Over more than 30 years in vivo MR spectroscopic imaging (MRSI) has undergone an enormous evolution from theoretical concepts in the early 1980s to the robust imaging technique that it is today. The development of both fast and efficient sampling and reconstruction techniques has played a fundamental role in this process. State-of-the-art MRSI has grown from a slow purely phase-encoded acquisition technique to a method that today combines the benefits of different acceleration techniques. These include shortening of repetition times, spatial-spectral encoding, undersampling of k-space and time domain, and use of spatial-spectral prior knowledge in the reconstruction. In this way in vivo MRSI has considerably advanced in terms of spatial coverage, spatial resolution, acquisition speed, artifact suppression, number of detectable metabolites and quantification precision. Acceleration not only has been the enabling factor in high-resolution whole-brain $^1$H-MRSI, but today is also common in non-proton MRSI ($^{31}$P, $^2$H and $^{13}$C) and applied in many different organs. In this process, MRSI techniques had to constantly adapt, but have also benefitted from the significant increase of magnetic field strength boosting the signal-to-noise ratio along with high gradient fidelity and high-density receive arrays. In combination with recent trends in image reconstruction and much improved computation power, these advances led to a number of novel developments with respect to MRSI acceleration. Today MRSI allows for non-invasive and non-ionizing mapping of the spatial distribution of various metabolites' tissue concentrations in animals or humans, is applied for clinical diagnostics and has been established as an important tool for neuro-scientific and metabolism research. This review highlights the developments of the last five years and puts them into the context of earlier MRSI acceleration techniques. In addition to $^1$H-MRSI it also includes other relevant nuclei and is not limited to certain body regions or specific applications.
1 | INTRODUCTION

Shortly after the introduction of in vivo MRI and non-localized in vivo MRS, in vivo MR spectroscopic imaging (MRSI) was demonstrated in the early 1980s. Two distinct acquisition methods were suggested: (i) “NMR chemical shift imaging in three dimensions” in 1982 by Brown et al.1 and “Spatially resolved high-resolution spectroscopy by 4-dimensional NMR” by Maudsley et al.2 in 1983 as well as (ii) “Spatial mapping of the chemical shift in NMR” in 1984 by Mansfield.3 While (i) corresponds to classical phase-encoded and thus non-accelerated MRSI, (ii) represents the very first description of the most popular spatial-spectral MRSI acceleration method, echo-planar spectroscopic imaging (EPSI).4 In these early days hardware limitations such as gradient strength and fidelity as well as static magnetic field strength (B0) and homogeneity hindered the translation of these theoretical concepts into the excellent results that we can obtain today. However, during the last 30 years in vivo MRSI has undergone an enormous evolution in terms of spatial coverage, spatial resolution, acquisition speed, artifact suppression, number of detectable metabolites, and quantification accuracy and precision. Today it allows for non-invasive and non-ionizing whole-organ (e.g., brain) mapping of various metabolites’ tissue concentrations in animals and humans (e.g., up to 12 brain metabolites5 and nine macromolecular compounds6), up to 300 times faster than conventional phase-encoded 1H-MRSI.7 While mainly conventional point resolved spectroscopy (PRESS)-localized Cartesian-sampled MRSI and quantification accuracy and precision. Today it allows for non-invasive and non-ionizing whole-organ (e.g., brain) mapping of various metabolites’ tissue concentrations in animals and humans (e.g., up to 12 brain metabolites5 and nine macromolecular compounds6), up to 300 times faster than conventional phase-encoded 1H-MRSI.7 While mainly conventional point resolved spectroscopy (PRESS)-localized Cartesian-sampled MRSI is currently applied for clinical diagnostics,8 basic and advanced MRSI protocols have been established as important tools for neuro-scientific and metabolism research.8

