10.1148/radiol.2020191529

Appendix E1

3D MR Spectroscopy Acquisition

The whole-brain 3D MR spectroscopy data were acquired at 3T using an adiabatic spin echo (ASE) and weighted stack-of-spiral pulse sequence (23) with following parameters: TR/TE = 1800/97 ms, FOV = 240 × 240 × 120 mm^3, k-space matrix size 46 × 46 × 10, spectral window 1450 Hz, 400 time points, constant density spirals with 3 temporal interleaves and 12 angular interleaves for (k_x,k_y), 3 averages with cosine-weighted phase encoding for k_z, acquisition time of 18:22 min. The echo time 97 msec (TE1 = 32 msec and TE2 = 65 ms) of the double refocusing ASE excitation was set for optimized D-2HG detection. Inversion recovery (TI = 210 ms) with hypergeometric single band (HGSB) asymmetric adiabatic pulses of 44 msec duration, 2 kHz inversion bandwidth, 48 Hz transition band, 0.75 kHz B1 max was used before to suppress upfield signals (< 1.6 ppm) of scalp lipids. For adiabatic spin echo, a BIR-4 pulse of 8 ms, 1 kHz bandwidth, 1 kHz B1 max, flip angle 78 degrees was followed by a pair of gradient offset independent adiabatic GOIA-W(16,4) refocusing pulses of 5 msec duration, 20 kHz bandwidth, 0.75 kHz B1 max. Water suppression was achieved with WET scheme. Second order shimming of MR spectroscopy was performed until the global line width of the water signal over the entire FOV was less than 24 Hz. A volumetric echo planar imaging navigator was interleaved every TR for real-time motion and shim correction of 3D MR spectroscopy. For clarity on the acquisition, we include Figure E2 with the pulse sequence. Anatomic MRI was performed with: 1) MEMPRAGE T1 weighed structural imaging at 1 mm isotropic resolution, TI/TR/TE1/TE2/TE3/TE4/ = 1200/2530/1.64/3.5/5.36/7.22 ms, FOV 256 × 256 × 176 mm^3, 256 × 256 × 176 matrix, 5:56 acquisition time; 2) FLAIR (Fluid Attenuated Inversion Recovery) with TR/TI/TE = 10000/2500/70 ms, FOV = 220 × 186 × 138 mm^3, matrix = 256 × 192 × 23; 3) B0 field map with double gradient echo sequence TE1/TE2 = 5/7.46 ms, FOV = 240 × 240 × 120 mm^3, matrix 138 × 138 × 40.

3D MR Spectroscopy Processing

MR spectroscopy reconstruction included the following steps: 1) coil combination using a sensitivity map for spatial normalization (41); 2) phase correction for time evolution along spiral k-space trajectories points (42); 3) density compensation for the nonuniform k-space weighting of spirals (43); 4) gridding to Cartesian k-space using a Kaiser-Bessel kernel (44); 5) Hamming filtered in k-space; 6) residual lipid removal with L1 norm regularization (45); 7) Fourier transformation; 8) overdiscrete B0 field correction (46); 9) frequency alignment; 10) phase correction;11) baseline correction; 12) and spectral fitting. The last four steps were performed as part of LCModel (47) spectral fitting, which used a simulated basis set that included D-2-hydroxyglutarate and twenty normal brain metabolites (Alanine, Ascorbate, Aspartate, Creatine, γ-Aminobutyric acid, Glycerophosphocholine, Glutathione, Glucose, Glutamine, Glutamate, Glycine, myo-Inositol, Lactate, *N*-acetylaspartylglutamate, *N*-acetyl-aspartate, Phosphocholine, Phosphocreatine, scyllo-Inositol, Serine, Taurine). Values from all voxels fitted by LCModel were used to obtain brain maps for metabolite levels, Cramer-Rao lower bounds (CRLB) goodness of fit, linewidth (LW) and signal-to-noise ratio (SNR).

