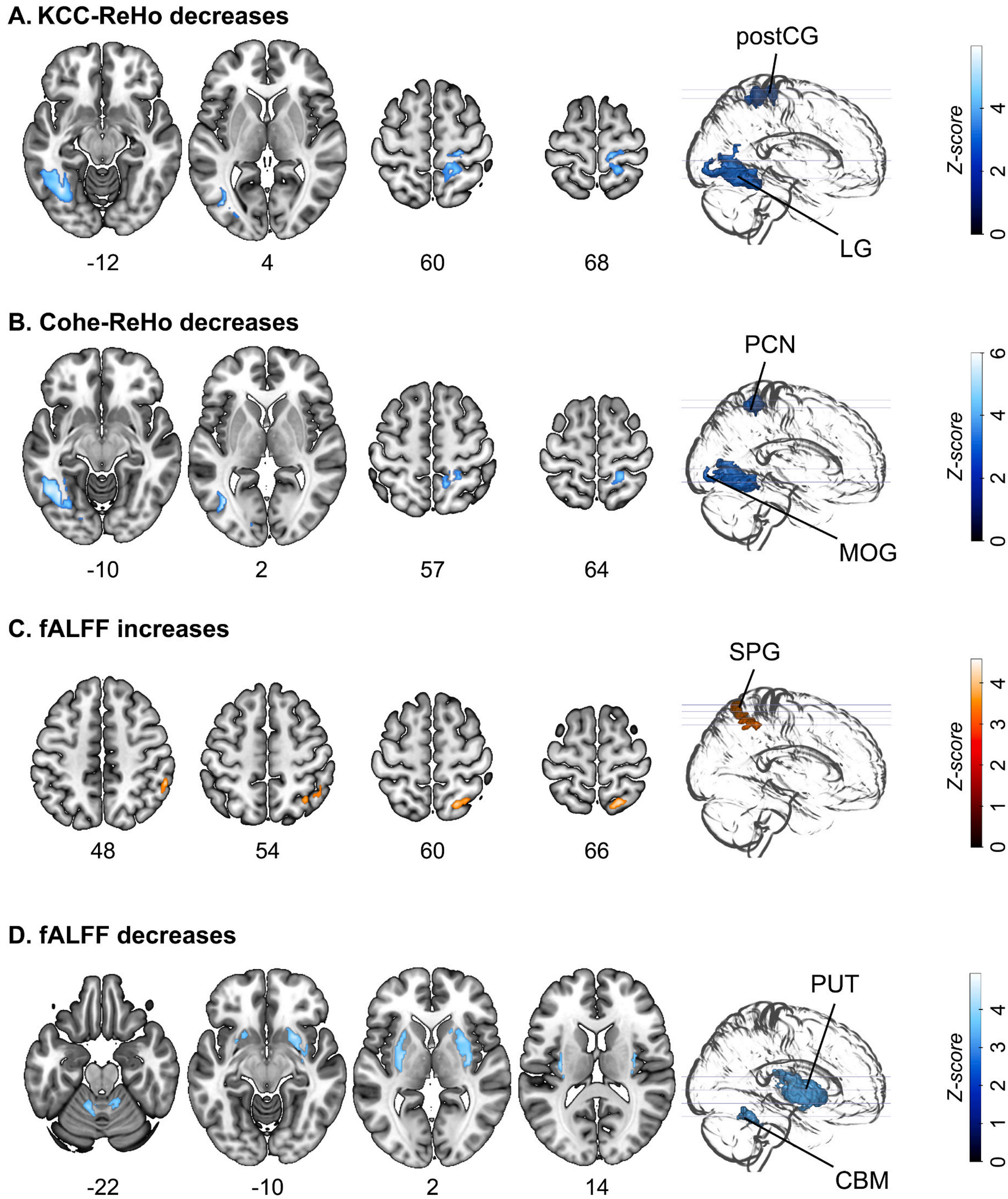

Fig. 3. Results of regression analyses predicting ReHo and fALFF from reading performance overlaid on axial slices and a 3D glass-brain of the MNI152 template provided with MRIcroGL software. (A) Decreases in KCC-ReHo associated with reading performance; (B) Decreases in Cohe-ReHo associated with reading performance; (C) Increases in fALFF were associated with associated with reading performance; (D) Decreases in fALFF associated with reading performance. CBM = cerebellum, LG = lingual gyrus, PCN = precuneus, MOG = middle occipital gyrus, postCG = post-central gyrus, PUT = putamen, SPG = superior parietal gyrus.

