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Recommended Resting-State fMRI Acquisition and Preprocessing Steps for Preoperative Mapping of Language and Motor and Visual Areas in Adult and Pediatric Patients with Brain Tumors and Epilepsy

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ABSTRACT

Resting-state (rs) fMRI has been shown to be useful for preoperative mapping of functional areas in patients with brain tumors and epilepsy. However, its lack of standardization limits its widespread use and hinders multicenter collaboration. The American Society of Functional Neuroradiology, American Society of Pediatric Neuroradiology, and the American Society of Neuroradiology Functional and Diffusion MR Imaging Study Group recommend specific rs-fMRI acquisition approaches and preprocessing steps that will further support rs-fMRI for future clinical use. A task force with expertise in fMRI from multiple institutions provided recommendations on the rs-fMRI steps needed for mapping of language, motor, and visual areas in adult and pediatric patients with brain tumor and epilepsy. These were based on an extensive literature review and expert consensus.

Following rs-fMRI acquisition parameters are recommended: minimum 6-minute acquisition time; scan with eyes open with fixation; obtain rs-fMRI before both task-based fMRI and contrast administration; temporal resolution of ≤2 seconds; scanner field strength of 3T or higher. The following rs-fMRI preprocessing steps and parameters are recommended: motion correction (seed-based correlation analysis [SBC], independent component analysis [ICA]); despiking (SBC); volume censoring (SBC, ICA); nuisance regression of CSF and white matter signals (SBC); head motion regression (SBC, ICA); bandpass filtering (SBC, ICA); and spatial smoothing with a kernel size that is twice the effective voxel size (SBC, ICA).

The consensus recommendations put forth for rs-fMRI acquisition and preprocessing steps will aid in standardization of practice and guide rs-fMRI program development across institutions. Standardized rs-fMRI protocols and processing pipelines are essential for multicenter trials and to implement rs-fMRI as part of standard clinical practice.

ABBREVIATIONS: BOLD = blood oxygenation level–dependent; EC = eyes closed; EO-F = eyes open with fixation; EO = eyes open without fixation; FC = functional connectivity; GSR = global signal regression; ICA = independent component analysis; rs = resting-state; rs-FC = rs-functional connectivity; RSN = resting-state networks; SBC = seed-based correlation analysis; STC = slice timing correction; tb = task-based; TR = repetition time

Resting-state (rs) fMRI has been found promising for presurgical mapping of eloquent brain areas for brain tumor and epilepsy surgery.[1] For example, rs-fMRI is beneficial in localizing language areas when task-based (tb) fMRI cannot be performed due to cognitive impairment or limited tb-fMRI.[2] However, more studies are needed to validate the clinical utility of rs-fMRI for preoperative localization of language in adults and pediatric patients.

Rs-fMRI can be performed while the patient is at rest, and it can be acquired without the need for highly trained personnel. However, rs-fMRI is more susceptible to head motion than tb-fMRI.[3,4] It is critical to specify rs-fMRI acquisition and preprocessing steps and parameters to isolate the blood oxygen level-dependent (BOLD) signal corresponding to networks of interest. Additionally, not all preprocessing steps may be needed because

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some potentially carry the risk of removing the intrinsic BOLD signal.[3]

Yet, there is no standardization of rs-fMRI acquisition and preprocessing steps across institutions, hindering data sharing, comparison of results, and scientific transparency. Therefore, an expert task force consisting of 16 neuroradiologists, 2 pediatric neuroradiologists, 2 imaging physicists, and 1 clinical neuropsychologist with expertise in fMRI was formed to provide recommendations for specific rs-fMRI acquisition and preprocessing steps based on literature review and expert consensus for presurgical mapping of language, motor, and visual areas in patients with brain tumor and epilepsy. This task force hopes to encourage multicenter studies to implement rs-fMRI for widespread clinical use. Unlike tb-fMRI,[5] our recommendations can be used for both adult and pediatric patients.

LITERATURE SEARCH STRATEGY AND REVIEW PROCESS

References were identified through a literature search on PubMed and the Web of Science using the following keywords: (functional connectivity OR resting state OR resting-state) AND (fMRI OR functional MR imaging OR functional MR imaging) AND (brain neoplasm OR brain tumor OR epilepsy) AND (motor OR sensorimotor OR language OR visual OR vision) in July 2022. Although in some publications, the terms are used interchangeably, for the purpose of this article, rs-fMRI refers to BOLD signal acquisition during rest and rs-functional connectivity (rs-FC) refers to postprocessed resting-state correlation results. Rs-FC data are often represented as resting-state networks (RSN) of closely connected areas across the brain (eg, language).

From the total of 1291 articles that were identified from the initial keyword search, 305 duplicate articles were removed. The abstracts of the remaining 986 articles were evaluated and further subselected for the following criteria: rs-fMRI studies written in English that localized and/or lateralized individual language, motor, and/or visual areas in patients with brain tumor and/or epilepsy for preoperative planning from January 2008 until July 2022. Studies that used rs-fMRI to localize seizure-onset zones to examine connectome or local properties of the rs-fMRI signal with an amplitude of low-frequency fluctuation and regional homogeneity analysis without localizing functional areas were excluded. A total of 75 articles met the inclusion criteria.

