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Limitations of rsfMRI in the setting of focal brain lesions

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Synopsis

Methods of image acquisition and analysis for resting state fMRI (rsfMRI) are still evolving. Neurovascular uncoupling (NVU) and susceptibility artifact are important confounds of rsfMRI in the setting of focal brain lesions such as brain tumors. This article will review the detection of these confounds using rsfMRI metrics in the setting of focal brain lesions. In the near future, with the wide range of ongoing research in rsfMRI, these issues likely will be overcome and will open new windows into brain function and connectivity.

Keywords

resting state fMRI; motor activation; neurovascular uncoupling; presurgical mapping

INTRODUCTION

In 1995, Biswal and colleagues discovered that, even during rest, in the absence of any explicit task, the BOLD signal within the brain's sensorimotor network fluctuated synchronously.¹ Contrary to unstructured neuronal activity at rest as expected, a correlation has been found among brain regions which were known to function together within a single network. Later, in a series of experiments, Raichle and colleagues showed that the brain is constantly active even when the person is not engaged in a specific task (i.e. the resting state), and the brain's energy consumption is increased by less than 5% of its baseline energy consumption while performing a focused task.² The findings suggested that networks of brain regions that activate or deactivate together during tasks maintain signatures of their connectivity even at rest.³ "Resting-state functional connectivity"^{4–6} is a promising approach to study the functional organization of both the healthy and abnormal brain, particularly in subjects who cannot complete challenging cognitive tasks. Unlike task-based fMRI (tbMRI), which typically highlights a single brain network associated with any given task, resting-state fMRI (rsfMRI) allows one to observe many networks at once with a single

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imaging acquisition. The simplicity of the procedure and its relatively short duration are other advantages of rsfMRI. Further, synchronized resting state networks (RSNs) have been found even during sleep and under anesthesia.^{7,8} Scientists hope to use resting-state functional connectivity to help improve treatments for many different neurologic and neuropsychiatric conditions.^{9–11}

Clinical applications of resting-state functional connectivity have continued to increase over the past decade. In recent years, there has been an increase in interest in the application of rsfMRI for presurgical planning in patients with brain tumors and other focal brain lesions such as brain neoplasms, arteriovenous malformations and other vascular malformations, cortical dysplasias, and other epileptogenic lesions. Presurgical mapping with task-based fMRI has already been established as standard of care at many academic centers around the world, but resting state fMRI has not yet been widely accepted for this purpose.

The purpose of this article is to review the feasibility of rsfMRI in the settings of focal brain lesions. Therefore, the remainder of the article will focus on various problems associated with performance and analysis of resting state fMRI in the setting of focal brain lesions. This includes susceptibility artifacts and neurovascular uncoupling (NVU), which predominantly affect resting state fMRI analysis in cases of structural brain lesions, as well as more generic problems such as bulk head motion which can result in similar image degradation.

Susceptibility Effects

Susceptibility effects are often an issue at 3T and higher field strength. Susceptibility reflects the extent of magnetization of a substance in the presence of external magnetic field.¹² Diamagnetic substances such as calcium in cortical bone strongly disperse the external magnetic field while tissues such as muscles, fat, water are weakly diamagnetic. The largest susceptibilities, field distortions and MR artifacts are prominent around metal objects and implants.¹³ These objects contain ferromagnetic materials such as Fe/Co/Ni, which strongly concentrate the external magnetic field. Susceptibility distortions are also seen at natural interfaces such as at the skull base.¹⁴ Susceptibility-induced signal loss from T2*-dephasing results in “geometric distortion” with regions of signal void and “piling up” with regions of very bright signal resulting from accumulating signals assigned to the wrong areas. Susceptibility artifacts are worse at high fields and can be minimized by using shorter TE values (less time for dephasing) and by using fast spin-echo instead of gradient-echo sequences.¹⁵ 7T imaging is restricted by increased susceptibility artifacts near the frontal sinuses and skull base resulting in spatial distortion and signal drop out, increased dielectric artifacts due to signal inhomogeneity, and shimming. “Z-shimming” results in a longer TR, which means that portions of the original image not suffering from susceptibility-induced signal loss can be dephased by the z-shimming gradients and become worse. Such loss of fMRI signal due to dephasing cannot be restored by distortion correction techniques such as field mapping, unwarping, and z-shimming which are used to reassign recorded signals to the proper points in space from which they arose. Other ways to reduce susceptibility artifacts include increasing gradient strength, use of thinner slices and use of parallel imaging techniques.^{16,17}