ReHo were examined, a negative correlation was observed between reading performance and ReHo in left occipito-temporal and right superior parietal regions. When examined relative to fALFF, reading performance was associated with increases in fALFF in the right superior parietal gyrus but decreases in fALFF subcortically in the putamen bilaterally and in the left cerebellum. Together, these findings indicate possible mechanisms that explain reading performance in individuals in the chronic phase post-brain tumor surgery.

4.1. ReHo

Although the functional networks of brain tumor patients are often considered to have undergone substantial re-organization both prior to and following surgical resection and adjuvant treatments (for review, see Cargnelutti et al., 2020a, b), our findings for ReHo were surprisingly consistent with results reported for reading performance in healthy participants. For example, the significant associations we observed in the left occipito-temporal regions are consistent with the role identified for these regions in orthographic processing in meta-analyses of reading using task-based fMRI in healthy participants (e.g., Martin et al., 2015; Murphy et al., 2019; Taylor et al., 2013). Similarly, the right superior parietal regions have been implicated in word reading (Martin et al., 2015) with the precuneus involved in the semantic processing of words (Binder et al., 2009).

For all regions, lower ReHo was associated with better reading performance. This pattern of negative brain-behavior correlations was consistent with Koyama et al.'s (2020) observations in young healthy adults, although they found that lower ReHo in the thalamus was associated with better reading performance. ReHo measures local functional coupling or synchronization and an inverse relationship with behavior might reflect greater (but less efficient) recruitment of neural resources in those with reduced performance. Notably, we did not find significant associations for the thalamus, however, this may reflect differences in the single word/non-word reading tasks employed in our study vs. the Letter Word Identification subtest from the Woodcock-Johnson Tests of Achievement Third Edition (Woodcock et al., 2007) in Koyama et al. (2020). A negative ReHo-behavior correlation has also been found for other disorders. For example, higher local connectivity has been associated with more severe symptomology in autism spectrum disorder and schizophrenia (Dajani and Uddin, 2016; Zhao et al., 2019).

We also did not observe any evidence for differential sensitivity of Cohe-ReHo and KCC-ReHo measures, despite our expectation that the latter might be more affected by physiological noise due to the potential for neurovascular uncoupling to introduce phase delay in the time series (Liu et al., 2010). However, there were slight differences in the anatomical localization of the peak reading-related activity identified by both measures, with Cohe-ReHo revealing relationships in the left middle occipital gyrus and right precuneus and KCC-ReHo showing associations in the left lingual and right postcentral gyrus. Consequently, we suggest future rs-fMRI studies of brain tumor patients continue to report results from both measures.

4.2. fALFF

Our cortical findings for fALFF were also broadly consistent with those reported for reading performance in healthy participants. The significant positive association between fALFF in the right superior parietal gyrus and reading performance is consistent with this region being involved in the processing of words and nonwords when reading aloud (Murphy et al., 2019). Koyama et al. (2020) also showed a significant positive correlation between fALFF in the superior parietal gyrus and reading performance, however, their finding was in the left hemisphere. The difference may have arisen due to patients in the current study having a large lesion overlap in the nearby left angular gyrus. Resection of this region and/or neurovascular uncoupling may have impacted local intrinsic brain activity and the measure of fALFF in the left hemisphere. Note, however, that a cluster spanning the left superior parietal and postcentral gyri did approach significance (peak MNI = [−20, −44, 70], Z-score = 3.88, cluster size = 162, p = .051, FWE corrected).

Subcortically, the significant negative associations between fALFF in the bilateral putamen and left cerebellum (lobules IV/V) and reading performance are also consistent with prior findings; these regions have been implicated in meta-analyses of task-related reading activity in healthy participants (e.g., Martin et al., 2015; McNorgan et al., 2014; Murphy et al., 2019; Turkeltaub et al., 2002) and studies of functional connectivity associated with reading (e.g., Alvarez and Fiez, 2018; Seghier et al., 2014). Lesion-symptom mapping studies in post-stroke patients have also shown that damage to the putamen results in worse reading scores on the CAT (Seghier et al., 2014). The putamen has traditionally been associated with speech motor functions (Chang and Guenther, 2020; Cler et al., 2021; Copland and Angwin, 2019), while cerebellar lobules IV and V have been associated with sensorimotor processing (Stoodley and Schmahmann, 2010), but not specifically speech motor processing more commonly associated with lobule VI (Guenther, 2016; Turkeltaub et al., 2002). The right cerebellum has also been implicated in orthographic processing during reading (Alvarez and Fiez, 2018). Given the direction of the effect, reading aloud may increase the demand to these sensorimotor regions; a possible mechanism of disruption in brain function for those with poor reading performance.