Due to the need to encode the chemical shift along with spatial information, classical MRSI utilizes phase encoding along all directions, which is intrinsically slow. Another complication is the very low signal intensity of metabolites. In comparison to 1H-MRI of tissue water, 1H-MRSI of tissue metabolites is about 10 000 times less sensitive due to the concentration difference between water and metabolites. In addition, abundant water and fat signals lead to much stricter needs to control related artifacts. MRSI of other nuclei such as 31P, 2H or 13C is yet another order of magnitude less sensitive and lacks the possibility to use anatomical images as reference and to generate prior knowledge, which further restricts the acceleration options. Hyperpolarized 13C-MRSI has sufficiently high signal-to-noise ratio (SNR) and only a few metabolite peaks, but suffers from acquisition time restrictions. Thus, hyperpolarized 13C-MRSI has benefitted particularly from the development of fast MRSI encoding techniques in the past, achieving nowadays time resolutions needed for assessing real-time metabolic fluxes in clinical settings.9

While the basic principles of 1H-MRI acceleration are applicable to 1H- and non-proton MRSI as well, they usually need substantial adaptation to encode chemical shift, work robustly in a low-SNR regime and in the presence of strong nuisance signals (e.g., water, fat) or meet the scan time restrictions in hyperpolarized 13C-MRSI.

There are four main principles for accelerating MRSI: (i) short repetition times (TR), (ii) acquisition of multiple k-space points per TR, (iii) k-space undersampling and (iv) data reconstruction using spectral or spatial prior knowledge. Reports on the short-TR principle range from moderately short TR values to true steady-state free precession (SSFP). The acquisition of multiple k-space points per TR can be accomplished by either multi-spin-echo sampling or more commonly spatial-spectral encoding (SSE) including EPSI or non-Cartesian k-space trajectories. In a broad sense “k-space undersampling” methods include widely available methods such as elliptical k-space shuttering10 or MRS pre-localization (i.e., allowing field-of-view reduction with fewer required k-space points). “Real” k-space undersampling approaches include parallel imaging (PI), multi-band acquisition, and compressed sensing (CS). Finally, there are reconstruction techniques that use prior knowledge from high-resolution anatomical images and spectral priors, and combinations with low-rank reconstruction. All these acceleration principles are complementary and can be combined. A detailed introduction of k-space formalism and filtering is outside the scope of this review. We refer the interested reader to two excellent books that provide a general introduction, before continuing with the more specific sections detailed below.10,11

Related MRSI encoding methods have been reviewed by a number of previous review papers and book chapters12-16 that either cover mostly literature from before 2014 or have a limited coverage with respect to acceleration methods or applications. Recent progress in MRSI encoding has significantly benefitted from ultra-high field (UHF) systems, high gradient fidelity and high-density receive coil arrays. In addition, a number of dedicated acceleration methods for hyperpolarized 13C-MRSI have been demonstrated. In combination with emerging trends in image reconstruction and much improved computation power, these advances led to a number of novel developments with respect to MRSI acceleration. Hence, this review highlights the developments of the last 5 years and puts them into the context of earlier techniques. In addition to 1H-MRSI it also includes other relevant nuclei and is not limited to certain body regions or specific applications. Thus, this review paper represents the most comprehensive and most up to date one of its kind.

KEYWORDS

acceleration, acquisition, compressed sensing, MR spectroscopic imaging, parallel imaging, reconstruction, spatial-spectral encoding, undersampling
2 | SHORT \( T_R/T_E \)

The most straightforward way to speed up MRSI is by either shortening the \( T_R \)^{17-19} or acquiring multiple spin echoes (SEs) per \( T_R \).^{14,15} This approach has its roots in the early 2000s, when highly SNR-efficient SSFP as well as turbo-SE sequences were proposed for MRSI.\(^{17-21}\) These sequences benefit either from fast point-by-point sampling of the \( k \)-space with short \( T_R \)^{17-19} or from sampling of multiple \( k \)-space points per \( T_R \) in the case of multiple SEs\(^{20,21}\) (i.e., their relative contribution is a function of the \( T_1/T_2 \) ratio and flip angles). Both methods restrict the acquisition time for the spectral readout to the inter-pulse delay. Due to the resulting reduced spectral resolution,\(^{21,22}\) SSFP-MRSI was initially confined to well separated resonances (e.g., fat/water mapping, only the singlets of NAA, Cr and Cho in \(^1\)H-MRSI, or \(^{31}\)P/\(^{13}\)C-MRSI)\(^{19,23,24}\) and animal studies (i.e., featuring faster encoding gradients and higher spectral resolution due to available high-\( B_0 \) MR scanners).\(^{17,18}\) This change when improved hardware became available also for human whole-body MR systems and enabled the acquisition of true SSFP-based \(^1\)H-MRSI (\( T_R < 200 \) ms) of the human brain with sufficiently high spatial and spectral resolution.\(^{25-27}\) Although SSFP-based MRSI yields the highest possible SNR efficiency, major downsides include the low spectral resolution, limited water suppression, potential banding artifacts and strongly \( T_1/T_2 \)-weighted metabolite signals, which make metabolic maps highly qualitative without relaxation corrections, and interpretation of the exact neurochemical underpinnings in pathologies challenging. Recent implementations overcome problems with banding artifacts by using balanced SSFP with either a very narrow pass-band frequency selective excitation and frequency sweeping\(^{28}\) or successive measurements with phase increments to achieve the spectral separation in a similar manner to the Dixon approach\(^{29}\)