Head motion and physiologic noise

Head motion¹⁸ and physiologic noise from the respiratory and cardiac cycles¹⁹ are unavoidable sources of variance that adversely affect rsfMRI signal. While these problems are inherent in all applications of rsfMRI, these tend to be especially problematic in patients with focal brain lesions, since many of these patients are neurologically or cognitively impaired and thus may be less able to cooperate for satisfactory data collection. Since respiratory fluctuations produce aliased signals in the range of 0.1–0.3 Hz and cardiac pulsations produce signals in the range of 0.8–1.3 Hz, physiological noise is a much greater problem for rsfMRI wherein low-frequency (0.01–0.1 Hz) BOLD fluctuations show strong correlations at rest even in distant gray matter regions. Physiological noise becomes more prominent than thermal noise at higher fields, and therefore, may reduce the effects of SNR improvement at 7T and higher fields. False positive BOLD signals due to eye motion, random noise, partial volume effects, and physiological pulsations along with post-processing statistical issues such as thresholding, clustering and improper estimation of p-values may adversely impact the reliability of fMRI studies.

Head restraints or navigator echoes are used to reduce the effects of head motion.²⁰ Motion detection parameters from a navigator echo can be used for motion correction during postprocessing. Similarly, signals representing physiologic cardiac and respiratory cycles can be obtained through the use of a respiratory belt. Besides these parameters obtained during image acquisition, there are retrospective motion and physiological noise correction methods available.^{21–24} These include motion correction considering head as a rigid body with three directions of translation (displacement) and three axes of rotation, removal of low frequency drifts (known as “detrending”), correction for the non-neural noise from white matter and cerebrospinal fluid (known as “nuisance regression”^{25,26}) and removal of volumes with excessive motion, which is known as “scrubbing”²⁷ Figure 1, shows surgical hardware-related susceptibility artifacts at 3T.

Figure 2, shows 3T rsfMRI and 7T rsfMRI comparison indicating geometric distortion at ultra-high field.

Neurovascular Uncoupling

Impaired blood oxygenation level-dependent (BOLD) fMRI activation in the eloquent cortex in the vicinity of brain tumors or other focal brain lesions can lead to inaccurate pre-surgical planning which can result in inadvertent eloquent cortical resection. These false negative or abnormally decreased BOLD responses in the vicinity of focal brain lesions often occur due to the disruption of coupling between neuronal activity and adjacent microvasculature, known as “neurovascular uncoupling” (NVU).^{28,29} Such NVU may also adversely affect other applications of task and resting state fMRI in the setting of focal brain lesions that may alter regional hemodynamics or otherwise disrupt local networks. The mechanisms underlying brain tumor-induced neurovascular uncoupling are not yet completely understood, but preclinical studies have suggested that tumors induce a variety of physiologic changes in the microenvironment that may contribute to this phenomenon.³⁰ Previous studies^{31–39} have demonstrated prevalence of NVU in high-grade gliomas as well as with low-grade gliomas. NVU in high-grade gliomas is due to tumor angiogenesis which

compromises cerebral autoregulatory capacity in the tumoral and peritumoral regions.^{34,38} The mechanism underlying NVU in low-grade gliomas differs from that of high-grade gliomas due to the fact that glial tumors are infiltrating lesions which disrupt the neuronal contacts with surrounding microvasculature and astrocytes^{40–42}, also known as “gliovascular uncoupling” (GVU)⁴³, and that in turn results in reduced cerebrovascular reactivity (CVR).

NVU is a critical limitation of clinical fMRI and has been widely studied in task-based BOLD fMRI (tbfMRI).^{31,33,34,37,38} NVU is characterized by the presence of abnormally decreased tbfMRI activation in the ipsilesional hemisphere when the patient neither exhibits substantial neurological deficit that would be indicative of tumor-related destruction of eloquent cortex, nor displays inability to adequately perform the required tasks.³¹ NVU may not necessarily be an all-or-none (i.e binary) phenomenon, but rather may be present to variable degrees, resulting in variable degrees of reduction of expected ipsilesional BOLD activation in eloquent cortical regions and complete absence of detectable activation only in some cases.