All the acquisition and preprocessing steps that each article used were recorded. For articles that used >1 parameter for a step, they would be counted more than once for analysis. For example, if an article used 2 different temporal resolutions, this article would be counted as 2 different studies. Articles that used a near-equivalent number of patients with brain tumor and epilepsy would also be counted as 2 distinct studies. Additionally, when we recorded the number of studies that used specific preprocessing steps, they were separated on the basis of whether they used seed-based correlation analysis (SBC), independent component analysis (ICA), and/or other algorithms such as multilayer perceptron, cortical parcellation, or deep learning analysis. If articles used >1 type of algorithm, they would be included in the analysis more than once. Thus, a total of 86 studies were used for the literature review. In addition, for articles that did not report the length of the scan, this was calculated by multiplying the temporal resolution used by the number of volumes scanned.

Individuals with expertise in fMRI were invited to form a task force to reach expert consensus on the specific rs-fMRI acquisition and preprocessing steps for presurgical planning in patients with brain tumors and epilepsy (Tables 1 and 2). Across a total of 4 Webinar meetings, the task force members anonymously voted on every acquisition and preprocessing step after presentation of the literature review and after the ensuing group discussion. On the basis of a Delphi method, expert consensus was reached when ≥60% of the members recommended a specific acquisition/preprocessing step.[6] The parameters that were not recommended were deemed optional. Subsequently, 2 American Society of Pediatric Neuroradiology neuroradiologists with expertise in pediatric fMRI were invited to provide additional input as it related to pediatric rs-fMRI.

Table 1: Resting-state fMRI acquisition parameters

Acquisition Parameters	Recommended
Length of scan	Minimum of 6 minutes
Eye status	EO-F
Order of rs-fMRI vs tb-fMRI	rs-fMRI before tb-fMRI
TR	≤2 Seconds
Physiologic noise source monitoring	Optional
IV contrast administration	After rs-fMRI
Scanner field strength	3T or higher

Table 2: Resting-state fMRI preprocessing steps

Preprocessing Steps	Recommended
Motion correction	Yes, for SBC and ICA
STC	Optional for TR ≤2 Recommended for TR >2 for SBC and ICA
Elimination of systematic odd-even slice-intensity differences	Optional
Despiking	Yes, for SBC only
Volume censoring/scrubbing	Yes, for SBC and ICA
Linear detrending	Optional
Nuisance regression: CSF/white matter	Yes, for SBC only
Nuisance regression: head motion	Yes, for SBC and ICA
Nuisance regression: global signal	Optional
Temporal filtering	Yes, bandpass filtering for SBC and ICA
Spatial smoothing	Yes, with smoothing kernel at twice the voxel size for SBC and ICA

RECOMMENDATIONS OF ACQUISITION AND PREPROCESSING STEPS

Acquisition Steps

Length of Scan: Recommend Minimum of 6 Minutes. Because the scan acquisition time for rs-fMRI can influence the sensitivity, reliability, and stability for detecting rs-FC, determining the appropriate scan length is important. The task force recommends a minimum rs-fMRI scan time of 6 minutes for preoperative mapping of the motor, language, and visual areas in patients with brain tumor and epilepsy.

The reliability, consistency, and strength of rs-fMRI increases with scan duration. Birn et al[7] have shown that the reliability across the 153 rs-FCs increased with scan duration and demonstrated improvement in the intrasession reliability of rs-fMRI FC by 20% at 12 versus 6 minutes. An even greater improvement in intrasession reliability was noted at 6 minutes (intraclass correlation coefficient = 0.4) compared with 3 minutes (intraclass correlation coefficient = 0.2).[7] Stronger reliability of the functional connectivity (FC) was noted with increased scan acquisition, but this improvement plateaued at around 13 minutes.[7] However, these studies were conducted on healthy subjects.

For patients with neurologic deficits who need mapping of large cortical areas, shorter scan duration may be more clinically optimal.[8] In most preoperative MR imaging examinations, patients need to undergo scanning for extended periods of time to include anatomic registration images, tb-fMRI, DTI, and other clinical sequences, and lying still in a scanner will likely be tiring and uncomfortable, especially for patients who are claustrophobic.[8] Furthermore, longer scan times could increase the chance of excessive head motion and patients falling asleep. Six minutes of scanning time was shown to be sufficient for the correlation strengths within and between major RSNs to stabilize in healthy participants, with only minimal benefits beyond this duration.[9] Even shorter scan times, approximately 3–4 minutes, have been shown to reliably detect motor and language areas, using a high-speed multiband acquisition with a very short (eg, <500 ms) temporal resolution in patients with glioma.[10]

For the purposes of presurgical mapping of motor, language, and visual areas, we thus recommend a minimum of 6 minutes of scan time, acknowledging that more scan time may be needed to map other rs-fMRI networks. From our literature review, 79/86 (92%) studies reported the scan length per session that they used. The mean, mode, and median scan lengths per session were the following: 7, 6, and 6.1 minutes with the scan length ranging from 4.3 to 28 minutes. In addition to reporting the total length of the scan, we chose to report the scanning time by the length of scan per session: 67/79 (85%) studies had 1 rs-fMRI acquisition session, 9/79 (11%) studies had 2 rs-fMRI sessions, and 3/79 (4%) had 4 rs-fMRI sessions. Thus, on the basis of the literature review, most of the studies used only 1 rs-fMRI acquisition session.