Albeit not as SNR efficient as SSFP-MRSI, the lack of undesired \( T_2 \)-weighting or \( J \)-coupling effects has made pulse-acquire or free induction decay (FID)-MRSI sequences with Ernst angle excitation and gradient spoiling after each \( T_R \) (Figure 1) an increasingly popular alternative, not only for \(^{31}\)P-MRSI\(^{30-34}\) and \(^{13}\)C-MRSI\(^{24,35-38}\) but also recently for \(^1\)H-MRSI.\(^{39-42}\) The FIDLOVS (FID acquisition localized by outer volume suppression) sequence\(^{43}\) had still a fairly complicated design with a large number of outer volume suppression (OVS) pulses causing high specific absorption rate (SAR) demands at 7 T and consequently long \( T_R \) values, but it motivated simpler \(^1\)H-FID-MRSI approaches that allowed for much shorter \( T_R \) values of a few hundred milliseconds by confining the sequence to water suppression and excitation pulses.\(^{39,44}\) The \( T_R \)-shortening of this type of sequence is only limited by a possible compromise in water suppression quality, \( T_1 \)-weighting and spectral resolution (a side-effect of reducing the FID sampling). Some implementations have even completely abandoned all suppression pulses and replaced these by retrospective nuisance removal.\(^{45}\) In particular at UHF \(^1\)H-FID-MRSI overcomes critical limitations in SAR, chemical shift displacement error (CSDE), \( B_0 \)-inhomogeneity, \( T_2 \)-weighting, \( J \)-evolution and coverage of cortical regions in comparison with traditional MRSI. On the other hand, \(^1\)H-FID-MRSI lacks high-quality volume selection to reduce nuisance signals (e.g., extracranial lipids) and macromolecule signals are enhanced. While this makes accurate metabolite quantification challenging, it has enabled the high-resolution mapping of macromolecules.\(^{46-48}\) Since then, FID-MRSI acquisitions with short \( T_R \) values (~60 to 600 ms) have become an integral part of many UHF \(^1\)H-MRSI sequences at 7 T (References 41.48-53) and 9.4 T (References 5,40,54-57) (Figure 2) and an increasing number of 3 T MRSI implementations.\(^{51,54,58}\) FID-MRSI is also the method of choice for \(^31\)P-MRSI\(^{30-34}\) due to the fast \( T_2 \) relaxation of most \(^31\)P-MRS signals, and for \(^2\)H-MRS\(^{59}\) due to the absence of water and fat suppression modules. FID-MRSI applications are so far limited mostly to the human brain but also for the investigation of skeletal muscles and \(^31\)P-MRSI\(^{30,42}\) where volume pre-selection is secondary. First clinical examples have been demonstrated in patients with brain tumors,\(^{7,31,49}\) multiple sclerosis,\(^{7,50,60}\) and mild cognitive impairment.\(^{51,62}\)

In principle, also SE-MRSI sequences can be used with shorter \( T_R \), but this is uncommon, since SSFP-MRSI is more efficient and especially the high bandwidth and SAR demands of refocusing pulses tailored for UHF (e.g., adiabatic RF pulses in particular) are a major constraint.

