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GSH and GABA decreases in IDH1-mutated low-grade gliomas detected by HERMES spectral editing at 3 T in vivo

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Abstract

Isocitrate dehydrogenase 1 (IDH1) mutational status is an important prognostic biomarker in gliomas. γ-aminobutyric acid (GABA) and reduced glutathione (GSH) play an important role in energy production, which is related to tumor progression. Hadamard Encoding and Reconstruction of Mega-Edited Spectroscopy (HERMES) is able to detect GABA and GSH in healthy controls. This study aims to examine GABA and GSH alterations in IDH1-mutated low-grade gliomas using HERMES. We prospectively enrolled 14 suspected low-grade gliomas and 6 healthy control patients in this study, all cases underwent a 3T MRI scan, including T1-weighted imaging and HERMES acquisition with a volume of interest 3×3×3 cm^3. HERMES detects a "GABA+" signal that includes contributions from macromolecules and homocarnosine. GABA+ and GSH in tumor foci (group 1), contralateral cerebral regions (group 2) and healthy controls (group 3) were quantified using Gannet. The fitting errors and SNR of HERMES for GABA+ and GSH were analyzed; FWHM of the unsuppressed water signal was also recorded. The Wilcoxon signed-rank

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test was performed to test for differences between contralateral GABA+ and GSH levels, and differences in GABA+, GSH and fitting errors/SNR between the three groups were analyzed using analysis of variance (ANOVA). Eleven IDH1-mutant low-grade gliomas (5 Female and 6 Male, age 33–69) and 6 healthy subjects (2 Female and 4 Male, age 35–60) were finally enrolled this study. The mean water linewidth across all subjects was 9.67 ± 2.28 Hz. The Wilcoxon signed-rank test revealed that GABA+ and GSH were decreased significantly in glioma foci compared with contralateral regions, whereas no differences were seen between the left and right regions in healthy controls. ANOVA showed that GABA+ and GSH levels in tumor were lower than contralaterally and in healthy controls, while no differences were observed between the contralateral healthy tissue and healthy controls. No differences of fitting errors or SNR were found between tumors, contralateral regions or healthy controls. Our results suggest that HERMES is a reliable tool to simultaneously measure GABA and GSH alterations in low-grade gliomas with IDH1 mutations.

Keywords

glioma; isocitrate dehydrogenase; HERMES; GABA; glutathione

Introduction

Glioma is the most common type of primary brain tumor, classified as either low-grade (WHO grade I and II) or high-grade (WHO grade III and IV) based on the histopathological and clinical criteria, and the prognosis remains poor (Louis et al., 2007; Wen and Kesari, 2008). The incidence of isocitrate dehydrogenase 1 (IDH1) mutations is very high in low-grade gliomas (Cancer Genome Atlas Research et al., 2015), and IDH1-mutant gliomas are associated with much better prognosis than IDH1 wild-type (Sanson et al., 2009). IDH1 mutational status was integrated into the 2016 WHO classification as a vital biomarker of gliomas (Louis et al., 2016).

The metabolic alterations seen in gliomas with IDH1 mutation are the subject of much recent interest, including gamma-aminobutyric acid (GABA) (Jalbert et al., 2017) and GSH (Gu et al., 2015). GABA is extensively metabolized in astrocytes, playing an important role in providing carbon backbone for glutamine, supporting and regulating neuronal functions of glioma-related astrocytes, and it can be also used as an alternative fuel to support astrocyte oxidative metabolism(Andersen et al., 2020). GABA is derived from the tricarboxylic acid (TCA) cycle intermediate alpha-ketoglutarate, which is itself formed by IDH1catalyzed oxidative decarboxylation of isocitrate (Turkalp et al., 2014). Cells with mutant IDH1 produce 2-HG rather than alpha-ketoglutarate (Gelman et al., 2018), and we hypothesis that the lack of availability of this important GABA precursor in IDH1 glioma would affect the GABA concentration.

GSH is the most abundant intracellular antioxidant (Gu et al., 2015), functioning in the protection of cells against oxidative damage caused by reactive oxygen species (ROS) (Juan et al., 2008), and low GSH was reported in gliomas before (Kudo et al., 1990). NADPH is a required cofactor to reduce oxidized glutathione (GSSG) back to GSH (Ren et al., 2017).