Eye Status: Recommend Eyes Open with Fixation. Three eye status conditions during presurgical rs-fMRI were considered: eyes closed (EC), eyes open with fixation (EO-F), and eyes open without fixation (EO). The specific eye status condition can impact the strength, reliability, and consistency of rs-FC.[11] As discussed below, the task force recommends EO-F, typically to a crosshair. At institutions that cannot accommodate EO-F, the EC is considered acceptable for presurgical planning.

Patients closing their eyes during a rs-fMRI scan increases their risk of falling asleep.[12,13] Tagliazucchi et al[13] demonstrated in 71 healthy subjects with EC during a rs-fMRI scan that after 4 minutes of scanning, one-third of the participants fell asleep, and within 10 minutes, one-half were asleep. However, in EO-F, they stayed awake longer compared with either EC or EO.[13] Most importantly, Tagliazucchi et al showed changes in rs-FC in various brain areas, including the sensorimotor and visual areas, during sleep compared with the awake state.[13] Furthermore, Wang et al[14] showed that being awake increased test-retest reliability across various RSNs, including the somatomotor and visual networks. Furthermore, Agcaoglu et al[15] noted that the EC condition likely led to subjects being drowsy and daydreaming, which led to more variability and no interactions with demographic covariates in contrast to the EO-F condition.

Conversely, the EC and EO states are considered true resting states and not as cognitively demanding as EO-F.[16] Additionally, multiple studies have shown that variability in the strength or reliability of the FC of sensorimotor[15,17,18] and visual[11,16,17] networks to other networks depends on the eye status condition. While this result would be a factor to consider if we were to quantify or analyze FC, for the purpose of preoperative mapping of cortical areas, ensuring that the patients are awake and minimizing movement should be emphasized. In this regard, both the EC and EO are less favorable because of potential excess eye movement during the scan compared with EO-F.[11] In EC, patients falling asleep could lead to excessive head motion.

From our literature review, 70/86 (81%) studies reported the eye status condition of their patients. Thirty-five of 70 (50%) studies had their patients close their eyes, 24/70 (34%) studies had patients fixate their eyes on a crosshair, 6/70 (8.6%) studies had patients open eyes without fixation, and 5/70 (7.1%) studies had sedated patients. More rs-fMRI studies using the eyes closed condition may be because it is logistically easier than displaying a crosshair.

Order of rs-fMRI versus tb-fMRI: Recommend rs-fMRI before tb-fMRI. The task force recommends that rs-fMRI be obtained before tb-fMRI when feasible. The FC of rs-areas can be influenced by tasks.[19,20] Wang et al[19] reported changes in the nodal degree and global efficiency across intra- and extra-default mode areas and FC during the posttask relative to pretask resting states in healthy participants. Tung et al[20] noted a transient (5 minute) effect of increased FC between the motor cortex in the post-motor task resting state compared with pretask.[20] This effect was not noted in the control group. Because tb-fMRI protocols can vary among patients and institutions, having patients undergo rs-fMRI and then tb-fMRI will allow better standardization for multicenter studies. Furthermore, because rs-fMRI is more sensitive to motion artifacts than tb-fMRI,[4] acquiring it near the start of the imaging session would reduce the chance of these artifacts. Nevertheless, if tb-fMRI needs to be obtained before rs-fMRI due to established institutional protocols and subject limitations, it is the opinion of the task force that rs-fMRI can still be analyzed. A compromise is that other structural imaging such as DTI can be performed between tb- and rs-fMRI acquisitions to minimize potential tb-fMRI influences on rs-fMRI FC.

From our literature review, 58/86 (67%) studies reported using both rs-fMRI and tb-fMRI paradigms. Twenty-six of 58 studies (45%) reported a specific order in which they performed both fMRI scans. Eighteen of 26 (69%) studies acquired rs-fMRI before tb-fMRI paradigms, whereas 8/26 (31%) studies performed tb-fMRI before rs-fMRI.

Repetition time (TR): Recommend TR of ≤2 Seconds. For rs-fMRI, using a single-shot EPI sequence is most common. TR

defines the repetition time or the rate of sampling of the low-frequency rs-BOLD signal fluctuation. The task force recommends a TR of ≤2 seconds.

An accelerated TR can improve the discrimination of different components with ICA because of the increase in temporal information.[21] The Human Connectome Project (https://www.humanconnectome.org/) used a TR of 0.7 seconds to scan 1200 controls, improving identification of resting-state signal fluctuations and increasing their ability to detect physiologic noise.[22] Voets et al[23] reported similar findings and compared the use of 3 different temporal sampling rates at 0.72, 1.56 , and 3.5 seconds to localize the motor region in patients with gliomas. Using a TR of <2 seconds compared with 3.5 seconds resulted in greater success in localizing and spatially separating the motor region into its 3 functional zones.[23] Additionally, a long TR of >4–5 seconds approaches the Nyquist limit frequency for typical BOLD frequencies (<0.1 Hz). Using simulated tb-fMRI, Parker et al[24] observed a decrease in *t*-statistics with longer TRs.[24] The gain in *t*-statistics due to the slice timing correction (STC) was negligible at a TR of <2 seconds compared with a TR of >2 sections (see STC correction below).

