

Motion Correction Methods for MRS: Experts' Consensus Recommendations

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Abbreviations.

NoCo = No Motion Correction

MoCo = Motion Correction

ShMoCo = Shim and Motion Correction

ReShMoCo = Reacquisition of corrupted TRs with ShMoCo

FAST(EST)MAP = Fast, Automatic Shim Technique (using Echo-planar Signal readout) for Mapping Along Projections

FID = Free Induction Decay

SVS = Single Voxel Spectroscopy

MRS = Magnetic Resonance Spectroscopy

MRSI = Magnetic Resonance Spectroscopic Imaging

GABA = gamma-amino-butyric acid

GSH = glutathione

2HG = D-2-hydroxyglutarate

Abstract.

Long acquisition times due to intrinsically low signal-to-noise and the need for highly homogeneous B_0 field make magnetic resonance spectroscopy (MRS) particularly susceptible to motion or scanner instability compared to MRI. Due to strong coupling between localization and shimming (i.e., B_0 homogeneity), MRS data quality is severely degraded by motion. To mitigate the effects of motion or scanner instability, three approaches can be employed: 1) subject immobilization, 2) retrospective correction, and 3) prospective real-time correction using internal and/or external tracking methods. The best data quality can be obtained by prospective real-time correction which simultaneously updates localization and the B_0 field. While localization errors can be corrected with both internal (navigators) and external (optical camera, NMR probes) tracking methods, the B_0 field correction requires internal navigator methods to measure the B_0 field inside the imaged volume and the possibility to update the scanner shim hardware in real time. Internal and external tracking can rapidly update the MRS localization with sub-millimeter and sub-degree precision, while scanner frequency and 1st order shims of scanner hardware can be updated by internal methods every TR. These approaches are best developed for neuroimaging, for which rigid transformation is primarily applicable. Real-time correction greatly improves the stability of MRS acquisition and quantification as shown in clinical studies on subjects prone to motion, including children and patients with movement disorders, enabling robust measurement of metabolite signals including those with low concentrations, such as gamma-aminobutyric acid (GABA) and glutathione (GSH). Thus, motion correction is recommended for MRS users and calls for tighter integration and wider availability of such methods by MR scanner manufacturers.

Keywords: Magnetic resonance spectroscopy; Motion correction; Shim correction; Real-time; Navigator; Optical tracking; NMR probes; Metabolites; Neurochemistry; GABA; GSH.

1. INTRODUCTION

The requirements of long scan time to compensate the inherent low signal-to-noise ratio (SNR) of metabolites and stringent B_0 homogeneity to resolve spectral overlaps among metabolite signals make magnetic resonance spectroscopy (MRS) particularly susceptible to subject motion and hardware instability. Motion artifacts and incorrect signal localization in MRS are not always apparent,¹ especially in single voxel spectroscopy (SVS) that has no anatomical information, unlike MRI. Motion during acquisition of SVS may be suspected sometimes by the presence of signals that originate from outside the localized volume such as from extracranial lipids. However, even in the case of MR spectroscopic imaging (MRSI), motion artifacts are hard to recognize visually at the spatial resolution typically achieved in MRSI with limited structural information, which makes it difficult to correct motion artifacts in MRSI through post-processing as may be done in MRI.

Furthermore, the correct fitting and estimation of metabolite concentrations depend on having adequate spectral resolution, which requires spectral linewidth narrower than the separation of neighboring signals. Improving linewidth is achieved by B_0 shimming of the volume of interest before MRS measurement.² A change in the pose will be accompanied by a change in the B_0 field, rendering the original B_0 shimming suboptimal for the new pose. This results in degradation of spectral quality that manifests either as line splitting or broadening depending on the speed and nature of head motion. Because of this strong relationship between B_0 shimming and spectral quality, undoing the effects of motion in MRS requires the correction of both localization and B_0 shimming. Hence, the problem of motion correction in MRS includes the problem of B_0 shimming, and the experts' recommendations for B_0 shimming apply in the case of MRS motion correction. This is more demanding than in typical MRI where correction of spatial encoding may be sufficient to mitigate the effect of motion. Furthermore, even in the absence of motion, B_0 field changes occur due to extrinsic sources such as magnet field drifts or heating and cooling of the shim iron, which causes slow drifts in the B_0 field.³ Such scanner instability leads to broadening and distortion of spectral lineshape, or inefficient water suppression and spectral editing. Since MRI scanners do not have a frequency lock channel such as NMR spectrometers, other methods are needed to correct frequency drifts. In the case of MRSI, motion causes inconsistencies between k-space points, which result in signal smearing in image space along the directions of motion. This becomes particularly problematic

when artifacts originate from the large nuisance signals of water and lipid that can overwhelm metabolite signal. Because these artifacts do not obey the rules predicted by spatial response functions (SRF), improving SRF does not eliminate them. Efficient lipid/water suppression^{4,5} and lipid/water removal^{6,7} are necessary to mitigate them.

⁸ Lipid/water suppression that use frequency selective methods benefits from real time shim update that can maintain the frequency stability and efficiency of these suppression methods.

While various motion correction methods are commonly used for MRI,⁹⁻¹² currently these have not been widely used in the MRS community outside of a few research labs, despite the fact that MRS is more susceptible to motion degradation compared to MRI. This is mainly due to the limited availability of methods that are easy to integrate and use with the MRS acquisition and processing, or they are suboptimal because they do not mitigate B_0 field changes that are critical in MRS. Both retrospective¹³ (post-processing) and prospective¹⁴⁻¹⁶ (real-time) motion correction methods for MRI have been proposed and reviewed. The present paper focuses uniquely on methods for prospective motion and B_0 shim correction as these approaches offer the most comprehensive solution for MRS applications. The paper aims to (i) provide minimum recommendations that may be adopted by the MR community at large, and (ii) advocate for their implementation by MR scanner manufacturers.