Mutant IDH1 is a cytosolic enzyme that draws upon the cellular pool of NADPH, oxidizing it to NADP+ while converting alpha-ketoglutarate to the metabolite 2-hydroxyglutarate (2-HG) (Dang et al., 2009). Altered NADPH might change the GSH/GSSG redox balance but may not necessarily lead to less actual glutathione, and we hypothesize the decrease of NADPH in mutant IDH1 glioma may result in the imbalance of GSH/GSSG, exhausting the levels of GSH.

The concentration of GABA and GSH in the brain is too low to be detected using conventional single-voxel magnetic resonance spectroscopy (MRS). However, edited MRS, e.g. Mescher-Garwood Point-resolved Spectroscopy (MEGA-PRESS), is able to detect GABA+(Gong et al., 2018b; Mescher et al., 1998) (an edited signal combining GABA and co-edited macromolecular and homocarnosine signals) and GSH (Dhamala et al., 2019; Sanaei Nezhad et al., 2017). Typically only one metabolite can be edited at a time with relatively long acquisition times. Hadamard Encoding and Reconstruction of Mega-Edited Spectroscopy (HERMES) applies orthogonal editing encoding, allowing both GSH and GABA+ spectra to be reconstructed from a single sequence (Chan et al., 2019; Saleh et al., 2016).

Although previous studies have indicated that GABA and GSH levels are altered in low-grade gliomas, the relatively small number of publications is sparse offer conflicting information(Hujber et al., 2018; Hulsey et al., 2015; Jalbert et al., 2017; Lai et al., 2018; Moren et al., 2015; Shi et al., 2015) and no studies have sought to investigate both metabolites using HERMES. Thus this study set out to examine GABA+ and GSH alterations in IDH1-mutated low-grade gliomas using HERMES at 3T magnetic field in vivo.

Methods and materials

Human subjects

This study was performed under the approval of the local ethical committee; all subjects provided written informed consent. Glioma subjects, enrolled at Shandong Provincial Hospital, met these criteria: suspected low-grade glioma; age over 18 years old; tumor volume >30 cm^3; candidate for resection or biopsy. IDH mutational status for glioma was determined by Sanger sequencing combined with automated immune histochemical analysis. Additionally, 6 age-matched healthy subjects were enrolled in this study as controls.

Magnetic Resonance Imaging and Spectroscopy

All MR data were acquired using a 32-channel phased-array head coil on a 3T MR scanner (Siemens, Erlangen, Germany), including three-dimensional anatomical images: T1-weighted magnetization-prepared rapid gradient-echo; repetition time/echo time (TR/TE) 2300/2.29 msec; slice thickness 1 mm; field of view 24×24 cm^2; matrix size 256×256; flip angle 8°, acquisition time was ~5 min

Edited MRS was acquired using the HERMES experiment, which allows simultaneous editing of multiple metabolite targets (Saleh et al., 2016); in this study, HERMES was

acquired with the 'universal' sequence timings(Saleh et al., 2019), with parameters: TR/TE 2000/80 ms; 320 averages; voxel size 3×3×3 cm^3; ~10 min acquisition time (per region). HERMES ROIs were set in the glioma foci and contralateral control regions (Figure 1a and b) in patients; for healthy controls, six pairs of ROIs were set in the region of most common glioma onset: white and gray matter junctions of frontal, temporal or parietal lobes, as shown in Figure 1d and e.

MRS data were analyzed using the Gannet 3.0 analysis toolkit (Edden et al., 2014). The edited 3-ppm signal also contains contributions from macromolecules (MM) and homocarnosine in addition to GABA (Oeltzschner et al., 2018), so we refer to it as GABA+. Gannet-standard preprocessing was performed, followed by nonlinear least-squares modeling to quantify the GABA+ and GSH peaks (as shown in Figure 1 c and f) (Gong et al., 2018b; Mikkelsen et al., 2018; Saleh et al., 2016). GABA+ and GSH were quantified relative to the unsuppressed water signal, as a concentration in institutional units (i.u.), assuming a bulk water concentration of 55.5 mM, and a water transverse relaxation time constant of 150 ms. The relative fitting error (FitError) and signal-to-noise ratio (SNR) of GABA and GSH in Hermes determination by GannetFit, together with the full width at half maximum (FWHM) of the water signal were also recorded.