In modern scanners, multiband acquisition allows shorter TR while maintaining whole-brain coverage, which can increase rs-fMRI sensitivity[21] and statistical power. If one is not using simultaneous multislice scanning, shortening the TR will compromise the spatial resolution or section coverage.[22] Multislice scanning capability may not be readily available on clinical scanners at this time.

From our literature review, 85/86 (99%) studies reported the TR they used. The mean, mode, and median TRs were the following: 2.2, 2, and 2 seconds with the TR ranging from 0.14 to 5 seconds.

Physiologic Noise-Source Monitoring: Optional. Physiologic noise-source monitoring of cardiac and respiratory origins aims to remove low-frequency physiologic fluctuations unrelated to neuronal activity that could introduce artifacts and decrease the sensitivity of rs-fMRI.[25] The 2 main sources of physiologic fluctuations are heart-related variations, typically around 0.9–1.2 Hz, and respiratory variations, around 0.2–0.4 Hz,[26] which can be detected via photoplethysmography on the index finger and a pneumatic belt around the abdomen, respectively.[27] Cardiac pulsations can cause CSF and brain parenchymal movement, which can cause changes in the BOLD fMRI series, specifically in the vertebrobasilar system.[26] Respiratory movement can affect rs-fMRI.[26] The task force considers physiologic noise monitoring optional.

Although physiologic recording correction for physiologic variations is possible using retrospective correction techniques like RETROICOR,[28] the signal variation can also be minimized through a combination of appropriate data-preprocessing steps.[9] RETROICOR can suppress both cardiac and respiratory fluctuations by 68% and 50%, respectively.[28] Finite impulse response band-reject digital filters and retrospective gating in *k*-space using data-driven algorithms can also remove cardiac and respiratory fluctuations.[26] However, these steps require external physiologic monitoring, which would be additional steps that could unnecessarily lengthen the fMRI procedure in the clinic. In contrast, there are software solutions that do not require such external monitoring. For example, Behzadi et al[29] have shown that by using anatomic component correction, cardiac and respiratory noise can be simultaneously removed by conducting white matter and CSF regression without external monitoring. Van Dijk et al[9] showed that regressing nuisance correlations from white matter, ventricular, and whole-brain signals can adequately remove artifacts from cardiorespiratory sources. Bandpass filtering out low-frequency fluctuations can also remove physiologic fluctuations. Separating noise components with independent component analysis could offer additional correction.[30]

Monitoring physiologic noise for removal may be helpful in patients anticipated to have excessive physiologic variation, such as pediatric patients or those with movement disorders. Notably, variations in respiration could be <0.1 Hz, which overlaps with BOLD signal fluctuations between 0.01 and 0.1 Hz,[9,25] precluding straightforward removal by bandpass filtering. However, even in the situation above, using a short TR, ICA, or a combination of various preprocessing techniques, such as nuisance regression[9] or global signal regression,[31] can reduce the noise contributions and make it feasible to detect the rs-BOLD signal relevant to preoperative mapping of rs-FC. In multislice fMRI data, physiologic noise sources at greater frequencies than the expected bandwidth of rs-fMRI BOLD fluctuations can, through undersampling, be aliased down into the target signal band.[32]

Two of 86 (2.3%) studies in our literature review externally monitored and adjusted for cardiac and respiratory sources of variation in the BOLD signal.

Gadolinium-Based Contrast Agent Administration: Recommend rs-fMRI before Contrast Administration. There is limited literature support for IV administration of gadolinium-based contrast agents before or after rs-fMRI. Clinical decisions on when to administer gadolinium-based contrast agent will typically depend on institutional policy, experience, and/or the purpose of the fMRI scan. In a tb-fMRI study, Naganawa et al[33] showed that administering gadolinium-based contrast agents decreased the sensitivity at which the primary motor cortex could be localized in 8 healthy participants who underwent a self-paced motor task compared with precontrast imaging.

The task force recommends obtaining the rs-fMRI scan before contrast administration. However, in cases in which a patient's standard-of-care imaging needs to be prioritized and information gleaned from rs-fMRI might be helpful, postcontrast rs-fMRI data could still be interpreted with caution. This suggestion is especially relevant in cases in which the patient may not be able to complete the entire scan.

Scanner Field Strength: Recommend 3T or Higher. Based on the literature review, the most common MR imaging field strength used for rs-fMRI is 3T. Scanners of all 3 field strengths (1.5T, 3T, and 7T) can be used for preoperative mapping of rs-areas. Scanners with higher field strengths produce higher SNRs, which can be used to achieve higher spatial resolution.[34] Additionally, the greater magnetic susceptibility effects at higher magnetic field strengths increase the expected BOLD signal change. Garcia-Eulate et al[35] showed that 3T MR imaging showed improved localization of the motor and somatosensory areas with rs-fMRI compared with 1.5T. Krasnow et al[36] also determined activation

in several regions such as the inferior frontal gyrus, orbitofrontal gyrus, and lingual gyrus with 3T, which could not be detected with 1.5T.