While the acquisition time saving associated with \( T_R \) reduction does not match that of common SSE approaches, the achievable acceleration factors are nevertheless good (~2- to 20-fold) compared with typical undersampling techniques and come with only minor side effects (e.g., \( T_1 \)-weighting, possible FID truncation), while benefitting among other advantages from a slight boost in SNR per unit time (SNR/\( t \)).\(^{39}\) Combinations with other acceleration methods, which all have the tendency to reduce SNR efficiency, are straightforward. Successful combinations have been shown with PI,\(^{41,51,52,55,56}\) CS,\(^{57}\) SSE\(^{63,64}\) or several approaches at once to enable high-resolution rapid whole-brain MRSI\(^{64}\) or dynamic 2D-MRSI with high temporal resolution.\(^{65}\)

3 | SPATIAL-SPECTRAL ENCODING

Even higher accelerations can be achieved using SSE. The basic principle of SSE was introduced by Mansfield\(^5\) in 1984, but early implementations were limited by gradient hardware imperfections.\(^{66,67}\) It took decades until SSE developed into the robust metabolic imaging tool that it is today.\(^{68-71}\)

In contrast to phase-encoded MRSI, where spatial and spectral encoding are strictly separated, SSE utilizes high-slew-rate gradient waveforms to sample spatial information (by sampling along \( k \)-space trajectories) simultaneously with spectral information (by repeating the same trajectory a few hundred times per \( T_R \)) (Figure S1). This is possible since the encoding of the spectral dimension (sampling period in ms) is a slow process compared with the encoding of spatial dimensions (sampling period in \( \mu s \)). SSE enables highly efficient and about 25 to 170 times faster
MRIs scans than pure phase-encoding. The SNR/t is similar to that of conventional phase-encoding, provided that the most efficient sampling (e.g., ramp sampling for EPSEI) is used.

SSE can employ a variety of different Cartesian or non-Cartesian trajectories that have very different gradient requirements and k-space densities (Figure 3), with EPSEI75 and spiral-based MRSI76 being the most prominent examples. However, gradient hardware limitations and the need for higher spectral bandwidth (SBW) at spatial resolution at higher B0,73,77,78 as well as the desire to reduce voxel bleeding by an improved spatial response function (SRF) (i.e., to mitigate extracranial lipid artifacts), have made alternative SSE strategies increasingly attractive79–82 Overall, the use of SSE becomes challenging at UHF (i.e., the SNR efficiency suffers) since the maximum time permitted for one trajectory repetition (i.e., spectral dwelltime) is inverse proportional to the SBW, and trajectory repetitions become challenging for the higher spatial resolutions at UHF (Figure 4). Although temporal interleaving can somewhat alleviate this otherwise hard limit at the cost of measurement speed, the number of temporal interleaves is limited to three or less for 1H-MRSI, while it is freely adjustable for multi-nuclear MRSI.7,30,63,83 The reason is that for more than three temporal interleaves high unsuppressed water signal lead to spectral aliasing artifacts in the spectral range of interest (e.g., between water and lipid signals), the intensity of which scales with temporal instabilities between temporal interleaves and cannot be easily removed.15 A completely different approach is reduction of acquisition time using partition of the signal decay in spectroscopic imaging (RAPID-SI),84which is similar to an approach shown earlier by Cao et al for hyperpolarized 13C-MRSI.85 Both speed up MRSI acquisition along a phase-encoding direction approximately 2- to 16-fold by separating the acquired FID into equidistant fractions via blipped phase-encoding gradients (this resamples jumping from one k-space point to the next during FID readout rather than moving along a continuous trajectory).

Since EPSEI is in principle equivalent to multi-echo MRI with extremely short echo spacing (i.e., spectral dwelltime in MRSI), Dixon-based spectral separation can be considered an extreme case of SSE with very few (i.e., originally two), sometimes non-equidistantly distributed, echoes. To quantify a few well-separated spectral resonances (e.g., water and fat87,88 or four resonances in 13C-MRSI89), only a few echoes (i.e., EPSEI lines or any other SSE trajectories) must be acquired. The basic idea is to exploit the difference in precession frequency between two or multiple resonances. For instance, to separate fat and water, two images with slightly different TE values are acquired. For the first image the TE is adjusted to show fat and water signals in phase, while the TE for the second image is adjusted by a few milliseconds to have fat and water signals out of phase. Adding the two images leads to a water image and subtracting the two images to a fat image. The Dixon method and the related iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL) can be extended to the separation of multiple resonances by using multiple spin or gradient echoes. IDEAL has been combined with spiral and echo planar imaging (EPI) readouts as well as k-t undersampling approaches for hyperpolarized 13C-MRSI89–93 (the processing pipeline is shown in Figure 5) and 129Xe-MRSI.94