Statistical Analysis

Quantitative results are presented as mean ± standard deviation (SD). Wilcoxon signed-rank test was used to test for differences in GABA+ and GSH levels between the tumor foci (group 1) and contralateral regions (group 2), and between left and right regions in healthy controls (group 3). The GABA+, GSH, fitting errors and SNR generated by GannetFit of GABA + and GSH in three groups were also analyzed using ANOVA and least significant difference (LSD) tests. Statistical analyses were carried out by GraphPad Prism 7.00, the threshold of significance was set at $P < 0.05$.

Results

Fourteen patients (5 Female and 9 Male, aged 33–69 years), with a suspected diagnosis of low-grade glioma and who were scheduled to receive surgery, were prospectively enrolled in this study. All subjects were at first diagnosis without prior treatment. Histopathologic findings indicated that one case was inflammatory pseudotumor (IPT), not a tumor. The genotyping assay for IDH1 indicated 13 IDH1-mutant and 1 IDH1 wild-type cases; one IDH1-mutant tumor was classified as high-grade (WHO III) according to the histopathological result. Thus, 11 IDH1-mutant low-grade gliomas were finally enrolled this study, and the subject information was listed in Table 1. Another 6 healthy subjects (2 Female and 4 Male, age 35–60) were enrolled as controls.

HERMES could perform simultaneous measurement of GABA+ and GSH levels in glioma patients, with edited spectra shown in Figure 1. Water linewidths were 9.67 ± 2.28 Hz, all smaller than 15 Hz. HERMES data of the tumor foci, contralateral regions, and right/left regions in healthy controls was plotted using PaperPlot in Gannet, as illustrated in Figure 2. Wilcoxon signed-rank test revealed that GABA+ and GSH were significantly lower in glioma foci compared with contralateral regions (p=0.011, t=2.781; p=0.007, t=2.977

respectively), while no differences were seen between left and right regions in healthy controls, as shown in Figure 3. The ANOVA showed no differences of fitting errors and SNR between three groups, as listed in Table 2. ANOVA did indicate that both GABA+ and GSH levels in tumor were lower than contralaterally or in controls (p=0.023/0.005; p=0.001/0.047, respectively), while no differences between CR and control subjects was observed (p=0.065/0.619), as shown in Figure 3.

Discussion

This study has shown that HERMES can be applied for the simultaneous detection of GABA and GSH signals in low-grade gliomas with IDH1 mutations; we further found that GABA and GSH levels were both significantly lower in the region of tumor foci compared with contralateral cerebral regions and healthy controls, while no differences were found contralaterally in controls or between controls and tumor-contralateral tissue.

HERMES of GABA and GSH (Saleh et al., 2016) uses Hadamard encoding to perform two MEGA-PRESS experiments simultaneously. Most studies (Berrington et al., 2018; Gong et al., 2018a; Saleh and Mikkelsen, 2018; Saleh et al., 2019) applying HERMES have involved further methodological development, and the method has not yet been widely applied for clinical studies. So, this is the first time to prove the capability of HERMES in detecting the GABA and GSH alterations in gliomas, and to illustrate that it is sufficiently robust for clinical research studies in general.

GABA is the main inhibitory neurotransmitter and extensively metabolized in astrocytes, serving a key role in shaping and regulating patterns of neuronal activity, providing carbon backbone for the synthesis of glutamine in Glutamine-Glutamate/GABA Cycle(Walls et al., 2015), and can also be as an alternative fuel to support astrocyte oxidative metabolism (Andersen et al., 2020). There is growing evidence (El-Habr et al., 2017; Hujber et al., 2018; Smits et al., 2012) indicating that GABA could drive the proliferation of tumor by regulation of neuronal stem cells and tumor stem cells. As in astrocytes, GABA is assumed to enter the mitochondria in exchange with glutamate, and both glutamate and GABA are derived from the TCA cycle intermediate alpha-ketoglutarate. IDH1 catalyzes the oxidative decarboxylation of isocitrate to alpha-ketoglutarate (Turkalp et al., 2014), while mutant IDH1 consumes alpha-ketoglutarate in production of the metabolite 2-HG while oxidizing NADPH to NADP+ (Gelman et al., 2018). The alteration of alpha-ketoglutarate level in IDH1 glioma would affect the GABA concentration. Records on GABA in glioma in previous research are sparse and inconsistent. Lina et al. (Moren et al., 2015) found that GABA concentration in foci were lower in GBM than that in oligodendroglioma, while another study (Faria et al., 2011) failed to detect GABA in high-grade tumors. In low-grade gliomas, Faria et al. (Faria et al., 2011) showed GABA levels decreased in tumors compared to healthy brain, in line with the results of this study. Similarly, lower GABA levels in tumors than healthy brain have been reported in animal studies (Hulsey et al., 2015; Lai et al., 2018). One hypothesis (Faria et al., 2011) is that the GABA decrease is driven by the absence of mature and/or well-differentiated neurons and glial cells in these tumors; and the IDH-mutated status would further decrease the GABA levels (Jalbert et al., 2017).