Although the simplest method to mitigate motion is to immobilize the subject using head restraints and bite bars, this strategy is often unsatisfactory or impossible because it reduces patient comfort and still permits some movement. In body imaging, respiratory and cardiac related movement cannot be suppressed. Even under an ideal condition with a non-moving sample or subject, scanner instability might arise that compromise data quality. Dynamic B_0 field changes can result from changes in magnetic susceptibility of the air in the lungs during respiration, which can modulate the B_0 field in the brain at ultra-high field (≥ 7 T).¹⁷ In cardiac and abdominal applications, periodic movements of organs associated with cardiac pulsation and breathing are also accompanied by periodic B_0 field changes. In such cases, cardiac and respiratory gating will be necessary to obtain reliable spectra although it reduces data acquisition efficiency.¹⁸

In practice, perfect correction of motion may not be possible under various hardware and software limitations, and it is necessary to specify the required level of performance to make motion correction worthwhile. Recommendations for acceptable performance of motion correction methods can be made by considering the precision and accuracy of MRS

measurements under ideal conditions and research questions that are addressed by an MRS study. Research studies under ideal conditions e.g., by experienced MR operators with well optimized protocols in compliant subjects, showed that the intrinsic variability of metabolite concentrations measured by MRS is on the order of 5-15% for primary metabolites (e.g., N-acetylaspartate (NAA), creatine (Cr) and choline (Cho)), though it may be higher for metabolites with lower SNR and more complicated spectra (e.g., GABA, GSH, taurine).¹⁹⁻²² On the other hand, clinical applications are often interested in measuring metabolite changes either cross-sectionally between healthy controls and patients, or longitudinal time courses in patients. Well-controlled studies²³⁻²⁵ have shown that MRS can measure 5-20% change in metabolite levels due to disease conditions. Hence, as a rule of thumb an advanced motion correction method should be able to provide at least 5% stability or better for primary metabolites in patient populations under clinical situations.

Numerical specifications for performance of motion correction for MRS could be proposed considering the worst case scenario for motion that causes a 5% change in metabolite concentrations. Considering a voxel in single voxel spectroscopy (SVS) that is at the edge of the brain compartment (either next to the skull or ventricles), if motion occurs at the beginning of an MRS acquisition causing a displacement of the voxel volume by 5%, if maintained until the end of the acquisition, this would cause 5% change in the metabolite concentrations in the given voxel. For a voxel size of 1 cm³, this means that motion would cause a displacement of 0.05 cm³ in volume localization. Since position is a combination of both translation and rotation, it is hard to visualize the amount of motion in most cases. However, for the 0.05 cm³ volume change, in the simple case of pure translation this would amount to an average 0.17 mm displacement along three orthogonal axis, or in the case of pure rotation this would mean an angle between 0.26-2.9 degrees, depending on the distance of the voxel to a rotation axis through the center of the brain and the atlanto-axial joint. A correction method that would provide 95% stability of metabolite estimations in the presence of motion should be able to detect translations and rotations with a precision better than previous examples in order to update the voxel position. However, these examples do not consider the motion effects on B₀ field homogeneity that leads to **changes in spectral linewidth and lineshape, resulting in errors in metabolite fitting**. In brain locations where B₀ has large spatial variation e.g., prefrontal and temporal areas, , even small motions as defined above for the 5% volume displacement may lead to a larger change in metabolite quantification, and B₀ shim update is necessary to restore spectral quality and reduce variability of metabolite quantification. More information regarding

specifications and requirements on B_0 homogeneity and spectral linewidth for adequate MRS quality is presented in the B_0 shimming consensus paper of this special issue.^{2,26}

2. MOTION CORRECTION METHODS

2.1 Retrospective post-processing methods

Post-processing methods have historically been the easiest to implement for SVS data, however, they are limited in their ability to reverse all the changes caused by motion. When motion artifacts corrupt only a few of the transients in SVS with multiple transients, those corrupted transients could be discarded selectively, while frequency and phase changes could be corrected by spectral alignment of the remaining transients. Though this approach may improve the spectral quality, it cannot correct the fact that averaged spectra are collected from different voxel locations or the fact that narrow-band selective pulses used for, e.g., water suppression or spectral editing will be out of band due to frequency shifts caused by changes in the voxel position in the organ. In addition, spectral distortion due to higher-order spatial B_0 inhomogeneities that accompany position changes cannot be corrected in post-processing.

While prospective motion correction approaches require hardware/software adjustments that may be difficult to implement on all scanners/software platforms, retrospective motion correction by post-processing is simpler to perform and requires minimum adjustments to the scanner. The retrospective motion correction methods are primarily based upon correcting for motion-induced frequency drift and incoherent phasing, as well as discarding motion corrupted data sets. Shot-to-shot phase and frequency offset reduces the SNR of the averaged spectrum – the theoretical loss of SNR has been shown to be a factor of $\text{sinc}(\sigma_\phi\sqrt{3}/\pi)$, where σ_ϕ is the standard deviation of the phases of the individual transients.²⁷

MRS data can be phase-corrected on a shot-by-shot basis using an interleaved water FID navigator signal acquisition during metabolite recovery time (within a single TR), and performing a deconvolution of individual metabolite signals with the navigator information. Phase-coherent averaging of the individual transients has been demonstrated to be effective in correcting for motion-induced frequency drifts in SVS²⁸. Degraded quality of water suppression has also been used to detect and discard severely motion corrupted data in SVS.^{28,29} Using a scheme similar to that by Thiel et al.,²⁸ signal fluctuation of the water navigator data has been shown to be a good indicator of subject motion, and discarding datasets following water signal fluctuation beyond a certain threshold (>3%), motion corrupted data have been analyzed retrospectively in J-difference edited SVS.³⁰ Ernst and colleagues used a phase and frequency navigator using

water suppression cycling (resulting in positive and negative water signals).³¹ In this method, motion correction during SVS scans was achieved by shot-to-shot frequency and phase alignment of residual water, with the average spectrum resulting in almost complete elimination of the residual water signal, thus minimizing baseline distortion. Performing shot-to-shot phase correction using the phase of a high SNR resonance peak with subsequent constructive averaging of phase-coherent data has been shown to improve the SNR of SVS by ~15%.²⁷ Phase- and frequency-correction using residual water of the individual transients as reference has been shown to restore SNR and remove lineshape distortion in SVS.³² Using spectral registration in time domain by fitting each transient to a reference scan, efficient phase- and frequency-correction is possible³³.

However, in order to eliminate mis-localization and other motion effects, it is necessary to use real-time correction methods to update both the localization and B_0 shimming for each voxel position relative to the organ during acquisition as described in the next section.