Evaluating cerebrovascular reactivity (CVR) is often useful for identifying cortical regions affected by NVU.⁴³ CVR is defined as the change in cerebral blood flow (CBF) per change in a vasoactive stimulus. Mostly either breath-hold (BH) or exogenous gas administration methods are used for CVR mapping.⁴³ Breath-holding has been used to induce hypercapnia and thus produce an increase in the arterial partial pressure of CO₂ with time, which consequently raises CBF through a vasodilatory mechanism. In most patients, the BH technique is easier to implement and produces similarly useful BOLD CVR maps as those achieved by using gas-inhalation techniques.^{44,45} BOLD BH CVR maps display the change in the BOLD-MRI signal in response to the BH hypercapnia challenge relative to a normocapnic baseline condition. BH CVR maps have been compared with T2* dynamic susceptibility contrast (DSC) MR perfusion imaging to demonstrate the increased effectiveness of BH CVR over DSC perfusion imaging in the detection of NVU in patients with brain tumors of varying grades.³⁵ In another study, BH CVR maps were compared with tbfMRI and were shown as an effective method for assessment of NVU in patients with low grade perirolandic tumors.³¹

Biswal and colleagues showed that in rsfMRI only very low-frequency amplitude (0.01, 0.03, and 0.04Hz) correlated with BH-related activity.⁴⁶ Studies have also been performed to represent resting state fluctuation of amplitude (RSFA) as an alternative approach to represent CVR.^{47–50} These studies examined the correlation between end-tidal CO₂ fluctuations & low frequency BOLD fluctuations available from rsfMRI and established RSFA as a strong CVR correlate.^{47,48} A recent study proposed a different resting-state CVR map which exploits the natural variation in respiration to map CVR using resting state BOLD data.⁵¹ Because of its easy implementation and less stringent requirements for patient compliance, rsfMRI has been attracting wide attention for use as a preoperative mapping tool.^{52,53} However, rsfMRI also suffers from similar important clinical limitations of false negative BOLD signals due to brain-tumor related NVU;^{54–56} thus, to use rsfMRI as a reliable pre-surgical tool, it becomes all the more important to study NVU in cases of focal resectable brain lesions such as tumors to evaluate its effects on rsfMRI.

Examples of each of the above-mentioned limitations in the setting of focal brain pathology

In the remainder of this article, various examples of the above-described limitations of resting state functional connectivity related to focal brain lesions will be provided. All of the presented data was acquired and processed using the following protocol at our institution:

3T scanning was performed using our standard clinical sequences for fMRI studies on a 3.0T Siemens Trio MRI system (Siemens Medical Solutions, Erlangen, Germany) equipped with a 12-channel head matrix coil. Imaging protocol included a 3D T1 MPRAGE (TR=2300 ms, TI= 900 ms, TE= 3.5 ms, 9° FA, 24-cm FOV, 256× 256×176 matrix, slice thickness 1 mm) as well as an axial 2D T2 fluid attenuated inversion recovery (FLAIR) imaging sequence (TR=9000 ms, TI=2500 ms, TE=116 ms, flip angle=1418, FOV=17.2 cm × 23 cm, acquisition matrix=240 × 320 × 53, slice thickness=3 mm with 3 mm gap between slices) for structural imaging and multiple 2D gradient echo-echo planar imaging (GE-EPI) T2* weighted BOLD sequences for both task & resting functional imaging (TR=2000 ms, TE=30 ms, flip angle=90°, field of view=24 cm, acquisition matrix=64×64×33, slice thickness=4 mm with 1 mm gap between slices, interleaved acquisition).

7T scanning was performed using research sequences on a 7.0T Philips MRI system equipped with a 32-channel head matrix coil. Imaging protocol included a 3D T1 3D MPRAGE imaging sequence (TR= 4.023 msec, TE = 1.81 msec, flip angle = 7, field of view= 22 cm, acquisition matrix = 224×224×180, slice thickness = 1mm) for structural imaging and multiple 2D fast echo planar imaging T2*-weighted BOLD sequences for functional imaging (TR= 2500 msec, TE= 22 msec, flip angle = 80, field of view= 19.2 cm, acquisition matrix = 128 × 128 × 31, slice thickness =3mm). The BOLD parallel imaging acceleration (SENSE) factor = 3.

For **rsfMRI**, subjects were instructed to remain still with eyes closed without falling asleep during the scanning period of 6 minutes.^{55–57} For **motor task fMRI**, bilateral simultaneous sequential finger tapping (FingM) task to map hand representation area and vertical tongue movement (TM) task to map face representation area of primary motor cortex (PMC) were used.³¹ Both paradigms were block design with alternating active and control blocks lasting 30 seconds each for a total of 3 minutes. For **language task fMRI**, sentence completion (SC) task to map both expressive & receptive language areas was used. This paradigm was block design with alternating active and control blocks lasting 20 seconds each for a total of 4 minutes.⁵⁸ a breath hold (**BH**) task includes normal breathing period of 40 seconds followed by a 4 second block of inspiration that immediately preceded a 16-second BH period.³¹ This cycle was repeated four times and at the end of the last BH period an additional normal breathing period of 20 seconds was added.