The metabolic ratio ([D-2HG]+[Gln])/[Glu] was calculated as a possible marker of mutant IDH metabolism because the levels of D-2HG, glutamine and glutamate are inversely correlated through coupled metabolic pathways (48,49), hence their ratio may exhibit a larger dynamic range than individual metabolites. For comparison, also the metabolic ratio of total Cho versus total *N*-acetylaspartate (NAA) (tCho/tNAA) was calculated, as it is the most widely used metabolic ratio in glioma MRS (50). The low resolution metabolic maps and ratios were upsampled with the superresolution framework. The tumors were segmented using ITK-SNAP 3.8.0 (51) on upsampled metabolic maps and FLAIR for quantitative analysis of histogram distributions, thresholds, volumes, Dice coefficients, and contrast-to-noise ratio

$$CNR := \frac{mean(Tumor) - mean(Background)}{std(Background)}.$$

Human Subjects

IDH1-mutational status in glioma participants was first tested by immunohistochemistry (IHC) analysis using an antihuman R132H antibody (DIANOVA) (29) and subsequently confirmed by genetic sequencing (SNaPshot) (30).

Phantom

The D-2HG concentration was chosen to be different across the six compartments, respectively 0, 1, 2, 3, 4, and 5 mM. The same background of brain metabolites was used in all compartments, assuming a tumor metabolic profile: 6 mM of NAA, 8 mM of glutamate, 1 mM of GABA, 4 mM of creatine, 5 mM of choline, 8 mM of myo-inositol, and 4 mM of lactate.

Appendix E2

Algorithm 1 for the initialization of superresolution with weighted Total Variation (wTV) was implemented using Alternating Direction Method of Multipliers (ADMM).

Algorithm 1: Alternating Direction Method of Multipliers (ADMM) for weighted Total Variation (wTV)

Initialization: Choose 0 < $\theta < 1, 0 < \eta < 1, \rho > 0.$ Set $\mathbf{x}^1 = \mathbf{r}^1 = \mathbf{s}^1 = 0.$

For k = 1, 2, …, n

1. $\mathbf{x}^{k+1} = \arg\min_{\mathbf{x}} \left\{ < H^T\left(H\left(\mathbf{x}^k\right) - \mathbf{y}\right), \mathbf{x} > + \frac{1}{2\eta}\left\|\mathbf{x} - \mathbf{x}^k\right\|^2 + \frac{\rho}{2}\left\|\nabla\mathbf{x} - \mathbf{r}^k + \frac{\mathbf{s}^k}{\rho}\right\|^2 \right\},$

2. $\mathbf{r}^{k+1} = \arg\min_{\mathbf{r}} \left\{ \frac{\boldsymbol{\rho}}{2}\left\|\nabla\mathbf{x}^{k+1} - \mathbf{r} + \frac{\mathbf{s}^k}{\rho}\right\|^2 + \boldsymbol{\lambda}\|\boldsymbol{r}\|_{2,1} \right\},$

3. $\mathbf{s}^{k+1} = \mathbf{s}^k + \rho\left(\mathbf{r}^{k+1} - \nabla\mathbf{x}^{k+1}\right),$

EndFor

Output: $\hat{\mathbf{x}} = \mathbf{x}^{n+1}$

Since TV($\mathbf{x}$) = $\boldsymbol{\lambda}\sum_{i=1}^{m}\sum_{j=1}^{n}\sqrt{\left(\nabla_h \mathbf{x}_{ij}\right)^2+\left(\nabla_v \mathbf{x}_{ij}\right)^2}=\boldsymbol{\lambda}\left\|\nabla\mathbf{x}\right\|_{2,1}$, where ∇_h and ∇_v denote the forward difference along horizontal and vertical axis, respectively,

$\boldsymbol{\lambda} := \left(\lambda(\mathbf{v}_1),\lambda(\mathbf{v}_2),\ldots,\lambda(\mathbf{v}_{mn})\right)$ and $\lambda(\mathbf{v}_l) := \dfrac{\theta}{\sqrt{\theta^2+|\nabla\mathbf{x}_a(\mathbf{v}_l)|^2}}$, $l = 1, 2, \ldots,$ mn, where $\mathbf{x}_a(\mathbf{v}_l)$ denotes the intensity value of anatomic image at voxel $\mathbf{v}_l$ and ∇ is a gradient operator, by setting $\mathbf{r} = \nabla\mathbf{x}$, the constrained minimization [2] and [3] can be solved by Algorithm 1. For convenience, we present the definitions of all involved variables in Algorithm 1.