2.2 Prospective real-time methods

Prospective real-time methods track the organ throughout the acquisition and correct for changes in position or gate the acquisition in response to the estimated motion. There are two major classes of such methods, namely (i) internal navigator methods that use the MR signal itself to discern the position of the organ, and (ii) external tracking systems that use external hardware such as a camera and some sort of marker, which may be a marker on the face, or the face itself, to discern the patient's head position. Both systems have advantages and disadvantages. A comparison of different systems and methods is provided in Table 1. In addition to these methods, real-time frequency update is also used in prospective motion correction, as discussed briefly at the end of this section.

i) Navigator sequences³⁴⁻³⁶ can update position and some are capable of updating B_0 shimming, however, they require additional pulse sequence elements that have to be physically compatible with the timing of the MRS sequence, estimating position and shim parameters at a limited rate (e.g., typically once per TR, hence ~1 s), and possibly extending the total acquisition time. Some navigators have been designed only for frequency or shim correction, to be used in combination with external camera that provide position correction.

ii) External cameras³⁷⁻³⁹ estimate position independent of the MR sequence at rates typically much greater than a TR (e.g., up to 60 Hz) and can track motion continuously even when no active MRI sequence is played. However, these systems cannot directly estimate the B_0 field inside the body. While positions are estimated independent of the sequence, corrections must be applied in a manner consistent with the physics of the acquisition, reducing the correction rate. Nevertheless, the availability of a rapid stream of position estimates may reduce the lag time between position estimates and corrections. In MRS, dynamic shimming (real-time B_0 shim correction) during motion is critical to ensure the spectral quality.

i)+ii) Hybrid systems may also be realized, where motion is corrected using an external camera, while B_0 shim is corrected using an internal navigator.¹⁶ The schematic in Figure 1 illustrates the concept of prospective real-time methods and provides examples of motion artifacts and correction of these artifacts in MRS data.

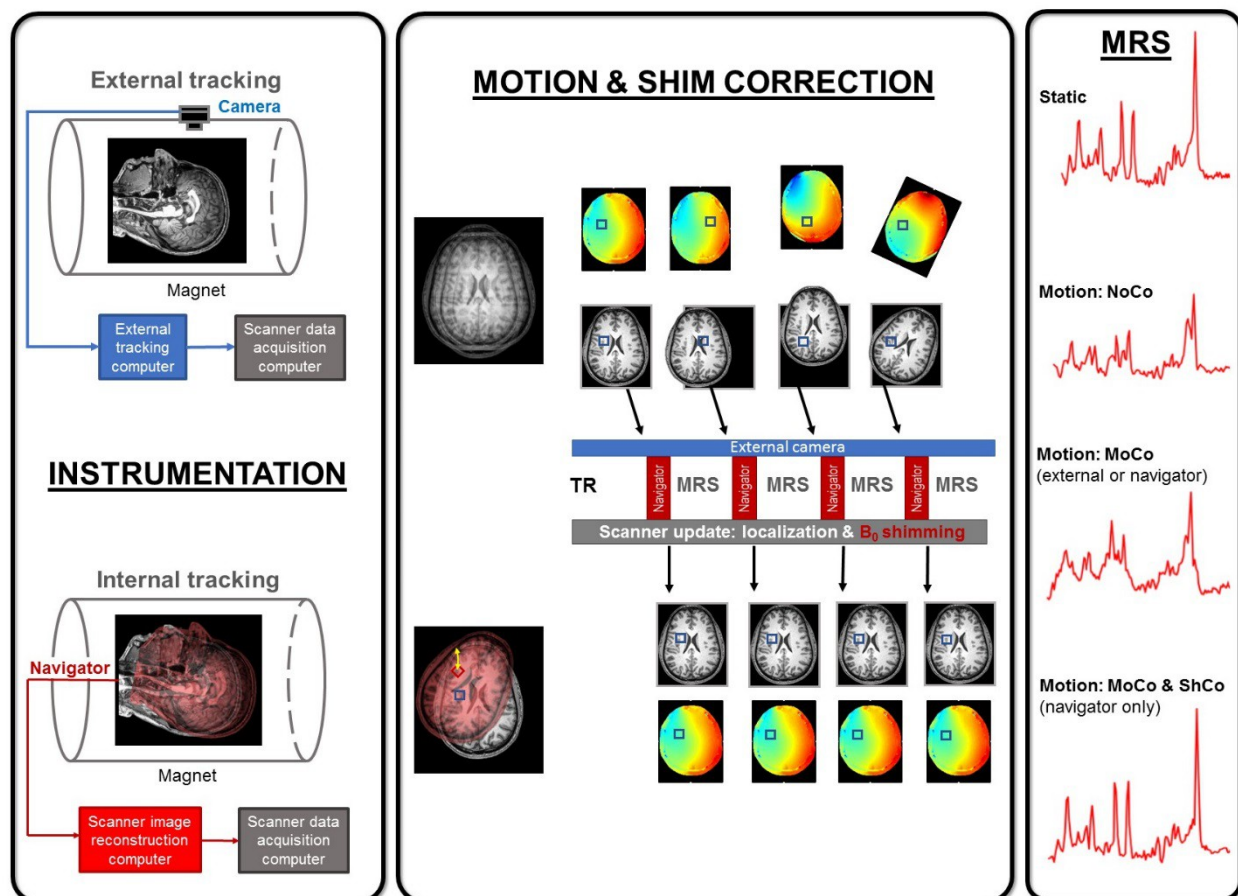


Figure 1. Prospective real-time motion correction for MRS. Left panel: External (optical camera) and internal (navigator) tracking systems. Note that NMR probes use a combination of external and internal tracking. Middle Panel: Localization update is possible with both external and internal tracking, however, B_0 shimming is possible only with navigators with B_0 field mapping. Right panel: Examples of MR spectra under static conditions and in the presence of motion with no correction (NoCo), motion correction only (MoCo), and with both motion and shim correction (ShMoCo). Decreased SNR and line broadening/splitting are noticed in NoCo spectra. MoCo recovers partially the SNR and linewidth, while the full spectral quality is restored only if both motion and shim corrections (ShMoCo) are performed.

2.2.1 Internal MRI tracking with navigator sequences

Internal MRI tracking methods interleave navigator sequence modules with a slower parent modality such as MRS. Typically, the position is estimated once per TR, in accordance with the physics of the MRS sequence, which cannot usually be corrected more than once per TR given that a long readout period follows a single excitation pulse or train of preparatory pulses (e.g., pre-localization and suppression), and given that motion correction requires modifying the properties of the pulse and gradient encoding to adapt the region of excitation and encoded orientation. Most navigators use a very low flip angle pulse to excite water or a higher flip frequency selective angle pulse to excite water or lipid to minimize disturbing metabolite magnetization. Navigators may also be acquired after a block of multiple TRs of the parent sequence to reduce their time requirement, although every TR is preferred for precise localization/shim update and spin history. The navigator can measure position¹¹ (e.g., position and orientation of the brain) and some even the B_0 field.⁴⁰ Hence, ideally the navigators can update both the localization and the B_0 field, which may range from simple frequency update to full shim update depending on the navigator type and the shimming hardware.