GSH is the primary redox compound in the central nervous system, functioning in reducing the damage caused by ROS. In the production of GSH, NADPH is a required cofactor for the reduction of glutathione disulfide (GSSG) back to GSH (Ren et al., 2017); while mutant IDH1 results in the loss of the enzyme's ability to produce NADPH and confers a gain of enzyme function that oxidizes NADPH to NADP+ (Dang et al., 2009). Lower NADPH slows the production of GSH in IDH1-mutated gliomas, lowering the GSH level accordingly. The results of this study suggests the decrease of GSH in IDH1-mutated gliomas consistent with several pioneering human MRS studies (Andronesi et al., 2018; Bisdas et al., 2016; Pope et al., 2012) and animal or cell studies (Shi et al., 2015; Shi et al., 2014a; Shi et al., 2014b; Tang et al., 2020; Yu et al., 2020). To our knowledge, this is the first study conducted to determine GSH variations in low-grade gliomas using edited MRS at 3T MRI.

Previous studies (Dubbink et al., 2009; Sanson et al., 2009) have confirmed that IDH1 mutation in low-grade gliomas could result in better prognosis compared with wild-type, but the mechanisms remain largely unknown. GABA and GSH play a role in energy production through reducing oxidative stress, which is related with the neoplastic behavior of a tumor. One limitation of this study is that it only enrolled IDH1-mutant gliomas, the incidence of IDH1 wild-type gliomas is very low, only 1 case in the prospectively enrolled 12 patients. More data is needed to further evaluate the differences of GABA and GSH between IDH1-mutant and wild-type gliomas.

In conclusion, HERMES can noninvasively detect GABA and GSH alterations in low-grade gliomas with IDH1 mutation; it may be a valuable tool in the search for latent biomarkers characterizing of low-grade glioma. Noninvasive detection of GSH and GABA may prove to be a valuable diagnostic and prognostic biomarker of IDH1-mutant low-grade glioma.

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Abbreviations

GABA	γ-aminobutyric acid
GSH	reduced glutathione
IDH1	in isocitrate dehydrogenase 1
HERMES	Hadamard Encoding and Reconstruction of Mega-Edited Spectroscopy
ROS	reactive oxygen species
MEGA-PRESS	Mescher-Garwood Point-resolved Spectroscopy
3D	three-dimensional

ROI	region of interest
CR	contralateral region
DA	diffuse astrocytoma
OD	oligodendroglioma
AA	anaplastic astrocytoma
IPT	inflammatory pseudotumor

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Highlights

- HERMES is a reliable tool to simultaneously measure GABA and GSH levels in IDH1-mutant low-grade gliomas;
- GABA and GSH both decreased in IDH1-mutant low-grade glioma foci compared with contralateral regions