Compared with 3T, a 7T study has shown more precise mapping of RSNs,[37] and another study showed that the measured rs-fMRI signal increased almost 2-fold.[38] However, not only is 7T less widely available than 3T, it can introduce more physiologic, motion, and susceptibility artifacts.[34] If a patient has implants that are MR imaging–conditional at only 1.5T or metal objects that are expected to cause susceptibility artifacts near the functional areas of interest, then 1.5T may be preferable.

From our literature review, 85/86 (99%) studies that used rs-fMRI for presurgical mapping reported the scanner field strength used. Seventy-five of 85 (88%) studies acquired rs-fMRI with 3T scanners, 9/85 (11%) studies used 1.5T scanners, and 1/85 (1.2%) studies used a 7T scanner.

Preprocessing Steps

Motion Correction: Recommended for Both SBC and ICA. Motion correction involves spatially realigning the dynamic volumes acquired during the rs-fMRI scan to a reference volume that is usually the first or the middle volume of the scan.[39] The task force recommends including motion correction as a preprocessing step for both SBC and ICA.

Head movement, even in the order of millimeters, can prevent accurate rs-fMRI estimates.[3] Head motion can cause a change in tissue composition within a voxel, which can, in turn, affect its net magnetization and introduce spin-history artifacts that could be difficult to distinguish from true rs-fMRI signal.[3] Head motion introduces distance-dependent bias,[40] in which movement can increase BOLD signal changes in certain regions of the brain but cause a decrease in others.[41] Finally, head motion can introduce BOLD signals that may not be distinguishable from neural activity,[3] contributing to false-positive connections. Especially with the high susceptibility to motion artifacts of rs-fMRI, motion correction is essential to improve its sensitivity[3] and specificity.[42]

Jo et al[40] showed a decrease in distance-dependent correlation bias after motion correction.[40] Maknojia et al[3] noted that motion correction was essential to isolate true rs-networks from noise, and Beall et al[43] showed a reduced image temporal standard deviation (SD) after motion correction. Additionally, motion parameters can be included in the general linear model for nuisance regression.[44] Oakes et al[42] did a comparative analysis of commonly used software programs such as Analysis of Functional Neuro Images (AFNI; http://afni.nimh.nih.gov/afni), SPM (http://www.fil.ion.ucl.ac.uk/spm/software/spm12), FSL http://www.fmrib.ox.ac.uk/fsl, AIR,[45,46] and BrainVoyager (https://www.brainvoyager.com/bv/doc/UsersGuide/BrainVoyagerUsersGuide.html) and concluded that all performed equivalently.

While motion correction can improve data quality, it cannot negate all the effects of head motion.[27,47] Head motion control should be emphasized to the patients being scanned. Additionally, other preprocessing techniques such as despiking, volume censoring, and/or head motion regression should additionally be considered.[27]

All the studies in our literature review, including those that used SBC, ICA, and other methods, conducted motion correction (100%, 86/86).

STC: Optional at a TR of ≤2 Seconds; Recommended at a TR of >2 Seconds for Both SBC and ICA. The majority of fMRI studies use a 2D multislice single-shot gradient-echo EPI sequence. Because the slices are acquired via a sequential or interleaved mode, each section is acquired at a different time within the TR.[24] These time differences cause temporal shifts in the data, which could result in a mismatch between the measured-versus-actual hemodynamic response.[48] STC accounts for such time differences by temporally realigning the individual slices to a reference section to correct for any phase shifts, to model the signal from the whole volume at the same time point.[49] The task force recommends STC at a TR of >2 seconds for both SBC and ICA. If the recommended TR parameter is followed at a TR of ≤2, then STC would be an optional step.

At a TR of ≤2 seconds, STC will likely have minimal benefit in detecting activation in the RSNs compared with not applying the correction.[49] At this short TR, acquisition delays between slices are minimal. The Human Connectome Project rs-fMRI used a subsecond TR and did not use STC because of unavoidable errors from temporal interpolation that could obscure high-frequency signals.[22] Parker et al[24] have shown that STC at a TR of <2 seconds for tb-fMRI TRs of 0.5 and 1.1 seconds using FSL and SPM resulted in only minimal benefits of 2.2% and 5% compared with uncorrected data at TR = 2 seconds for which the benefit was 15.6%.[24] Poldrack et al[50] do not recommend using STC at a short TR because artifacts in the reference image could be propagated to other slices.

At a longer TR, STC can improve detection of both rs-FC and tb-fMRI activations by removing temporal sources of variance,[22] particularly in cases with medium-to-high motion.[49] Parker et al[24] demonstrated a improvement of 55.7% in global *t*-statistics at a TR of 5 seconds compared with or without STC. STC is especially important when mapping the dorsal areas such as the motor cortex.[48] STC at a TR of >2 can also be synergistic when combined with other preprocessing steps. Because movement introduces both spatial and temporal artifacts, a combination of STC and motion correction is needed to avoid the time-series consisting of temporally nonuniform samples.[48] Additionally, STC is necessary when using spatial smoothing because slices with large delays could introduce residual data when averaged with adjacent slices with smaller delays.[24]

From our literature review, 62/86 (72%) studies performed STC, among which 26 studies were scanned at a TR of ≤2 seconds and the other 36 were scanned at TR >2 seconds.