Three types of navigators exist: 1) FID navigators that encode spatial information without gradients by using multiple spatially distributed RF receive coils,³ 2) k-space navigators that acquire constrained k-space trajectories,³⁶ and 3) image navigators that acquire entire images.^{11,41} First, FID navigators are used mostly for frequency update without updating voxel position and orientation as described in the previous section, but have recently been extended to exploit phased array coil technology to estimate head position.⁴² Second, k-space navigators are shorter, occupying less time in the MRS sequence, at the expense of navigator SNR and

resolution, leading to greater variance on the position estimates. Current k-space navigator implementations do not estimate spatial B_0 field components beyond the first order. Third, image navigators are longer but provide full position and B_0 field characterization of the entire organ.

2.2.1.1. FID navigators

With the advent of multi-channel phased arrays, the sensitivity profiles of the multiple coils can be used to add spatial information to the gradient encoding in MRI sequences to accelerate image encoding using parallel imaging techniques⁴², and to accelerate RF slice encoding in multiband/multislice encoding⁴³. In the lowest limit, gradient and/or RF encoding is unnecessary to produce a low-resolution image and even a field map. This approach has been used to track the head position⁴⁴ and even to obtain a field map. These techniques are extremely efficient, but rather ill-posed, requiring mapping or modeling to obtain the images with limited resolution. Hence, they have not been used in real time or MRS applications for position update. On the other hand, FID navigators have been used for frequency⁴⁵ and phase correction⁴⁶ caused by motion or magnet field drift³, as detailed in the sub-section 2.2.1.4.

2.2.1.2. k-Space navigators.

Acquisition of navigator echoes is a popular technique to detect and correct for subject motion in real-time in MRI.³⁴ Different k-space trajectories have been employed in k-space based approaches, e.g. orbital, spherical³⁵ and cloverleaf.³⁶ The orbital navigator provides rotation information in a plane, while the spherical trajectory provides 3D rotation information but takes substantially longer time to acquire and analyze than other k-space navigators, therefore finding applications in inter-scan registration. The cloverleaf navigators provide position information with 6 degrees of freedom (i.e., 3 translations and 3 rotations) as well as 0th- and 1st-order shim information in a few milliseconds, but require an initial map of k-space and those estimates are relatively noisy. With k-space navigators, rotation is typically obtained from the magnitude information, since rotations in image space are manifest as rotations in k-space, while translations are obtained from the navigator phase information since translations in image space result in a phase roll across k-space. Frequency information is obtained from the phase accumulation across the navigator with time from excitation, while higher-order field information

requires spatial encoding using the gradients or physical locations of the RF coils. Position estimates are fed back from the image reconstruction system to the RF and gradient control systems. RF pulse frequencies and accompanying gradients are modified to adapt the excitation orientation and position, while gradient pulse allocation across the physical gradient X, Y and Z coils determines the orientation of the spatial encoding by the gradients. Translations are corrected by adjusting the phase of each k-space sample consistent with its position in k-space. This doesn't have to be done in real time as long as it precedes the transformation from k-space to image space.

2.2.1.3. Image based navigators.

One of the earliest navigators, the pencil beam navigator,⁴⁷ is a method to obtain the respiratory phase using a columnar excitation across the diaphragm and combine it with a frequency encoding along this column (i.e., pencil). This may be considered to be a one-dimensional image navigator, since it is the Fourier transform of the signal, which provides the data for tracking the diaphragm motion. Pencil beam navigators are used for respiratory gating, which in combination with an electro cardio-gram (ECG) has been shown to significantly improve the quality of SVS in the heart.⁴⁸

With image navigators, motion of organs can be deduced directly from the images. For example, cardiac motion can be assessed with redundant radial sampling, a self-navigating technique.⁴⁹ In MRS, estimation of head motion followed by updates of rotations and translations has been shown for three orthogonal navigator images right before the MRS water suppression module⁵⁰.

While image-based navigators take longer to acquire than k-space navigators, the acquisition of a full image volume provides the flexibility to define the whole brain for motion correction while selecting a sub-region for B_0 shimming. Selecting a sub-region even for frequency tracking alone is very important if motion occurs since the average frequency over the entire head may substantially differ from the average frequency in the volume of interest.⁵¹ A full B_0 map also facilitates fitting of the field beyond linear shim terms, although this capability cannot be exploited with shim hardware of commonly available MR scanners, which does not allow higher-order ($\geq 2^{\text{nd}}$) shims to be changed in real time. Since typical TRs in MRS are on the order of 1 s or longer, whole-brain navigator imaging can be performed without prolonging the acquisition time of MRS with some dead time for signal recovery. Image-based navigators like

PROspective MOtion correction (PROMO)⁵² or EPI navigators^{11,40,53} make use of low-resolution images or volumes so that the imaging volume follows the object. Neither of these techniques provides B_0 maps by default, which require modifications of the framework to incorporate phase images for B_0 mapping besides magnitude images for position tracking. EPI volume navigators (“vNavs”) can easily be extended to interleave two echo times with the corresponding phase images from which a B_0 map may be derived.^{15,40,54,55} The double-echo navigators take a longer time (~600 ms), which limits the minimum TR, however, recently B_0 mapping has been demonstrated with shorter single-echo navigators by using the coil-dependent phase offsets.⁵⁶ Also, image-based spiral navigators in combination with PROMO have been used in SVS to update the position and orientation of MRS voxels as well as the B_0 shims.⁵⁷ Since the brain is enclosed by the rigid frame of the skull, the motion displacement can be rapidly determined through rigid image registration, which can be computed within <0.1 s by linear transformations using six degrees of freedom (3 translations and 3 rotations) running in image reconstruction computers on commonly available MR scanners. Phase unwrapping for both echo times and fitting of the spherical shim harmonics to the obtained B_0 maps can also be done in the same timeframe. Another advantage of image-based navigators is its capability to correct for changes in the B_1^- receive field changes due to motion, hence update the weights for coil combination of data acquired with phase arrays, thus improving SNR and reducing potential variability arising from coil combination.⁵⁸

Several other image-based navigator techniques have been proposed, including fat navigators,⁵⁹ collapsed fat navigators,⁶⁰ iNavs,⁶¹ but these techniques have not yet been extended to include field maps.