Instructions for all tasks were visually cued. A comprehensive pre-scan training session outside the MRI scanner ensured full patient understanding of task instructions and confirmed their ability to adequately perform the tasks. Patient task performance was monitored during the scan via use of a respiratory belt for the BH task and use of both a LCD monitor in the scan suite and real-time fMRI for patient observation and assessment of activation, respectively.

SPM12 (Wellcome Trust Center for Neuroimaging, London, UK) software implemented in Matlab R2014b (The Mathworks, Natick MA) was used for preprocessing of BH, tbfMRI & rsfMRI data (slice timing correction, realignment, normalization to MNI space at 2mm voxel resolution, and spatially smoothing using a 6 mm FWHM Gaussian kernel). Z-score maps for the motor and BH tasks were obtained using general linear model (GLM) analysis using SPM software (reflecting motor activation vs. rest and hypercapnia vs. baseline, respectively).

On the pre-processed rsfMRI data, detrending for removal of systematic linear trend and low frequency (0.01–0.08 Hz) bandpass filtering was performed using the REST (version 1.8)⁵⁹ toolkit. An Automated Anatomical Labeling (AAL) template^{60,61} was used to obtain a seed region circumscribing the combination of precentral gyri and postcentral gyri in contralesional (CL) hemisphere (i.e. contralateral to tumor). Pearson linear correlation was calculated using the REST toolkit between the seed region in CL to ipsilesional (IL) precentral gyri and postcentral gyri (i.e. ipsilateral to tumor) to obtain the functional connectivity map (Seed Correlation Analysis (SCA) Map) of the sensorimotor network.⁵⁵ Subsequently, ALFF (amplitude of low-frequency fluctuation⁶²) and ReHo (regional homogeneity^{63,64}) maps were calculated. fALFF (fractional ALFF⁶⁵) maps were calculated from de-trended rsfMRI data. For ReHo maps, smoothing was done after ReHo map calculation, not during pre-processing of rsfMRI data. Two additional pre-processing steps-- “scrubbing” and “nuisance regression”--- were performed on rsfMRI data before Independent Component Analysis (ICA)^{66–69} computation. Outlier volumes (i.e. volumes with excessive variation in volume-to-volume global signal and motion) identified with the ART repair toolbox⁷⁰ were removed to generate “scrubbed” rsfMRI data. White matter and cerebrospinal fluid masks were used to regress physiological noise (i.e. “nuisance regression”) from the fMRI time series.⁷¹ GIFT toolbox⁷² was used to perform ICA with 30 target components. The single best candidate ICA component for the rsfMRI sensorimotor network was selected.⁵⁵

For the BH task, during clinical scanning, the real time respiratory bellows on the MRI scanner console were observed for quality control purposes. On more rigorous quantitative post hoc evaluation of respiratory waveform plots, variations in the signals during the BH period were found within 10% of the corresponding median value which indicates the stability of the baseline during the BH period and confirms patient compliance during performance of the BH task.

Figure 3 shows an example of respiratory waveform and its quantitative evaluation for quality control purpose. The figure also displays BH CVR maps obtained at 3T and 7T with specific mention of motion and susceptibility artifact- related degradation of the CVR maps.

Below is critical evaluation of rsfMRI in the assessment of brain tumor- related NVU.

NVU effects on resting state functional connectivity (SCA & ICA)

Standard methods for determining various rsfMRI networks (RSN) include SCA and ICA of voxel time series.⁷³ Such analysis methods focus on the similarities of inter-regional time series, and therefore, investigate temporal synchronization of low frequency fluctuations

(<0.1 Hz), i.e., functional connectivity.⁷⁴ Agarwal and colleagues⁵⁵ demonstrated NVU on rsfMRI using ICA and SCA analysis approaches in patients with peritumoral tumors. In another study, they further assessed brain tumor-related NVU in rsfMRI at ultrahigh field (7T) and demonstrated that the higher SNR at 7T does not fully mitigate the effects of such NVU.⁵⁶ Mallela and colleagues examined the correlation of rsfMRI data with tumor characteristics and clinical information to characterize functional reorganization of RSNs and the limitations of rsfMRI in high-grade gliomas due to NVU.⁵⁴

Figure 4 displays a case of left hemispheric glioblastoma demonstrating severe NVU affecting the sensorimotor network. NVU is demonstrated on task fMRI, BH CVR and functional connectivity maps obtained from seed based (SCA) and independent component (ICA) analysis.