H : blurring and downsampling operator,

$\mathbf{y}$: the given low-resolution metabolite maps,

$\mathbf{x}_a$: the high-resolution anatomic image prior,

$\mathbf{x}$: unknown and to be estimated metabolite maps, which has the same size as $\mathbf{x}_a$.

$\mathbf{x}^k$: the upsampled metabolite maps at k^{th} step,

$\mathbf{r}$: unknown and to be estimated gradient components of $\mathbf{x}$, ie, $\mathbf{r} = \nabla\mathbf{x}$,

$\mathbf{r}^k$: gradient components of $\mathbf{x}^k$,

$\mathbf{s}^k$: lagrange multiplier at k^{th} step,

$\mathbf{x}^1, \mathbf{r}^1, \mathbf{s}^1$ are the initialization of $\mathbf{x}, \mathbf{r}, \mathbf{s}$,

η : plays the role of stepsize,

ρ : penalty parameter.

Following initialization, the Features based Nonlocal Means Method (FNLM) is used to obtain the final output of the superresolution which was implemented as the Algorithm 2.

Algorithm 2: Features based NonLocal Means (FNLM) for the final output of the superresolution

Initialization: Choose $\varepsilon \le 0.001$. Set $\bar{\mathbf{x}}^1 = \hat{\mathbf{x}}$ and coregister the image priors $\mathbf{x}_a$ to $\bar{\mathbf{x}}^1$. Estimate $\mathbf{w}^1(\mathbf{v},\mathbf{u})$ by setting $\alpha = 0$ in [8] and obtain $\bar{\mathbf{x}}^2$.

For k = 1, 2, …, n

1. Estimate $\mathbf{w}^{k+1}(\mathbf{v},\mathbf{u})$ by using the image priors $\mathbf{x}_a$ and $\bar{\mathbf{x}}^{k+1}$, where $0 < \alpha < 1$.

2. $\bar{\mathbf{x}}^{k+2} = \underset{\mathbf{x}}{\operatorname{argmin}} \sum_{\mathbf{v}} \left| \mathbf{x}(\mathbf{v}) - \sum_{\mathbf{u}\in\boldsymbol{\Omega}(\mathbf{v})} \mathbf{w}^{k+1}(\mathbf{v},\mathbf{u})\mathbf{x}(\mathbf{u}) \right|^2$ subject to $\left\|\mathbf{y} - H(\mathbf{x})\right\|^2 \le \varepsilon$,

EndFor

Output $\bar{\mathbf{x}}^{n+2}$

In Algorithm 2, the specific update for the minimization of step 2 we implemented is

$$\mathbf{x}^{k+2}(\mathbf{v}) = \sum_{\mathbf{u}\in\boldsymbol{\Omega}(\mathbf{v})} \mathbf{w}^{k+1}(\mathbf{v},\mathbf{u})\bar{\mathbf{x}}^{k+1}(\mathbf{u}),$$

$$\bar{\mathbf{x}}^{k+2}(\mathbf{v}) = \mathbf{x}^{k+2}(\mathbf{v}) - H^{T}(H(\mathbf{x}^{k+2}(\mathbf{v})) - \mathbf{y}).$$

For convenience, we also give the definitions of the variables shown in Algorithm 2.