Elimination of Systematic Odd-Even Section-Intensity Differences: Optional. During interleaved section acquisition, odd-numbered and even-numbered slices are acquired with a relatively large time difference, which can be up to half the TR. The task force considers elimination of systematic odd-even section-intensity differences an optional preprocessing step.

On the basis of expert opinion, it is no longer necessary to eliminate odd-even section-intensity differences with newer model scanners. However, before the advent of such scanners, elimination of odd-even section-intensity differences was necessary to exclude crosstalk between interleaved section acquisitions.[51] Additionally, limited studies and rs-fMRI software tools use this preprocessing step.

From our literature review, 11/86 studies (13%) eliminated systematic odd-even section-intensity differences.

Despiking: Recommended for SBC Only. Despiking is a method to correct spikes representing artifacts induced by sudden motion or system instability in the fMRI time-series by truncating,[40] removing, or interpolating[52] signal of the independent voxels. Spikes are often defined as signals that exceed the median and/or mean of the rs-fMRI time-series by a set SD. The task force would recommend despiking for SBC only. On the basis of the literature, a maximum threshold of <5% would likely be acceptable. Patel et al[52] reported wavelet despiking at an average of 1.5% and excluded patients with spike percentages of >5% because they had moved excessively. Power et al[53] also used the despiking setting of 4% with the ArtRepair software (https://www.nitrc.org/projects/art_repair/).

Despiking can identify and remove a wide range of movement-induced artifacts across different frequencies that may not be typically removed by other preprocessing techniques, such as linear regression.[52] Even small movements of the head can introduce secondary sources of artifacts, including spin-history artifacts, which have failed to be effectively removed by nuisance regression and/or volume censoring.[52] However, despiking, specifically wavelet despiking, recently introduced by Patel et al[52] has proved effective in removing these types of motion artifacts from low-to-high frequencies. Patel et al showed that combining wavelet despiking with regression was superior in removing both linear and nonlinear sources of artifacts related to movement and retained less signal variance compared with nuisance regression alone. When combined with nuisance regression, it could identify correlation estimates at strengths similar to those of volume censoring.[40] However, compared with volume censoring, despiking removes voxels with motion artifacts without removing the entire volume of data.[52] Despiking is especially recommended in patients with potentially rapid head movements, such as patients with epilepsy and/or pediatric patients.[52]

On the other hand, despiking can potentially flag too many data points for correction. Replacing flagged data by interpolating adjacent data could add too many artificial signals. Removing too many data points could prohibit detection of functional correlations. Therefore, when using despiking, users need to avoid being too aggressive.

From our literature review, only 8/86 studies (9.3%) used despiking, because it is not available in many commonly used software packages. However, among the 8 studies that used it, 14% of the studies that employed SBC used despiking, whereas 5% of the studies that utilized ICA used despiking.

Volume Censoring/Scrubbing: Recommended for Both SBC and ICA. Volume censoring or scrubbing is frame wise removal of any volume with excessive movement or signal changes over a predetermined threshold.[41] Such volumes are identified by first calculating the frame wise displacement of the head position, which measures how much the head moved compared with previous time points and/or DVARS (D: temporal derivative of time courses, VARS: RMS variance over voxels), which measures the rate of change of BOLD signal across the entire brain at each frame of data.[41] If the frame wise displacement or DVARS of specific volume exceeds a set threshold, that volume would be either dampened, removed,[41] or interpolated.[27] The task force would recommend volume censoring for both SBC and ICA.

The threshold will determine how much data will be removed. It will depend on various factors, such as the number of time points and the duration of the scan. The task force cannot recommend a specific threshold at this time. On the basis of the literature, Power et al[41] chose a value of 0.5 mm for frame wise displacement and a 0.5% change in BOLD signal for DVARS to represent the minimum threshold for movement in still adults. In healthy children, they reported approximately 25% of the rs-fMRI data being affected by motion artifacts. They required a minimum of at least 125 frames, around 5 minutes of data, to be kept after scrubbing, but they had no maximum threshold for how much data could be removed.[41]

Artifacts in rs-fMRI data can be caused by various sources.[41] Susceptibility artifacts can cause image distortions and signal dropouts.[41] Even a small head movement can cause a shift in the position of the brain in space, which can cause a large difference in the amplitude of the BOLD signal and subsequently changes in rs-FC.[41] Head movement can also cause short-range correlations to strengthen, whereas medium- to long-distance FC weakens them.[40] Volume censoring can correct for this bias.[40] Although volume censoring and despiking have similar goals in eliminating motion artifacts exceeding a threshold, volume censoring may be advantageous in patients with the potential for large movements,[3] removing entire frames of data instead of only affected voxels. Additionally, when slow, residual movements are spread over consecutive voxels, volume censoring may, in theory, perform better than despiking.

The disadvantage with volume censoring is that because entire frames of data are removed, more data are typically removed than in other preprocessing steps. Power et al[41] reported removing up to 39% of the data after volume censoring of 22 healthy children who underwent rs-fMRI. For cooperative patients with relatively little motion, volume censoring is expected to be beneficial; however, in patients who move excessively, volume censoring may be unfavorable.

From our literature review, 20/86 (23%) studies performed volume censoring.

Linear Detrending: Optional. Linear detrending removes linear BOLD signal drifts or trends typically caused by scanner instability, physiologic fluctuations, and/or head motion.[54,55] The task force considers linear detrending optional.