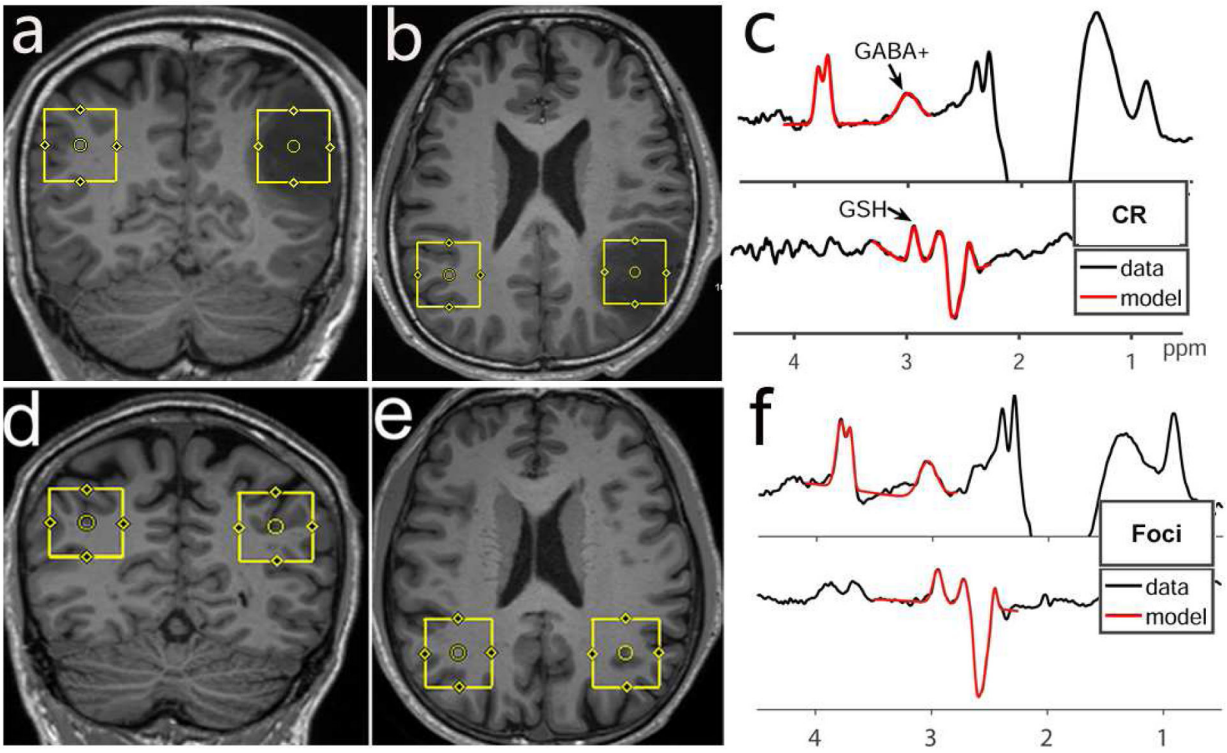

Figure 1.

Voxel position and HERMES fitting results in a patient with diffuse astrocytoma (WHO II, IDH1-mutant) and in a control subject. The location and size of the VOIs were shown on coronal (a/d) and axial (b/e) T1 weighted images; MR spectra data (black lines) of the glioma foci and healthy control (left region) are shown with Gannet model (red lines). Fitting errors for contralateral region (c) and foci spectra (f) were 5.4% (GABA+) / 4.2% (GSH) and 9.6% (GABA+) / 5.9% (GSH), respectively. CR = contralateral region.