Apart from the maximum possible acceleration factor and SNR efficiency, a main criterion for choosing the right SSE technique is the limitations imposed by the available gradient system. The targeted spatial resolutions are much lower in MRSI than in MRI. Hence, maximum gradient amplitudes do not impose any limitations, but a high gradient slew rate is critical to allow gradient trajectories to remain short and be repeated.

**FIGURE 1** Comparison of different MRSI sequence types that make use of short T2 values for acceleration. A, FID-MRSI sequences acquire an FID signal after an Ernst excitation pulse followed by a gradient spoiler to eliminate any remaining transverse magnetization. B, C, In contrast, SSFP-MRSI sequences revert the phase-encoding after signal sampling, so that the remaining transversal magnetization can be reused and the steady-state condition can be established. Using this magnetization the next RF pulse creates an echo. This transversal magnetization continues to be refocused until the signal decays to zero. Therefore, each sampling interval collects the sum signal of multiple echoes, the relative contributions of which are determined by their T2. Because of the short T2, the signal is additionally T1 weighted. The mix of T1/T2-weighting is specific for each resonance (not metabolite) and depends also on the local excitation flip angle. C, As a more robust alternative missing-pulse SSFP has been proposed to allow detection of complete SEs (eliminating the need for phasing, mitigating truncation artifacts and improving spectral resolution) and enabling the incorporation of improved spatial localization as well as water/fat suppression pulses. Courtesy of Philipp A. Moser.
rapidly. This is necessary to cover the target spectral range (increasing with $B_0$) and traverse a sufficiently large $k$-space (otherwise limiting spatial resolution). The extent to which different SSE trajectories are susceptible to or induce gradient imperfections varies substantially. Generally, $k$-space trajectory errors are more problematic for spirals, rosettes and radial EPSI than for other SSE alternatives (see below and Table 1), but these deviations between actual and real trajectories can be measured and considered during MRSI reconstruction.

### 3.1 Cartesian SSE

Cartesian SSE techniques acquire one spatial dimension and the spectral dimension simultaneously in a single readout via a series of periodically inverted readout gradients. Each semi-period encodes one line in $k$-space and the progression of gradient pulses encodes the spectral dimension. Symmetric-EPSI and flyback-EPSI are most commonly used (Figure S1).