Typically, linear signal drifts are low-frequency in nature and can mostly be accounted for by using bandpass and/or high-pass filtering. However, if temporal filtering is not performed, linear detrending is necessary and can help account for scanner instabilities or residual slow head movement.

From our literature review, 41/86 (48%) studies performed linear detrending.

Nuisance Regression: CSF/White Matter Regression—Recommended for SBC Only. Nuisance signal regression removes temporal components in BOLD signal time courses that are correlated with head motion and CSF/white matter signal fluctuations to eliminate non-

neural contributions.[29] Currently, the main method for nuisance signal regression is a general linear model–based approach in which motion time curves and tissue-based signal time courses are regressed from the rs-fMRI data.[56] The task force would recommend nuisance regression of CSF/white matter signal time curves for SBC only.

Because most neuronal activation occurs in the gray matter, signal changes in the white matter and CSF would mostly be non-neural in origin, such as cardiac and respiratory fluctuations.[29] These can be estimated from various sources including anatomic data, ROIs with high temporal SDs, and noise components from ICA or principal component analysis.[29,57] Nuisance regression of CSF, white matter, and head motion can reduce temporal SDs[29] and improve the specificity at which FC can be estimated.[56] Muschelli et al[56] noted a decrease of motion artifacts, causing variability in FC while preserving the signal of interest with nuisance regression of CSF and white matter. While bandpass filtering without nuisance regression reduces BOLD signal fluctuations due to motion, it did not prevent the spread of motion-contaminated BOLD signal fluctuations.[58]

In cases of standard space transformation for individual patients, incorrect tissue segmentation or inclusion of nuisance signals that represent neural activity would reduce the performance of nuisance regression.[29] Furthermore, a portion of white matter or CSF can be misclassified by large brain tumors or other lesions, affecting the fidelity of the nuisance regressors. From our literature review, 51/86 (59%) studies performed nuisance regression of CSF and/or white matter. Forty-eight of 51 (94%) of these performed both white matter and CSF regression, while 3/51 (5.9%) performed regression for only CSF. Of these 51 studies, 79% of the studies used SBC compared with 33% of the studies that used ICA.

Nuisance Regression: Head Motion Regression—Recommended for Both SBC and ICA. Head motion regression is another type of nuisance regression in which translational and rotational motion estimates from image realignment are applied as the nuisance regressors.[27] The number of motion parameters ranges from 6 to 36,[27,59] with 6 being the most common.[27] The expert task force recommends head motion regression for both SBC and ICA.

Due to the complex effects of head motion, image spatial realignment is not enough to fully eliminate motion artifacts,[56] and additional correction is of benefit. Although volume registration works well for small movements, larger motion errors can arise during realignment.[3] Patients may move more than healthy adults.[3] Furthermore, head movement can warp the magnetization gradient,[3] possibly resulting in image distortions.

A possible problem with head motion regression is that in cases of extensive head motion, the realignment parameters may still not fully explain the motion-related signal changes.[27] Additionally, an excess of motion regressors could remove neuronal-related signal fluctuations,[27] especially in cases in which there is minimal head movement.[3] From our literature review, 45/86 (52%) studies conducted head motion regression.

Nuisance Regression: Global Signal Regression Optional. Global signal regression (GSR) is regressing out the average time-series across the whole-brain volume. GSR is an effective though controversial means of reducing widely shared variance and thereby improving the spatial specificity of computed maps.[60-62] The task force considers GSR an optional preprocessing step.

Part of the global signal is of neural origin;[63] however, much of the global signal represents non-neural artifacts attributable to physical effects of head motion[31,59,64,65] and variations in the partial pressure of arterial carbon dioxide.[66] GSR can reduce signal variances due to head motion and physiologic fluctuations better than CSF and white matter regression and motion correction combined.[31] Without GSR, all parts of the brain appear to be strongly positively correlated.[67-70] GSR causes all subsequently computed correlation maps to be approximately zero-centered; in other words, positive and negative values are approximately balanced over the whole brain.[60] Thus, GSR negatively biases all computed correlations but preserves relative iso-correlation contours. This negative bias has caused some to criticize GSR because it induces artifactual anticorrelations[71,72] and removes neural components in the global signal, though an alternative counter view is that widely shared variance in the fMRI signal induces artifactual positive correlations. More recent objections to GSR suggest that it can distort quantitative FC differences across diagnostic groups.[73,74] A more recent consensus article attempts to reconcile these opposing viewpoints.[75]

From our literature review, 27/86 (31%) studies conducted GSR.

Temporal Filtering: Recommended Bandpass Filtering for Both SBC and ICA. Bandpass, low-pass, or high-pass temporal filtering has been commonly applied for rs-fMRI. This preprocessing step removes BOLD signal components with frequencies typically lower than 0.01 Hz and/or higher than 0.1 Hz. The task force recommends bandpass filtering the rs-fMRI data for both SBC and ICA. On the basis of the literature, 0.01–0.08 Hz was the most common bandpass filtering frequency range.