4.3. Weak evidence of plasticity in the contra-tumoral region at whole brain level

The left middle frontal gyrus, the location of the maximum lesion overlap in the current study, has been implicated in meta-analyses of reading tasks (e.g., Martin et al., 2015). Given that neural plasticity both pre- and post-surgery can involve contra-tumoral regions (e.g., Cargnelutti et al., 2020a; Deverdun et al., 2020), we considered it reasonable to expect that the ReHo or fALFF measures in the right middle frontal gyrus may have been correlated with reading performance. This was not the case at the whole brain level, suggesting that reading performance post-surgery might not engage a more extensive, re-organized network. Note, however, that the negative correlation between Cohe-ReHo in the right middle frontal gyrus and reading performance did approach significance (peak MNI = 28, 30, 40], Z-score = 5.56, cluster size = 171, p = .055, FWE corrected). Given that we did not examine reading performance immediately following surgery and that reading performance may have been within normal limits at that point in time for the majority of participants, we acknowledge that plasticity may not have occurred in this cohort. This may especially be true for patients with low-grade gliomas who typically show strong potential for neural reorganization in response to slow-growing tumors (Desmurget et al., 2007; Duffau, 2005; Pasquini et al., 2022). It is also possible that the residual tumor cortex, as well as the edema and peri-treatment affected areas, may have continued to be recruited during reading (Aabedi et al., 2021), minimizing the need for recruitment of the contralateral regions.

4.4. Strengths and limitations

The current study has several strengths. To our knowledge, this study is the first to show relationships between reading performance and regional measures of spontaneous brain activity from rs-fMRI in chronic post-operative patients. These regional measures of rs-fMRI are relatively easy and quick to acquire clinically, compared to task-based fMRI, and have potential in examining change in functional reading networks over time. Additionally, the study was conducted rigorously, with a number of controls to ensure the validity of the data (e.g., double entry of behavioral scores, inclusion of relevant covariates of non-interest in all analyses). Finally, in the spirit of transparency, the processed study data are available on the Open Science Framework for other research groups to access and use.

The findings of the current study should also be considered in light of a number of limitations. First, four different rs-fMRI sequence acquisitions were used across the different data collection sites, which can introduce measurement bias into the dataset (Yamashita et al., 2019). We included acquisition as a nuisance regressor in our analyses to mitigate this bias, however, future studies should aim where possible to use homogenous sequence acquisitions across sites. Second, different tumor grades may have different mechanisms of neurovascular uncoupling; neurovascular uncoupling in high-grade tumors is thought to be related to tumor angiogenesis (Hou et al., 2006), whereas in low-grade tumors may be due to astrocytic dysfunction (Pillai and Zacá, 2011; Watkins et al., 2014). The different mechanisms may differentially affect the regional measures of rs-fMRI employed in this study. Again, we minimized the impact of tumor grade in our analyses by including it as a nuisance regressor. Third, patients' vision was within normal limits pre-operatively but was not re-assessed after surgery. To rule out the effect of vision deficits on reading performance, vision should be evaluated before and after surgery in addition to testing hemianopia with line-bisection as we did. Fourth, we assessed reading performance and resting-state connectivity at a single timepoint in the chronic phase post-surgery and cannot draw conclusions regarding reading reorganization occurring at different timepoints, e.g., presurgically and immediately post-surgery (Prasse et al., 2023). Finally, the reading subtests in the CAT measure reading performance at the single word/nonword level only (Swinburn et al., 2004) and the total reading score employed in our analyses does not consider the different routes that may be involved in, for example, word versus nonword reading. Future work in this area would benefit from examining the neural basis of more comprehensive measures of reading that may reflect more functional reading tasks and with a greater sample size that would allow evaluation of different pathways to reading.

4.5. Conclusion

In summary, this is the first study to show relationships between reading performance and regional measures of spontaneous brain activity from rs-fMRI in chronic post-operative patients. Our results show that low-frequency signal fluctuations in rs-fMRI may be a useful tool for characterizing functional networks implicated in reading in patients with chronic post-surgical aphasia and as a potential outcome measure for treatment. Overall, our findings are broadly consistent with reading networks reported in healthy participants, indicating reading ability following brain tumor surgery might not involve substantial functional re-organization.

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Declarations of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that support the findings of this study are openly available on OSF at https://osf.io/pgfv2/.

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