#### 3.1.1 EPSI

The original EPSI technique, also known as symmetric EPSI or proton EPSI (PEPSI), uses a series of alternating positive and negative trapezoidal gradients to produce a zig-zag trajectory in $k_x$-$t$ space. Ideally, the acquired $k_x$-$t$ data can be sorted into a matrix after phase correction of the negative echo data and reconstructed using Fourier transform. In practice, the positive and negative echo data are not equivalent due to asymmetries in gradient switching and eddy currents, and direct Fourier transform reconstruction of combined positive and negative echoes would lead to ghosting artifacts in the spectral domain. One way to avoid spectral ghosting is to perform a separate Fourier transform for positive and negative echoes followed by combination after phase correction, at the expense of halving the SBW. If data are acquired during the gradient ramps, there is only a small penalty in SNR/$t$ compared with phase-encoded MRSI, despite the significant acceleration (e.g., 32-fold). Figure 6 shows PEPSI results in the human brain. Alternatively, shift correction between positive and negative echo data can be performed using an interlaced Fourier transform approach to exploit the full SBW. Center-out EPSI readout, where the upper half of $k$-space is acquired during the first segment and...
the lower half of \( k \)-space during the second segment, has also been proposed to passively prevent formation of ghosting artifacts and optimize SBW, by computing the shift correction between positive and negative echo data directly from the differences between upper-half and lower-half \( k \)-space data.\(^9\)
FIGURE 4  Comparison of concentric rings, EPSI and spiral spectroscopic imaging: top left, acquisition time; top right, SNR efficiency; bottom left, bottom right, SBW and SBW with spectral interleaves. CRT requires half of the total acquisition time compared with EPSI trajectories, offers about 87% SNR efficiency and provides much wider spectral bandwidth than flyback-EPSI and symmetric EPSI. Although nominally spirals are the most efficient trajectories, offering the best acquisition time and SBW benefit while sacrificing the least SNR, they are limited by susceptibility to gradient infidelities. All designs assumed a gradient amplitude limit of 40 mT/m and maximum slew rate of 150 mT/m/ms. Top right, SNR efficiency of different trajectories for various resolutions. The SNR loss for flyback EPSI is mostly due to its low duty cycle. The finer the resolution is, the lower the duty cycle will be, and SNR efficiency decreases as the flyback portion requires more time. Although the duty cycle for symmetric EPSI with ramp sampling is 100%, the non-uniform ramp sampling reduces SNR efficiency. For the constant slew rate spiral trajectories, SNR efficiency decreases as the resolution becomes coarser with a fixed FOV, since there is proportionally less outer k-space sampling where spirals are more uniform. Non-uniformity causes most of the SNR loss of spirals, while duty cycle results in a smaller fraction of the loss. Benefitting from the design of constant slew rate, the spiral trajectories provide even better SNR efficiency than flyback EPSI and CRT. CRT offers a constant SNR efficiency, which is better than flyback EPSI with the chosen prescriptions. The loss of SNR efficiency for CRT is caused by the non-uniformity. Note that the SNR efficiency depends on the targeted k-space density. Here a constant density k-space was targeted. Given the same traversing velocity, the achieved SBWs for EPSI, CRT and spirals are decreasing (bottom left) without interleaves. To exploit the maximum SBW, both symmetric EPSI and flyback EPSI result in the same waveform, thus achieving the same SBW. They are only slightly better than CRT, since flyback EPSI requires flyback time and symmetric EPSI does not critically exploit the whole SBW. However, CRT and spiral trajectories are more scan-time efficient compared with EPSI. If we take advantage of scan-time efficiency by applying temporal interleaves, we can increase SBW. Bottom right, SBW of all trajectories was computed by accounting for the temporal interleaves constrained for the same total acquisition time. For this tradeoff, spirals offer the best SBW, while CRT’s SBW is doubled compared with EPSI. The non-monotonicity of the spiral trajectory SBW with respect to resolution in this analysis is due to using an integer number of interleaves. Reproduced from the work of Jiang et al.86
EPSI implementations have been shown for various pre-localization schemes including PRESS,79 semi-LASER (localization by adiabatic selective refocusing),78 whole slice with OVS99 and slab-selection.100 MRSI techniques that require multiple repetitions with different parameter settings benefit particularly from EPSI. This includes diffusion-weighted MRSI, the first implementation of which was shown in 1995,101 followed by more robust versions recently,102 with some even enabling diffusion tensor imaging of metabolites.103 Combining MRSI with encoding of two frequency dimensions simultaneously (e.g., J-resolved or correlation spectroscopy) is even more time consuming and has therefore been an active field of research. Correlated MRS (COSY)-EPSI has been predominantly used to map muscle metabolism,104–108 while J-resolved EPSI has been applied to prostate109 and investigations in the human brain.110–114 Spectrally edited MRSI requires subtraction of one spectrum from another, which doubles the scan time and prohibits short T$_R$, and hence can be efficiently accelerated by EPSI.115 Other less common applications include rapid temperature116 and metabolite T$_2$ mapping.117

Unquestionably, the most common application of EPSI is to enable time-efficient whole-brain MRSI,100 which has reached a high level of sophistication and automation after many optimization steps.118,119 It is used in clinical investigations for various brain disorders such as brain tumors,120–123 amyotrophic lateral sclerosis,124 schizophrenia125 or dyslexia.126 Applications outside the brain, including MRSI of the breast,127,128 liver129 and calf muscle,130 have been proposed as well.