Filtering out any frequencies outside the typical rs-fMRI frequency range of 0.01–0.1 Hz is important to eliminate any residual noise from head motion, physiologic origins, and/or low-frequency drifts.[76] Bandpass filtering increased the signal-to-noise separation within well-known RSNs and increased the test-retest reliability of whole-brain connectivity in both healthy controls and subjects with mild Alzheimer disease.[77] Bandpass filtering is often combined with nuisance regression of CSF/WM, motion, and global signal.[58] In a study conducted by Risk et al,[78] the accumulation of spatially heterogeneous multiband noise, the physiologic noise from CSF pulsations, and the variance from intracranial brain motion increased the SD and resulted in reduced rs-FC estimates, even when using nuisance regression. However, when nuisance regression was combined with bandpass filtering, they obtained higher functional correlations at higher multiband factors.[78] Additionally, Van Dijk et al[79] demonstrated that linear trends were removed with bandpass filtering, while maintaining frequencies of <0.08 Hz. Overall, bandpass filtering allows removal of extremes of high and low BOLD signal frequencies and would, therefore, allow the best estimate of localization of RSNs. The upper and lower thresholds at which the BOLD signal is filtered usually depend on the institution.

A disadvantage of bandpass filtering is that neural signal above or below the thresholds could be lost.[78] Physiologic

fluctuations in BOLD signal existing from 0.01 to 0.1 Hz may still not be removed with bandpass filtering. For example, low-frequency fluctuations due to the heart rate can occur at 0.04 Hz, and small fluctuations in breathing, at 0.03 Hz.[27] While such physiologic fluctuations are non-neural in nature,[27] they will be reflected in the BOLD signal in white matter and CSF, which can be removed through nuisance regression.

Low-pass and high-pass filtering can also be used in rs-fMRI preprocessing. Low-pass filtering is advantageous because it can filter out non-neural signals that are typically above 0.1 Hz.[27] Because most physiologic noise typically presents at high frequencies,[29] low-pass filtering can effectively remove such sources of noise while retaining the rs-BOLD signal of interest. However, intrinsic brain signal could still exist beyond 0.1 Hz.[27] Studies that used high-pass filtering detected only frequencies above, usually, 0.01 Hz, because any frequencies below 0.01 Hz most likely do not represent true rs-fMRI signal but represent noise instead. High-pass filtering can be used as an alternative to linear detrending because it can remove linear drifts that occur at low frequencies, below 0.02 Hz. However, high-pass filtering cannot remove motion artifacts at frequencies above 0.01 Hz.

From our literature review, 75/86 (87%) studies applied a temporal filter to the rs-fMRI data. Forty-five of 75 (60%) studies applied bandpass filtering, 20/75 (27%) studies applied low-pass filtering, and 10/75 (13%) studies applied high-pass filtering.

Spatial Smoothing: Recommended with a Kernel Size Twice the Voxel Size for Both SBC and ICA. For spatial smoothing, the signal at each voxel is averaged across a range of neighboring voxels to reduce noise[80] and increases sensitivity.[81] The task force recommends spatial smoothing for both SBC and ICA with a kernel size approximately twice the acquired voxel size. Kokkonen et al[82] reported unsuccessful mapping of sensorimotor areas when using unsmoothed data. Huang et al[83] reported that a Gaussian kernel size of 6-mm full width at half maximum with approximately 3-mm isotropic voxels increased the SNR of BOLD to enable more reliable mapping of motor and language areas. Alakorkko et al[80] showed that spatial smoothing can increase the correlation strength of voxels across rs-FCs. With young children with smaller brain sizes, the operator could consider proportionally reducing the voxel size and number of slices.

A smoothing kernel that is too small may have little benefit, while a kernel that is too large could reduce spatial specificity.[81] A kernel size that is twice the voxel size of the functional images has been recommended[84-86] to ensure the validity of the random field theory–based multiple comparison correction.[86]

From our literature review, 78/86 (91%) studies performed spatial smoothing. The kernel size ranged from 1 to 10 mm full width at half maximum, with a mean, mode, and median of 6.1, 6, and 6 mm full width at half maximum, respectively. Seventy-four of 78 (95%) studies reported the kernel size they used. Thirty-eight of 74 (51%) studies used a kernel size that was twice the voxel size.

CONCLUSIONS

The American Society of Functional Neuroradiology, the American Society of Pediatric Neuroradiology, and the American Society of Neuroradiology Clinical Translation of Functional and Diffusion MR Imaging Study Group suggests the use of the proposed standardized rs-fMRI acquisition and preprocessing steps as initial guidelines for institutions using rs-fMRI for preoperative mapping of language, motor, and visual areas in patients with brain tumors and epilepsy. The recommendations provided are based on a comprehensive review of the literature and consensus opinion from experts in fMRI from institutions in the United States and Canada. These rs-fMRI guidelines may lead to the development of a standard rs-fMRI pipeline as well as commercial rs-fMRI processing software. The rs-fMRI guidelines will also encourage and standardize multicenter studies that will help validate rs-fMRI for widespread clinical use. Future studies are needed to define a specific order of the rs-fMRI preprocessing steps, because currently, there is insufficient literature support and not enough expert consensus to provide an order for all the steps. Further studies are also needed evaluating the interactions of different preprocessing steps based on their order of implementation. Finally, the task force would emphasize that while the recommended acquisition/preprocessing steps are preferred, the ones that were deemed optional are not necessarily precluded and may be beneficial depending on the circumstances.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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