The use of image-based navigators may be more challenging at ultra-high field. For instance, vNavs are based on fast EPI readout, which may suffer geometric distortions and other imaging artifacts. The B_0 field changes due to organ motion or respiration are more severe at ultra-high field and correct estimation of those changes becomes more challenging. Hence, vNavs at 7 T have so far been implemented only without real-time B_0 shim updates.⁶² Another useful approach for MRSI could be to reduce effects of motion by employing acquisition strategies that null or minimize gradient moments used for k-space encoding.¹⁰ Spiral and radial trajectories that start at the center of k-space can achieve gradient moment nulling, which reduces phase errors between consecutive readouts. Such an approach using spiral out-in trajectories for gradient moment compensation has been shown be effective in reducing

respiratory motions in liver MRSI.⁶³ In addition, repeated sampling of the k-space center can be used for self-navigation correction methods.⁶⁴

2.2.1.4. Frequency/shim-only navigators

Motion is accompanied by B_0 field changes, including frequency (0th order spatial) changes and higher-order spatial changes, which adversely affect the resonance behavior and hence the spectral quality with broader/distorted lines and reduced SNR. Navigators that update only frequency or shimming have been used in combination with other methods such as external cameras that update position for correction of motion effects in MRS. Such navigators acquire only limited information about the B_0 field, e.g., frequency of the whole volume ^{3,45,46}, localized volume ⁵¹, or 1D projections along three orthogonal directions for 1st order shims.^{16,65} Their main advantage is that they are faster than full B_0 field mapping sequences. These navigator for frequency update can be used for both SVS and MRSI sequences. While acquiring three orthogonal projections is sufficient to sample the B_0 field for small volumes in SVS, it is too sparse to sample adequately the B_0 field pattern for larger volumes used in MRSI, which requires full mapping of the B_0 field by imaging sequences. Hence, projection-based shim navigators have been limited only to SVS and 1st order shimming.

Real-time frequency update has been achieved by following the position of residual water signal in each FID, subtracting the frequency from the center frequency and subsequently correcting for the drift in real time.⁵⁷ Linear shim offsets are typically implemented by applying a fixed offset current on the linear gradients. Modifying the shim induces a mean frequency change that must be corrected in a similar fashion.⁵⁷ A field-frequency lock has been effectively used to update frequency in real time with a whole-body spectrometer⁴⁵. This was achieved by acquiring a reference scan interleaved in the PRESS scan, measuring the frequency shift of the reference water signal in real time and adjusting the Z0 shim coil current of the spectrometer by applying a negative feedback. Real-time frequency adjustment during J-difference edited SVS has been performed by reading the FID signal during water suppression and using that to track and update the system frequency during each TR cycle.⁶⁶ It should be noted that detrimental effects of scanner center frequency drift from gradient heating following heavy duty echo-planar imaging (EPI) scans or various forms of spatial-spectral encoding in MRSI can also be corrected prospectively using these methods.^{3,51,67} However, in the case of motion, it is necessary to update other B_0 shim terms, such as 1st and 2nd spherical harmonics, which require more

complex navigators that encode more spatial information about the object, as described in the Section 2.2.1.3.

2.2.2. External tracking methods.

External tracking systems use methods other than the MR signal of internal water to determine the position of the organ. Clinical scanners typically include physiologic sensors that enable cardiac and respiratory gating (e.g., ECG sensors, pulse oximeters and respiratory belts), and these have been used to gate MRS acquisitions in body applications.⁴⁸ Since the brain moves rigidly with the head, tracking a marker attached to the head is a good proxy for tracking motion of the brain, provided that the marker remains rigidly attached to the head.

In addition to the optical and NMR probe tracking methods reviewed in detail below, other technologies were also used in the past. The EndoScout (Robin Medical Inc., Baltimore, MD, USA) electromagnetic position sensor uses a small sensor cube to detect gradient activity in the bore and determine position and orientation at a very high rate⁶⁸. Several sensors have been developed purely for research purposes, including a small wireless device, which uses gravity and the main B_0 field to determine its orientation in the scanner⁶⁹. Similarly, active markers (tuned coils) that provide fiducial points for position and orientation estimation along the B_0 field have been demonstrated.⁷⁰ However, these methods do not provide B_0 field estimates.

2.2.2.1. Optical tracking.

Optical tracking methods use one or more cameras to observe a marker on the head or the face to track the brain. Kineticor (Honolulu, HI, USA) provides a multi-camera system that observes a marker attached to the face and tracks the head inside the scanner. Together with Siemens, they provide the first FDA-approved prospective motion correction solution for MRI on the market. Hobbitview (San Jose, CA, USA) provides a similar system targeted at GE MRI & PET/MR scanners. Metria Innovation (Wauwatosa, WI, USA) provides camera systems based on the Moiré Phase Tracking (MPT) principle, which are very sensitive to rotations.^{14,46,71,72} Most recently, the TCL system (TraInnovations, Copenhagen, Denmark) provides a markerless tracking system that eliminates the marker and possible marker attachment problems using surface tracking of the face and computer vision algorithms to directly track the head motion. All of these systems provide rapid and continuous position updates independent of the MR

sequence, and these positions can be fed back to the scanner to provide real-time correction, or this time-synchronized information can be used to correct MR data offline. A comparison between optical tracking and MR-based tracking methods discovered a high degree of correlation between the **motion estimated provided by** both tracking modalities.⁷³ Optical tracking has been used for motion correction of SVS and MRSI,^{14,46,71} however as it was recognized early on, none of these systems provide B_0 field information which needs to be updated to restore the full spectral quality. Since the stability of B_0 is critical in MRS, external tracking for localization update was combined with interleaved water FID, which was used for retrospective frequency update,^{14,46,71} without higher-order shim updates.

2.2.2.2. NMR probes

NMR probes have been used extensively in tracking catheters and surgical instruments during interventional MRI.⁷⁴ Inductively coupled wireless NMR probes attached to the head can be used together with low flip angle interleaved navigators to detect head motion and update the localization of MRI sequences.⁷⁵ Essentially, this approach combines the use of external markers (NMR probes) with internal tracking measurement (navigators). Comparison between NMR probes and optical cameras revealed slightly higher precision for optical camera,⁷⁶ but more than sufficient in both cases to track head motion with an accuracy of tens of microns. However, as with optical systems no information about the B_0 field inside the head is obtained, and no such systems have been demonstrated yet for motion correction of MRS. NMR probes can be used to monitor the B_0 field over space-time, and advanced field cameras have been built by research groups or commercially (Skopec, Zurich, Switzerland) for rapid dynamic B_0 field information at multiple discrete points in space.⁷⁷ However, such systems probe B_0 field outside the head, and it has been shown for the brain that measuring the B_0 field just outside the body does not suffice to predict accurately the B_0 field inside the body^{17,78}. Currently no technique exists for measuring the B_0 field inside the body without using the MR signal. Predicting the B_0 field after motion based on electromagnetic models, head structure and an initial B_0 map has been proposed,⁷⁹ and with fast enough computation might offer an alternative to real-time measurements of B_0 field.