NVU effects on Regional Homogeneity (KCC-ReHo & Cohe-ReHo)

Zang and colleagues⁶³ proposed ReHo metrics of rsfMRI signals as a voxel-based measure of brain activity which evaluates the synchronization between the time series of a given voxel and its nearest neighbors. This measure was based on the hypothesis that intrinsic brain activity is manifested by clusters of voxels rather than single voxels. They used Kendall's coefficient of concordance (KCC)⁷⁵ as an index to evaluate the similarity of the time series within a cluster of a given voxel and its nearest neighbor voxels (KCC-ReHo). Values of KCC range from 0 to 1, with higher values indicating greater similarity between the BOLD signal of a given voxel and that of its neighbors. Later, Liu and colleagues⁶⁴ applied coherence to evaluate ReHo (Cohe-ReHo) in healthy participants as well as in patients with attention deficit hyperactivity disorder (ADHD). ReHo has been widely used to evaluate resting state cortical activity.^{75–80} ReHo does not require *a priori* definition of ROIs and can provide information about the local/regional activity of regions throughout the brain. Liu et al. (2010) has shown that the two measurements KCC-ReHo and Cohe-ReHo differed mainly in some brain regions where physiological noise is dominant.⁶⁴ We have shown previously that ReHo is sensitive to NVU in the sensorimotor network as well.⁸¹ ReHo findings may possibly complement findings on tbfMRI used for presurgical planning.

NVU effects on Frequency Domain Metrics (ALFF & fALFF)

rsfMRI focuses on spontaneous low frequency fluctuations (<0.1 Hz) in the BOLD signal. Studies have found that the relative magnitude of these low frequency fluctuations can differ between brain regions and between subjects, and thus may act as a marker of individual differences or dysfunction. Biswal and colleagues¹ found that amplitude of low frequency fluctuations was higher in gray matter than in white matter. Subsequently, as a measure of amplitude of regional activity (unlike SCA & ICA which measures functional connectivity), frequency domain rsfMRI metrics such as amplitude of low frequency fluctuations (ALFF)⁶²---defined as the total power within the frequency range between 0.01 and 0.08 Hz indexing the strength or intensity of low frequency fluctuations--- and fractional ALFF (fALFF)⁶⁵, which is defined as the ratio of the power spectrum of the low-frequency (0.01–0.08 Hz) range to that of the entire frequency range representing the relative contribution of specific low frequency fluctuation to the whole frequency range, were developed. Their usefulness in characterizing rsfMRI properties in healthy^{82–85} and diseased populations^{86–88}

has been studied. Studies⁸⁹ have also been performed using ALFF to reduce the distortions in task-based activation due to regional variance in neurovascular coupling. Our group has recently shown that ALFF may be sensitive for detection of NVU in brain tumors that affect the sensorimotor network.⁹⁰ Reliability of ALFF in gray matter regions tends to be higher than for fALFF. Figure 5 displays a case of a left hemispheric glioblastoma with severe NVU, as assessed on motor task fMRI, ReHo and ALFF.

Figure 6 displays a case of mild NVU affecting the sensorimotor network, as depicted via task fMRI and resting state fMRI, including ALFF, ICA and SCA approaches.

NVU effects on mapping of the Language Network

In case of the relatively non-lateralized primary sensorimotor network, contralesional values can serve as an internal reference standard with which the NVU-affected ipsilesional side can be studied at a single subject level in cases of unilateral lesion-induced NVU. In the above sections, regional alterations in ReHo and the frequency domain rsfMRI metrics ALFF & fALFF have been shown to correspond to similar ipsilesional abnormal activation reductions on tbfMRI & decreased BOLD signal in BH CVR maps in the setting of lesion-induced NVU involving sensorimotor cortical areas. The abnormally reduced ipsilesional task-based activation in the absence of corresponding neurological deficits or impaired task performance is direct evidence of NVU, whereas the findings on the other maps are resting state correlates of such NVU. Although some of the asymmetry observed may be due to differences in handedness, this degree of asymmetry is greater than what would be expected based on differences in handedness alone.^{31,91,92} rsfMRI based frequency domain and regional homogeneity metrics are not restricted by network specificity and provide information about the local/regional activity of regions throughout the brain. Therefore, they can be advantageous in the assessment of brain-tumor-related NVU in more lateralized networks⁹³ like language. Although this remains to be determined in the future, we present here two cases with lesions involving language areas representing clinically significant and insignificant NVU, respectively.