3.1.2 Flyback-EPSI and more

To reduce SBW limitations, the flyback-EPSI technique uses only the positive gradient part for spatial encoding and short gradient pulses with maximum slew rate for refocusing. The flyback-EPSI readout also mitigates eddy current effects and ghosting significantly, but at the loss of SNR due to gaps in data acquisition.131 Other less common approaches to increase the SBW are temporal interleaving and repeating the acquisition with reversed readout gradients, which double both the SBW and the scan time.79,132 Another solution that doubles the SBW of EPSI without prolonging the scan time is coherent k-t space EPSI.82,133 Finally, multi-shot EPSI was proposed, which samples not only a single k-space line along k, but a complete echo-planar trajectory to cover a large fraction of the k$_x$-k$_y$ plane with gaps in k$_y$ and time being filled up by the following shots, but this caused significant spectral aliasing artifacts and imposes SBW limitations.134 Flyback-EPSI has been applied clinically in brain tumors,135,136 prostate cancer137 and multi-nuclear MRSI (i.e., hyperpolarized $^{13}$C-MRSI138 and $^{31}$P-MRSI139 of the calf muscle).
| Category       | Method             | Pros                                      | Cons                                      | Application                                      |
|----------------|--------------------|-------------------------------------------|-------------------------------------------|-------------------------------------------------|
| Short-$T_R/T_E$| SSFP               | - highest SNR/t gain                     | - $T_1/T_2$-weighting                    | - metabolites with long $T_2$ and short $T_1$   |
|                |                    | - moderate acceleration                   | - low spectral resolution                 | - hyperpol. $^{13}$C MRSI/MRI                    |
|                |                    |                                           | - poor water and lipid suppression in $^1$H-MRSI | - $^1$H-MRSI possible but restricted to major singlets |
|                |                    |                                           | - banding artifacts/$B_0$ sensitive       | - preferably < 7 T                              |
|                |                    |                                           |                                           | - $^1$H-MRSI                                      |
|                | Turbo-spin-echo    | - low acceleration                        | - low spectral resolution                 | - metabolites with long $T_2$                     |
|                |                    |                                           | - $T_1$-weighting (in k-space)            | - singlets in $^1$H MRSI                         |
|                |                    |                                           | - $\Delta B_1^*$ sensitive               | - preferably < 3 T                              |
|                | FID-MRSI           | - SNR/t gain                              | - $T_1$-weighting                         | - short $T_2$/$J$-coupled metabolites            |
|                |                    | - moderate acceleration                   | - high SNR                                | - ultra-high field                               |
|                |                    | - high SNR                                | - $J$-coupled metabolites in phase        | - $^{13}$C/$^{13}$P/$^1$H-MRSI                   |
|                |                    |                                           | - $\Delta B_1^*$ insensitive             | - preferably > 1.5 T                             |
|                |                    |                                           | - low SAR                                 |                                                 |
|                |                    |                                           | - low CSDE                                |                                                 |
|                | Cartesian SSE      | - high acceleration                       | - some SNR/t loss                         | - $^{12}$C/$^{13}$P/$^1$H-MRSI                   |
|                |                    | - inherently constant k-space weighting   | - limited SBW/spatial resolution          | - preferably < 7 T                              |
|                |                    |                                           | - gradient demanding                      |                                                 |
|                | Non-Cartesian SSE  | - highest acceleration                    | - some SNR/t loss                         | - $^{12}$C/$^{13}$P/$^1$H-MRSI                   |
|                |                    | - any k-space weighting possible          | - limited SBW/spatial resolution          | - preferably < 7 T                              |
|                |                    |                                           | - gradient demanding                      |                                                 |
|                | Spinals            | - high acceleration                       | - some SNR/t loss                         | - $^{12}$C/$^{13}$P/$^1$H-MRSI                   |
|                |                    | - inherent k-space weighting possible     | - limited SBW/spatial resolution          | - preferably ≥ 3 T                               |
|                | CRTs               | - high acceleration                       | - some SNR/t loss                         | - $^{12}$C/$^{13}$P/$^1$H-MRSI                   |
|                |                    | - inherent k-space weighting (optimization possible) | - gradient demanding                  | - preferably ≥ 7 T                               |
|                | Rosettes           | can be tailored for either high speed or low gradient stress | - some SNR/t loss                     | - $^{12}$C/$^{13}$P/$^1$H-MRSI                   |
|                |                    | - inherently weighted k-space (optimization possible) | - moderate SBW/spatial resolution limitation | - preferably ≥ 7 T                               |
|                | Radial EPSI        | - high acceleration                       | - some SNR/t loss                         | - $^{12}$C/$^{13}$P/$^1$H-MRSI                   |
|                |                    | - inherent k-space weighting (fixed)      | - limited SBW/spatial resolution         | - preferably < 7 T                              |
|                |                    |                                           | - gradient demanding                      |                                                 |
|                | Coherent k-space undersampling | - no gradient demands | - some SNR/t loss             | - $^{12}$C/$^{13}$P/$^1$H-MRSI                   |
|                | SENSE              | - low acceleration                        | - needs multi-channel receive coils       | - preferably ≥ 3 T/better at UHF                 |
|                |                    |                                           | - needs explicit sensitivity maps         |                                                 |
|                |                    |                                           | - spatial aliasing                        |                                                 |
|                |                    |                                           | - motion sensitive                        |                                                 |
|                | GRAPPA             | - no gradient demands                     | - some SNR/t loss                         | - preferably $^1$H-MRSI                          |
|                |                    | - interleaving to reduce motion sensitivity | - needs multi-channel receive coils       | - $^{12}$C/$^{13}$P/MRSI possible               |
|                |                    | - low acceleration                        | - spatial aliasing                        | - preferably ≥ 3 T/better at UHF                 |