2.3. Hybrid methods

While external systems are expensive and require additional hardware, they provide some desirable properties for motion tracking, such as speed and independence from the pulse sequence. Navigators can be implemented entirely in software and use the existing MR scanner

hardware, and they provide the missing B_0 field information that cannot be measured with external tracking devices. Therefore, a hybrid approach leveraging the advantages of both approaches may be attractive. In fact, all demonstrations of motion correction for MRS based on external tracking have used some simple form of field correction with retrospective frequency update. In the absence of scanner instability, the requirements of monitoring B_0 field can be relaxed since the B_0 field update is only required when motion actually occurs. A B_0 field map could be collected only when necessary, triggered by the external device or an efficient internal navigator such as an FID.^{44,80} A combination of external tracking, structural head imaging and B_0 field modeling might also be implemented.⁷⁹ Recently, combination of prospective motion correction using optical tracking and prospective shim correction using an interleaved FAST(EST)MAP navigator has been reported for SVS measurements in the human brain at 7 T.¹⁶ Gradient and RF pulses used for localization were updated based on the feedback from an external camera, while the navigator measured the B_0 field along three orthogonal projections, which were used to update frequency and linear shim terms.

Table 1. Technical requirements, performance, and costs/availability for motion correction methods.

METHOD	System Requirements	Motion tracking (temporal and spatial resolution)	B_0 field tracking (temporal and spatial resolution)	Performance, costs and availability
Retrospective: Post-processing	Custom post-processing software	No localization update	Temporal resolution is determined by the TR of MRS sequence	Lower costs if programmed in-house
Prospective: Navigators	Custom MR sequence, on-line reconstruction and real-time feedback	0.05-0.5 mm & 0.05-0.5 deg tracking accuracy, 300-1000 ms update rate	0.05-0.5 mm & 0.05-0.5 deg tracking accuracy, 300-1000 ms update rate	Lower costs if programmed in-house
Prospective: External tracking (optical and other methods)	Additional hardware and software, integration with MR scanner	0.005-0.5 mm & 0.003-0.5 deg tracking accuracy, 12-30 ms update rate	No field update is possible without additional frequency navigators	Higher costs for commercial and custom-made systems
Prospective: NMR(?) probes	Additional hardware and software, integration with MR scanner	0.01-0.5 mm & 0.01-0.5 deg tracking accuracy, 300-1000 ms update rate	Field is measured outside the head, and computational EM modelling can approximate the	Higher costs for commercial and custom-made systems

			internal field with limited accuracy.	
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3. Applications

Motion correction methods have been used in clinical studies of MRS beyond technical proof of concept, and proven to be especially beneficial in subjects who have a predisposition to move such as children or patients with movement disorders. In pediatric studies of HIV and fetal alcohol syndrome, image based navigators were used.^{81,82} In the children in whom SVS PRESS in deep cerebellar nuclei was acquired, navigators resulted in an increase in a success rate from 50% to 73%, where success was defined as usable data with linewidths below 0.08 ppm and SNR > 8.⁸³ In a pediatric study, 73% of children moved between the anatomical data acquisition and MRS and 32% of them moved during the acquisition with the predominant

movement directions being sliding out of the coil and nodding (up—down rotation) and 1st-order

B_0 corrections being significant ($>10 \mu\text{T/m}$) in 18% of acquisitions.⁸⁴

When the MRS acquisition is not a single shot method and the transient spectra have different magnitude and phase modulations, **the** motion correction is extremely important. Spectral editing with J-difference spectroscopy is particularly susceptible to measurement instabilities arising from subject motion or scanner frequency drifts. MEGA editing is one of the most used techniques for editing gamma-aminobutyric acid (GABA)⁸⁵ as well as other important metabolites such as the oncometabolite D-2-hydroxyglutarate (2HG) in mutant isocitrate dehydrogenase (IDH) mutated gliomas,⁸⁶ and glutathione (GSH).⁸⁷ The MEGA-edited spectrum is the difference of spectra acquired in two consecutive TRs, and large subtraction artifacts can preclude quantification of edited signals in the presence of motion or B_0 field changes. Because of this extreme motion sensitivity, the reacquisition of corrupted TRs is often performed in addition to motion and B_0 shim correction (ReShMoCo) to achieve the minimum subtraction error.⁵⁴ Reacquisition was demonstrated to be also beneficial in MRI,¹¹ where damaged k-space regions affect the entire reconstructed image. Reacquisition is not mandatory in SVS if every transient is the same (i.e., in the absence of phase cycling or editing), since the corrupted transients can be discarded but at the cost of lower SNR. In contrast, the reacquisition is critical in MRSI because motion or B_0 field differences between spatial encoding steps during MRSI encoding between navigator blocks affect the entire MRSI data. Examples of motion subtraction artifacts and real-time correction with navigators are shown in Figure 2.