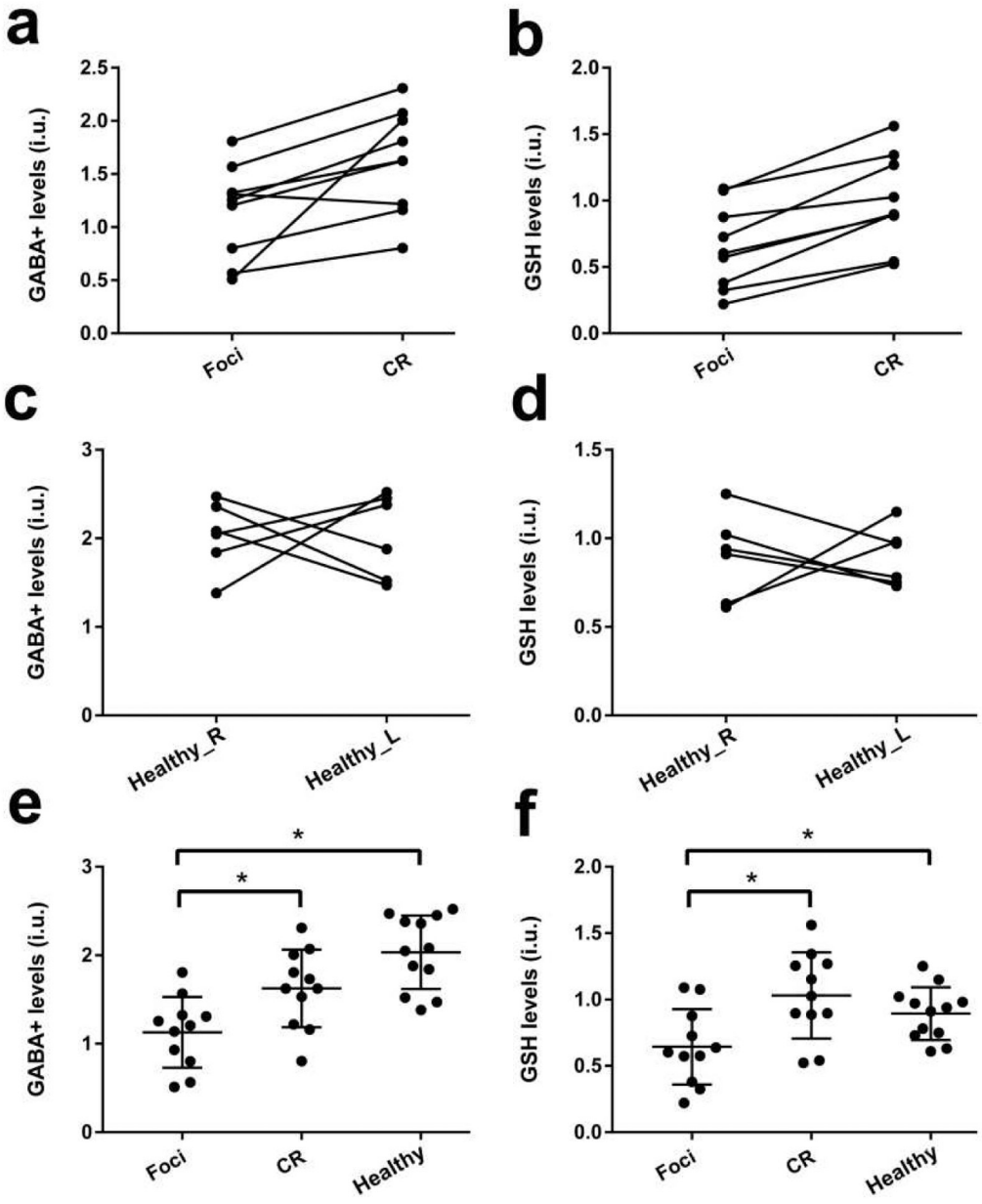

Figure 2.

The mean (± standard deviation) GABA-edited spectra (a) and GSH-edited spectra (b) from HERMES in tumor foci, contralateral regions, right and left regions in healthy controls. CR = contralateral region; Healthy_L = left regions in healthy controls, Healthy_R = right regions in healthy controls.