$\bar{\mathbf{x}}^{1}$: the initialization of upsampled metabolite maps,

$\mathbf{w}^{1}$: the weighting matrix, which is estimated by only using $\mathbf{x}_a$,

$\bar{\mathbf{x}}^{2}$: the interpolated upsampled metabolite map using $\bar{\mathbf{x}}^{1}$ and $\mathbf{w}^{1}$,

$\mathbf{w}^{k+1}$: the estimated weighting matrix at $(k+1)^{th}$ step,

$\bar{\mathbf{x}}^{k+2}$: the estimated upsampled metabolite map at $(k+2)^{th}$ step,

$\boldsymbol{\Omega}(\mathbf{v})$: search volume around voxel $\mathbf{v}$.

Image Quality Metrics

To assess the quality of superresolution image and the agreement with the ground truth the peak signal-to-noise ratio (PSNR) and the structure similarity index (SSIM) were calculated as following:

$$PSNR := 20log_{10}(I_{max}) - 10log_{10}(MSE),$$

where I is the given noise free image, I_{max} is the maximum possible voxel value of the image, and

$$MSE := \frac{1}{mnp}\sum_{i=1}^{m}\sum_{j=1}^{n}\sum_{k=1}^{p}(I(i,j,k) - K(i,j,k))^2,$$

where K is the noisy approximation of I and m,n,p are the dimensions of images in x, y, z direction. The unit is decibel (dB).

$$SSIM(\mathbf{x},\mathbf{y}) := \frac{(2\mu_x\mu_y + c_1)(2\sigma_{xy} + c_2)}{(\mu_x^{\,2} + \mu_y^{\,2} + c_1)(\sigma_x^{\,2} + \sigma_y^{\,2} + c_2)},$$

where $\mathbf{x},\mathbf{y}$ are the given images, μ_x and μ_y are the mean value of $\mathbf{x}$ and $\mathbf{y}$, σ_x and σ_y are the standard derivation of images $\mathbf{x}$ and $\mathbf{y}$, σ_{xy} is the covariance of $\mathbf{x}$ and $\mathbf{y}$, $c_1 = (k_1 d)^2$ and $c_1 = (k_2 d)^2$, and $k_1 = 0.01$, $k_2 = 0.03$, d is the dynamic range of the voxel-values. SSIM ranges from -1 to 1 and the value 1 is only reachable in the case of two identical images.

References

41. Brown MA. Time-domain combination of MR spectroscopy data acquired using phased-array coils. Magn Reson Med 2004;52(5):1207–1213.

42. Mayer D, Levin YS, Hurd RE, Glover GH, Spielman DM. Fast metabolic imaging of systems with sparse spectra: application for hyperpolarized 13C imaging. Magn Reson Med 2006;56(4):932–937.

43. Hoge RD, Kwan RK, Pike GB. Density compensation functions for spiral MRI. Magn Reson Med 1997;38(1):117–128.

44. Beatty PJ, Nishimura DG, Pauly JM. Rapid gridding reconstruction with a minimal oversampling ratio. IEEE Trans Med Imaging 2005;24(6):799–808.

45. Bilgic B, Gagoski B, Kok T, Adalsteinsson E. Lipid suppression in CSI with spatial priors and highly undersampled peripheral k-space. Magn Reson Med 2013;69(6):1501–1511.

46. Kirchner T, Fillmer A, Henning A. Mechanisms of SNR and line shape improvement by B_0 correction in overdiscrete MRSI reconstruction. Magn Reson Med 2017;77(1):44–56.

47. Provencher SW. Estimation of metabolite concentrations from localized in vivo proton NMR spectra. Magn Reson Med 1993;30(6):672–679.

48. Reitman ZJ, Jin G, Karoly ED, et al. Profiling the effects of isocitrate dehydrogenase 1 and 2 mutations on the cellular metabolome. Proc Natl Acad Sci U S A 2011;108(8):3270–3275.

49. Izquierdo-Garcia JL, Viswanath P, Eriksson P, et al. Metabolic reprogramming in mutant IDH1 glioma cells. PLoS One 2015;10(2):e0118781.

50. Nelson SJ. Multivoxel magnetic resonance spectroscopy of brain tumors. Mol Cancer Ther 2003;2(5):497–507.

51. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. Neuroimage 2006;31(3):1116–1128.