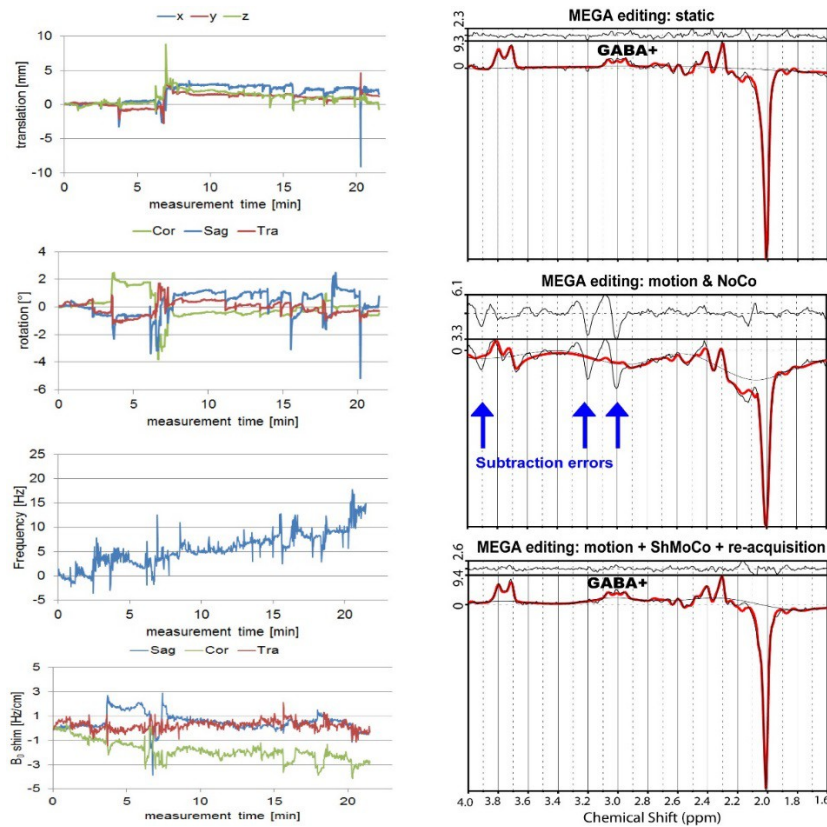


Figure 2. Real-time motion and B_0 field correction for MEGA edited MRS of GABA. Subtraction artifacts are eliminated with re-acquisition of corrupted TRs.

Real-time motion correction and shim update has been used in clinical MRSI studies with adult subjects, including clinical studies of patients with brain tumors,⁸⁸ amyotrophic lateral sclerosis (ClinicalTrials.gov/NCT02288091),⁸⁹ multiple sclerosis and neurodegenerative disorders (e.g., Parkinson and mild cognitive impairment).⁹⁰ Cancer IDH mutations (IDH 1&2) have high de novo production of the oncometabolite D-2-hydroxyglutarate (2HG), and in vivo imaging of 2HG is a key application of MRSI in neuro-oncology. Robust 3D MRSI of 2HG with real-time ReShMoCo MEGA-editing was used in mutant IDH glioma patients to assess tumor burden⁹¹, response to standard radiochemotherapy⁸⁸ and targeted therapy with novel mutant-IDH inhibitors^{92,88}. The same methodology was used to image GSH in the brain of patients with amyotrophic lateral sclerosis (ClinicalTrials.gov/NCT02288091)⁸⁹, including the motor cortex and corticospinal tracts, or in patients with mutant IDH glioma tumors⁹². GABA was imaged using the

same methods in patients with Parkinson's disease⁹⁰ as well as in healthy controls⁹³. Figure 3 shows examples of such metabolite maps using edited MRSI with real-time motion and shim-correction.

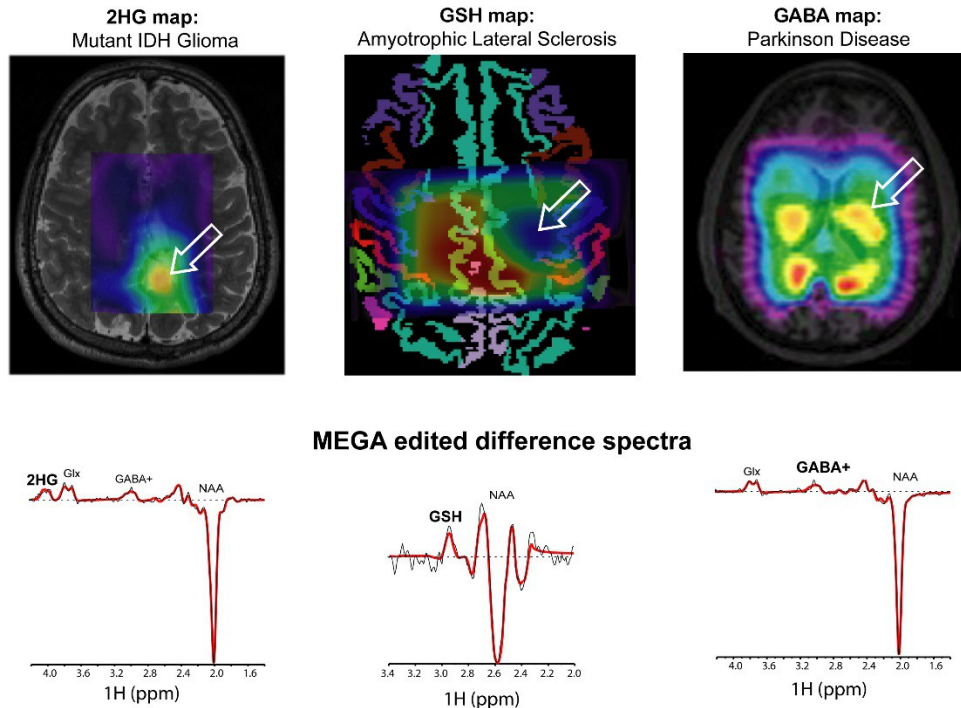


Figure 3. Applications of real-time motion and shim correction for edited MRSI of metabolites: i) oncometabolite D-2-hydroxyglutarate (2HG) in mutant IDH glioma; ii) antioxidant glutathione (GSH) in amyotrophic lateral sclerosis; iii) inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in Parkinson disease. Arrows indicate regions with abnormal metabolite levels in metabolic maps. Examples of edited spectra are shown at the bottom.

4. Recommendations

Recommendations regarding the technical performance for prospective real-time correction of motion effects in MRS may be specified based on the stability and precision that is needed for the metabolite quantification. Ideally the most advanced and effective motion correction should be used when possible. However, if this is not available or there are other limitations precluding it, practical guidelines for acceptable performance can be established based on the question/hypothesis to be answered/tested by MRS. Different levels of MRS precision may be

required depending on the effect size of each study. For example, a larger estimation error may be acceptable in diseases where there are large metabolic differences between the healthy tissue and pathological lesion such as cancer,⁹⁴ while such errors are not acceptable in diffuse diseases such as neurodegenerative or psychiatric conditions,^{95,96} where there are subtle metabolic differences compared to healthy controls. In the case of more demanding research paradigms, such as functional MRS (fMRS), the smallest estimation errors are needed to measure dynamic metabolite changes.⁹⁷

Simple guidelines for precision of MRS motion correction (Table 2) may be derived assuming an isotropic voxel in the case of SVS for either pure translation or rotation under the most unfavorable movement, i.e., motion starting at the beginning of the acquisition, which

moves the voxel outside the brain. For an isotropic SVS cube of side L , in order to have

volumetric error less than E the precision of motion correction for pure translation is given by ,

which is proportional to the side of the cube. For head rotations, the axis of rotation is given by the atlanto-axial joint and the same rotation angle will affect voxels more the farther away they

are from the axis. For the farthest away (frontal pole located), cube voxel of side L to have a

volumetric error less than E the precision of motion correction for pure rotation is given by: ,

where D is the anterior-posterior diameter of the brain and we assumed that the axis of the atlanto-axial joint passes through the center of the brain. However, for the case of MRSI and

simultaneous translation and rotation, such limits are harder to derive theoretically. In such cases, a more practical way is to empirically assess the performance and precision of a certain motion correction method with a test-retest design, in which the variability of metabolite quantification between static and motion conditions should be less than the desired precision for metabolite quantification either in vivo or in structural phantoms with the size of metabolite compartments comparable to the MRSI resolution.