Figure 7 illustrates a case of clinically significant language NVU since the NVU affects regions where critical language activation is expected.

Figure 8 illustrates a case of clinically insignificant language NVU since the ipsilesional expected critical language activation in Broca's area (BA) and Wernicke's area (WA) is still detectable despite the NVU.

NVU in the context of Network/Graph Theoretic Analysis

Graph theory is increasingly being used to describe functional and anatomic connectivity in the brain. For network analysis nodes (or vertices) at voxel level, gyral level or at much larger anatomic levels are defined via cortical parcellation. Nodes which have correlated activity or direct physical connections are linked by "edges." A network with nodes and links is represented either graphically or as a numerical array (also known as "adjacency matrix"). Various different graph theoretic metrics can then be defined in terms of various parameters such as path length and number of connections to individual nodes within the whole brain network. Such metrics include degree centrality, small worldness, global and

local efficiency among many others. Graph theory has been used to study many neurologic disorders such as Alzheimer disease, autism spectrum, and schizophrenia. A full discussion of these methods is beyond the scope of this article, and will instead be addressed more fully in other articles in this Neuroimaging Clinics issue. However, it is worth mentioning that such graph theoretic metrics represent another method of analysis of resting state fMRI data that may also be adversely affected by the effects of NVU in the setting of focal brain lesions such as tumors. In fact, several studies have shown that the effects of brain gliomas may not just be limited to local network disruption, but may also affect global networks with distant disruptions as well as local ones.^{94–97}

Summary

In this review, limitations affecting the results of presurgical mapping with resting state fMRI are discussed. Methods of image acquisition, monitoring and analysis are still evolving, and there is a need to standardize these to ensure reliability of rsfMRI results in clinical scenarios. In the near future, with the wide range of ongoing research in rsfMRI, these issues likely will be overcome and will open new windows into brain functional connectivity that will enhance both research and clinical applications of rsfMRI.

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Key Points

The purpose of this article is to review the feasibility of blood oxygen level dependent (BOLD) resting state functional magnetic resonance imaging (rsfMRI) in the setting of focal brain lesions. We will describe how assessment of resting state functional connectivity can be adversely affected by the presence of various lesion-related confounds.

1. Discussion of general confounds that adversely affect rsfMRI analysis
2. Challenges in processing/analysis of rsfMRI data in the setting of neurovascular uncoupling (NVU) and susceptibility artifact
3. Assessment of NVU related to focal brain lesions and its effect on visualization of different functional networks in lesions involving motor and language cortical areas with the use of various rsfMRI metrics.

Figure 1. surgical hardware–related susceptibility artifacts at 3T

Susceptibility artifact related to a left craniotomy in a patient with WHO grade II diffuse astrocytoma. White arrow pointing to the surgical hardware–related susceptibility artifact in T2-FLAIR structural images (row 1), susceptibility weighted images (SWI) (row 2), and resting state BOLD fMRI images (rsfMRI) (row 3). Note that the degree of susceptibility-related anatomic distortion is greater on the EPI images (row 3) than on the anatomic images (row 1). Row 4, shows breath hold cerebrovascular reactivity (BH CVR) map (Z -score > 2.5) overlaid on T1-weighted images. Notice that the BH CVR map shows ipsilesional apparent

loss of regional vascular reactivity (white arrow), but this is partially caused by surgical hardware–related susceptibility artifact rather than neurovascular uncoupling (NVU). Row 5, displays the auditory resting state network (RSN) from independent component analysis (ICA) of rsfMRI (Z-score>4.0) overlaid on T1-weighted images. Row 6, shows map of frequency domain metrics amplitude of low frequency fluctuations (ALFF) (ALFF>0.6) overlaid on T1-weighted images. Notice ipsilesional absent (white arrow) resting state BOLD signal within the auditory RSN component along the tumor as well as decreased tumor ALFF.