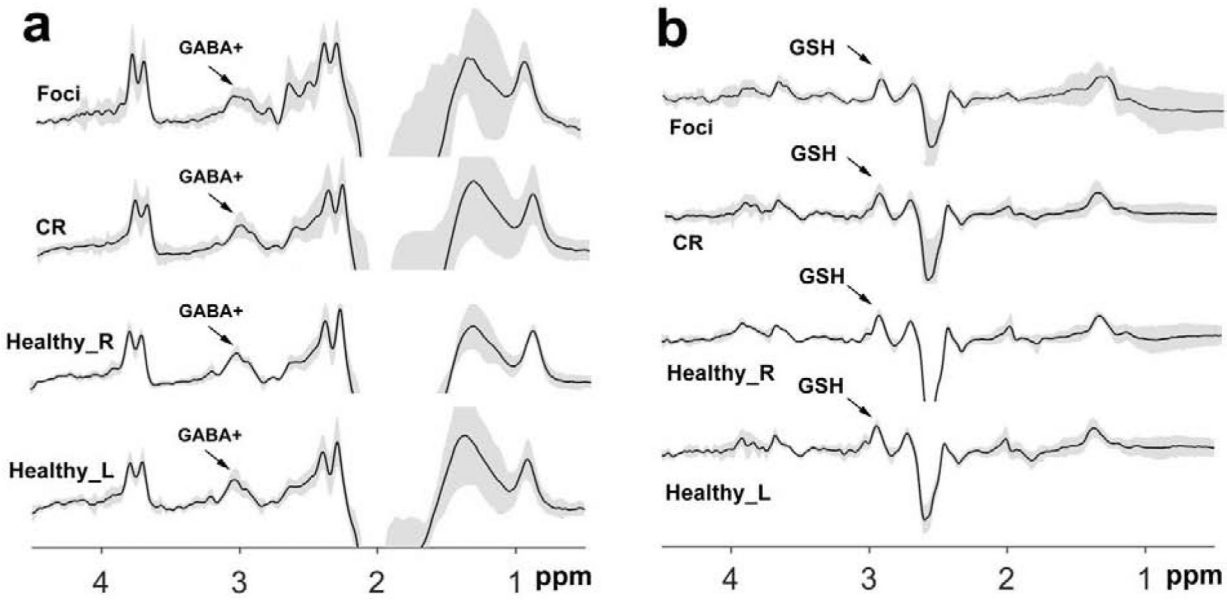

Figure 3.

GABA+ and GSH levels in gliomas (foci and contralateral region) and healthy controls (left and right region). Wilcoxon signed-rank test in gliomas (a and b) and healthy controls (c and d), results showed GABA+ and GSH decreased significantly in glioma foci compared with contralateral regions (p=0.004, Z=−2.845; p=0.003, Z=−2.934 respectively), while no differences was found between left and right regions in controls (p=0.843; p=0.844). ANOVA revealed GABA+ and GSH levels in foci region were lower than CR and Healthy groups (p=0.023/0.005; p=0.001/0.047, respectively), while no differences between CR and Healthy was observed (p=0.065/0.619). Healthy_L = left region in healthy controls, Healthy_R = right region in healthy controls; Healthy = Left + right regions in healthy controls; CR = tumor-contralateral regions.

Table 1.

Demographic, histomolecular features and HERMES data of the cohort

Subject #	Histological Diagnosis	IDH1 status	GABA+(i.u.) Foci/CR	GSH(i.u.) Foci/CR	Age	Sex
Subject 1	DA grade II	Mutation	0.802/1.162	0.220/0.522	46	F
Subject 2	DA grade II	Mutation	1.205/1.623	0.603/0.886	33	F
Subject 3	OD grade II	Mutation	0.510/2.006	1.089/1.343	50	M
Subject 4	DA grade II	Mutation	0.565/0.803	0.726/1.269	35	M
Subject 5	DA grade II	Mutation	1.309/1.218	0.379/0.895	49	F
Subject 6	DA grade II	Mutation	1.256/1.807	0.324/0.540	35	M
Subject 7	OD grade II	Mutation	1.324/1.623	0.573/0.896	69	M
Subject 8	DA grade II	Mutation	1.567/2.072	0.876/1.026	40	M
Subject 9	DA grade II	Mutation	1.807/2.308	1.076/1.560	38	F
Subject 10	OD grade II	Mutation	0.934/1.537	0.638/1.153	46	M
Subject 11	DA grade II	Mutation	1.143/1.736	0.576/1.254	39	F
Subject 12	AA grade III	Mutation	—	—	40	M
Subject 13	OD grade II	Wild-type	—	—	50	M
Subject 14	IPT	—	—	—	53	M

Abbreviations: CR = contralateral region; DA = diffuse astrocytoma; OD = oligodendroglioma; AA = anaplastic astrocytoma; IPT = inflammatory pseudotumor.

Table 2.

The GABA+ and GSH levels, Fitting Errors, and SNR of HERMES in IDH1-mutant low-grade gliomas

	GABA+(i.u.)	GSH(i.u.)	GABA+FitError (%)	GSH FitError (%)	GABA+SNR	GSH SNR
Glioma foci	1.15 ± 0.44	0.65 ± 0.32	9.83 ± 4.66	7.27 ± 3.23	11.58 ± 2.78	12.47 ± 4.27
Contralateral region	1.62 ± 0.47	0.99 ± 0.35	9.08 ± 2.31	6.45 ± 1.86	10.69 ± 2.68	13.76 ± 5.16
Healthy right and left	2.03 ± 0.41	0.89 ± 0.19	8.87 ± 2.36	6.78 ± 1.75	9.49 ± 2.87	12.31 ± 4.56
P values	0.001	0.006	0.43	0.96	0.32	0.73

ANOVA, $p < 0.05$ was considered significant. **Abbreviations:** i.u.= institutional units; FitError = fitting error; SNR = signal-to-noise ratio.