Table 2. Recommendations for the technical performance of prospective real-time motion and shim correction for different levels of precision requirements in MRS. Note: 1) for SVS, precision has been derived for either pure translation or rotation of an isotropic voxel; 2) for MRSI, similar precision thresholds are hard to be derived theoretically and the acceptable performance level for motion correction should be empirically evaluated by test-retest; 4) The values listed in the table below are calculated for a cube voxel of 10 mm x 10 mm x 10 mm and anterior-posterior brain diameter of 220 mm. A frontal pole voxel is displaced the most by rotation around an axis through the center of the brain and the atlanto-axial joint. All reported real-time methods have higher translation and rotation precisions than the values listed in the table. The guidelines for homogeneity of B_0 field are the same as recommended in the B_0 shimming consensus paper.²

Basic	Moderate	Advanced
20% error in estimation of metabolite concentration <ul style="list-style-type: none"> - 0.7 mm translation - 1.0° rotation - frequency update 	10% error in estimation of metabolite concentrations <ul style="list-style-type: none"> - 0.4 mm translation - 0.5° rotation - frequency update - shim update 	5% error in estimation of metabolite concentrations <ul style="list-style-type: none"> - 0.2 mm translation - 0.3° rotation - frequency update - shim update - reacquisition

Experts' recommendations

1. Motion correction is particularly beneficial for MRS, and should be applied whenever possible. Because of the long acquisition time that is typical in MRS, motion and scanner instability is likely to occur during the scan. Because of low SNR and the need for narrow spectral linewidth to resolve metabolite signals, any instability arising from subject motion or hardware can severely degrade the quality of MRS data.
2. B_0 field changes secondary to motion and/or scanner instabilities substantially affect spectral quality, and B_0 shim correction for these effects is recommended. While the effects of motion and hardware instability are easy to recognize in MRI through blurring of anatomical structures, these effects are harder to identify in MRS, because the anatomical information is not directly incorporated in the SVS data and the low spatial resolution in typical MRSI does not sufficiently resolve anatomical structures. Motion can be suspected when artifacts are present in the spectra such as line splitting or if signal from outside the organ of interest (e.g., subcutaneous lipid signals for brain MRS) is present. However, these spectral artifacts can be confounded by poor B_0 shimming and poor localization that can happen even under static conditions. In particular, for MRS there is a strong coupling between localization and B_0 homogeneity that makes MRS very susceptible to motion-related degradation. Both localization and the B_0 field must be corrected to adequately correct for the effects of motion on MRS.
3. The approaches recommended for MRS, similar to MRI, to minimize and mitigate effects of motion and scanner instability are: i) head immobilization; ii) retrospective correction; and iii) prospective real-time correction. However, the main difference is that correction of B_0 field is absolutely necessary to restore spectral quality in addition to localization update in MRS.
4. For retrospective correction, transients need to be stored separately, or raw data need to be used. Such corrections can improve data quality by correcting for frequency drifts or discarding badly corrupted transients. However, it cannot correct for localization error or the failure of frequency selective sequence blocks such as water suppression and spectral editing.

5. Prospective real-time correction is the method of choice for MRS if available. Methods that simultaneously track organ position and B_0 field inside the organ provide the best data quality restoration for MRS. Motion correction alone is insufficient, and at a minimum, frequency update has to be performed in real time or retrospectively. Scanner manufacturers such as Siemens have moved toward supporting external camera-based tracking systems [ref. Kineticor]. At present such certified solutions are only available for a limited set of imaging sequences, although the underlying software provides support for real-time position update in any pulse sequence. Furthermore, such systems cannot measure the B_0 field. Manufacturers should support dynamic field correction methods, including high-order shims, as part of the product approved for clinical use. Retrospective correction cannot be performed for high-order shim changes, and higher-order shim updates should be performed in real-time to provide significantly more data improvement compared to frequency update. While commercial scanners are limited to real-time update of 1st-order shims, the possibility of either real-time update of 2nd- or 3rd-order shims or shim arrays⁹⁸ should be considered by manufacturers if technically feasible to allow best data quality in MRS. To incentivize such effort, there is a high return as other MRI modalities could also benefit substantially from better B_0 field management such as fMRI, DTI, SWI and CEST.
6. If available, the best method for prospective motion correction should be used with the highest spatial and temporal resolution with B_0 shim updates. Criteria for minimal acceptable technical performance of prospective correction can be derived based on the effect size that needs to be measured by MRS. Less than 5% variability in quantification of the primary metabolite concentrations is sufficient for most clinical applications.
7. Spectral editing methods based on subtraction or multiple TE averaging are highly sensitive to motion compared to non-edited MRS and reacquisition of corrupted transients is necessary for full data restoration.
8. Oversampling of the center of k-space is recommended for motion robustness in MRSI. Trajectories that repeatedly sample the central part of k-space in the shortest possible time frame facilitate self-navigation as an alternative to interleaved navigation. Trajectories such as spirals⁹⁹ or rosettes¹⁰⁰ return to the k-space center and hence the repeatedly sampled central k-space point can be used for correction.⁶³

9. In MRSI, motion causes signal smearing and large image artifacts from nuisance signals of water and lipid that can overwhelm metabolite signals. Lipid/water suppression that use frequency selective methods benefit largely from B_0 field stability, and shim update is recommended to maintain efficiency of these suppression methods in the presence of motion and scanner instabilities.
10. At ultra-high field (≥ 7 T), controlling the B_0 field stability is even more important, with the added challenge that frequency modulation in the brain can result from changes in lung magnetic susceptibility due to respiration¹⁷ even if the head is perfectly static. For this reason, rapid B_0 field monitoring is especially recommended in addition to motion correction at ultra-high field.

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