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Figure 2. 3T rsfMRI and 7T rsfMRI comparison (geometric distortion at ultra-high field)
Top row shows “geometric distortion” (yellow arrow) in multiple 2D fast echo planar imaging T2*-weighted BOLD sequences for resting state functional imaging (rsfMRI) at ultrahigh (7T) field (repetition time/echo time 2500/22 milliseconds, acceleration factor =3) acquired in a patient with grade II oligoastrocytoma referred for fMRI presurgical mapping at our institution. Bottom row displays the corresponding slices of rsfMRI acquired at 3T using multiple 2D gradient echo- echo planar imaging (GE-EPI) T2* -weighted BOLD sequence (repetition time/echo time 2000/30 milliseconds). Notice that geometric distortions were much less prominent at 3T.

Figure 3. Respiratory waveform, Motion artifact and Susceptibility artifact

The respiratory wave form plot (row 1) for the 4 minute 20 second (i.e. 260 seconds) long BH paradigm. Red, green, cyan and magenta blocks indicate the BH periods, which are each 16 secs long. Yellow dot in each BH block represents the median value of all samples within the respective block. In each BH block, Median Absolute Deviation (MAD) which represents the median deviation of the absolute values of the differences of amplitude between each individual sample and the median of all samples within each BH block, was less than 10% of the median value of all samples within each respective BH block, which

indicates the overall stability of the baseline within each BH block, which in turn confirms the patient compliance during breath holding. Row 2, displays BH CVR map (Z -score >3.0) obtained at 3T. Note the artifact (white arrow) in image because of head motion that is not adequately corrected even when the respiratory waveform provides adequate quality control numbers. Row 3, displays BH CVR map (Z -score >4.0) obtained at 7T. Note the artifact created because of susceptibility (white arrow). Irrespective of artifact, 7T images shows high SNR and better resolution relative to 3T.

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Figure 4. Patient with left hemispheric glioblastoma demonstrating severe NVU: task, BH, SCA, ICA maps overlaid on precontrast T1-weighted anatomic images

Patient with a left hemispheric WHO grade IV glioblastoma. Top row shows the BOLD sensorimotor activation map obtained from a bilateral simultaneous sequential finger tapping task overlaid on T1-weighted structural images. Suprathreshold voxels (Z -score >3.5) in the expected hand representation area of the primary motor cortex are highlighted in yellow-white. Blue arrow points to the central sulcus (CS). Note that there is absence of ipsilesional activation (white arrow) during task performance in the left primary motor cortex (PMC). Second row shows BOLD breath hold cerebrovascular reactivity (BH CVR) maps overlaid

on T1 weighted anatomic images of the same patient displaying decreased regional cerebrovascular reactivity (CVR) in the ipsilesional hemisphere (Z -score >1.5). Third and fourth rows show the BOLD resting state sensorimotor network maps of the same patient displaying the functional connectivity maps derived from seed based correlation analysis (SCA) (yellow-orange suprathreshold voxels; Z -score >1.0) and independent component analysis (ICA) (Z -score >3.0) overlaid on structural T1-weighted images. Note that absent activation during task performance and decreased ipsilesional CVR in the expected hand representation area of the left primary motor cortex (precentral gyrus) corresponds to absence of BOLD signal in the resting state sensorimotor network within the same cortical region on the functional connectivity SCA & ICA maps. Ipsilesional reduction in BOLD signal on all maps compared to the contralesional PMC in the setting of preserved motor function and bilateral robust finger movement is indicative of lesion-induced NVU. Color-bar indicates Z -score in all panels.

Figure 5. Patient with left hemispheric glioblastoma demonstrating severe NVU: task, ReHo, ALFF

Patient with a left hemispheric WHO grade IV glioblastoma. Top row shows the BOLD sensorimotor activation map obtained from a bilateral simultaneous sequential finger tapping task overlaid on T1-weighted structural images. Suprathreshold voxels (Z -score >3.5) in the expected hand representation area of the primary motor cortex are highlighted in yellow-white. Second & third rows show regional homogeneity (ReHo) --KCC-ReHo and Cohe-ReHo, respectively-- maps ($KCC > 0.35$ & $Cohe > 0.26$) from resting state fMRI (rsfMRI). Fourth and fifth rows show maps of frequency domain metrics amplitude of low frequency

fluctuations (ALFF) & fractional ALFF (fALFF) (ALFF>0.4 & fALFF>0.25) from rsfMRI. Note that absent activation during task performance corresponds to absence/decrease of BOLD signal within the same cortical region on KCC-ReHo, Cohe-ReHo, ALFF and fALFF rsfMRI maps. The abnormally reduced ipsilesional task-based activation in the absence of corresponding neurological deficits or impaired task performance is direct evidence of neurovascular uncoupling (NVU), whereas the findings on the other maps are resting state correlates of such NVU. This is a case of clinically significant NVU since the NVU affects regions where critical motor activation is expected. White arrow in each map points to the ipsilesional decreased / absent BOLD signal.

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Figure 6. Mild NVU depicted via task fMRI, ALFF, SCA & ICA

Patient with a right perirolandic tumor of grade II oligoastrocytoma. It displays motor task-based activation at 3T (green box), and sensorimotor network resting state functional connectivity (SCA & ICA) maps along with frequency domain metrics ALFF at 3T (purple box) as well as 7T (blue box). This is a case of mild NVU. Notice ipsilesional decreased activation and ipsilesional decreased resting state BOLD signal within the sensorimotor network (as assessed with both seed-based analysis and independent component analysis) along the tumor as well as mildly decreased tumor ALFF. This case illustrates that SNR advantages for rsfMRI provided by ultrahigh field strength (7T) may not fully mitigate the effects of brain tumor-related NVU on rsfMRI.

Figure 7. Clinically significant language NVU

Patient with a left temporal lesion of grade II diffuse astrocytoma / grade III anaplastic astrocytoma. Top row shows language activation map (tbMRI) for a sentence completion (SC) task ($Z\text{-score} > 3.8$) overlaid on T1 weighted structural images. Note that absent activation (white arrow) during task performance both in Broca's and Wernicke's language areas. Second row shows BOLD breath hold cerebrovascular reactivity (BH CVR) maps overlaid on T1 weighted anatomic images of the same patient displaying decreased regional cerebrovascular reactivity (CVR) in the ipsilesional hemisphere ($Z\text{-score} > 2.5$). Third and

fourth rows show regional homogeneity (ReHo) --KCC-ReHo and Cohe-ReHo, respectively-- maps ($KCC > 0.42$ & $Cohe > 0.3$) from resting state fMRI (rsfMRI). Fifth and sixth rows show maps of frequency domain metrics amplitude of low frequency fluctuations (ALFF) & fractional ALFF (fALFF) ($ALFF > 0.35$ & $fALFF > 0.32$) from rsfMRI. Note that absent activation during task performance and decreased ipsilesional CVR in the expected Broca's and Wernicke's area of the left temporal lobe corresponds to absence/decrease of BOLD signal within the same cortical region on KCC-ReHo, Cohe-ReHo, ALFF and fALFF rsfMRI maps. The abnormally reduced ipsilesional task-based activation in the absence of corresponding neurological deficits or impaired task performance is direct evidence of neurovascular uncoupling (NVU), whereas the findings on the other maps are resting state correlates of such NVU. This is a case of clinically significant NVU since the NVU affects regions where critical language activation is expected. White arrow in each map points to the ipsilesional decreased / absent BOLD signal.

Figure 8. Clinically insignificant language NVU

Patient with a left temporal lobe grade II diffuse astrocytoma. Top row shows language activation map (tbfMRI) for a sentence completion (SC) task (Z -score >3.7) overlaid on T1 weighted structural images. Note the decreased activation (white arrow) during task performance both in Broca's area (BA) and Wernicke's area (WA). Second row shows BOLD breath hold cerebrovascular reactivity (BH CVR) maps overlaid on T1 weighted anatomic images of the same patient displaying decreased regional cerebrovascular reactivity (CVR) in the ipsilesional hemisphere (Z -score >2.2). Third and fourth rows show

regional homogeneity (ReHo) --KCC-ReHo and Cohe-ReHo, respectively-- maps (KCC>0.39 & Cohe>0.27) from resting state fMRI (rsfMRI). Fifth and sixth rows show frequency domain metrics amplitude of low frequency fluctuations (ALFF) & fractional ALFF (fALFF) maps (ALFF>0.5 & fALFF>0.34) from rsfMRI. Note that decreased activation during task performance and decreased ipsilesional CVR in the expected Broca's and Wernicke's area of the left temporal lobe correspond to decreased BOLD signal within the same cortical region on KCC-ReHo, Cohe-ReHo, ALFF and fALFF rsfMRI maps. In this case, the reduced ipsilesional task-based activation in the absence of corresponding neurological deficits or impaired task performance is direct evidence of neurovascular uncoupling (NVU), whereas the findings on the other maps are resting state correlates of such NVU. However, since the ipsilesional expected critical language activation in BA and WA is still detectable despite the NVU, this is a case of clinically insignificant NVU. White arrow in each map points to the ipsilesional decreased BOLD signal.