(Continues)
| Category                        | Method               | Pros                                                                 | Cons                                                                 | Application                                      |
|--------------------------------|----------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------------------------------|
| CAIPRINHA                      | - no gradient demands   | - better control of aliasing                                          | - some SNR/t loss                                                   | - preferably $^{1}$H-MRSI                        |
|                                | - low acceleration     | - interleaving to reduce motion sensitivity                          | - needs multi-channel receive coils                                 | - preferably $^{13}$C/$^{31}$P-MRSI possible     |
|                                |                      |                                                                      | - spatial aliasing                                                 | - preferably ≥ 3 T/better at UHF                  |
| Multi-slice excitation         | Multi-band/SMS        | - accelerate also in slice direction                                  | - some SNR/t loss                                                  | - preferably $^{1}$H-MRSI, but $^{13}$C/$^{31}$P-MRSI possible |
|                                | - low acceleration     |                                                                      | - needs multi-channel receive coils                                 | - better at UHF                                  |
|                                |                      |                                                                      |                                                                      |                                                  |
| Incoherent k-space undersampling | CS                  | - SNR/t gain through regularization                                   | - sparse data (representation) required                             | - in spectral domain only for long-TE $^{1}$H-MRSI or $^{13}$C/$^{31}$P-MRSI |
|                                | - moderate acceleration|                                                                      | - minimum SNR required to work robustly                            |                                                  |
| Prior knowledge based         | SLIM/SLOOP/SLAM        | - SNR/t gain through regularization and spatial averaging            | - sensitive to bias fields such as $B_0$ inhomogeneity              | - $^{31}$P-MRS(I)                                |
|                                | - high acceleration    |                                                                      |                                                                      | - potentially hyperpol. $^{13}$C-MRS(I)          |
|                                |                      |                                                                      |                                                                      | - spectra from multiple arbitrarily shaped compartments instead of metabolite maps (except for GSLIM) |
| SPICE                          | - SNR/t gain through regularization |                                                                      | - requires assumptions about spatial and spectral priors; nuisance removal challenging | - preferably sparse well resolved spectra ($^{13}$C, $^{31}$P), but $^{1}$H-MRSI possible |
|                                | - high acceleration    |                                                                      | - may lead to spatial averaging                                   |                                                  |
|                                |                      |                                                                      | - may lead to spectral information loss                            |                                                  |
| Super-resolution reconstruction |                      | - resolution increase via pure post-processing                      | - requires assumptions about spatial priors                         | - all                                            |
|                                |                      |                                                                      | - no true spatial resolution gain—only smoother appearance of metabolite maps |                                                  |
| Spectral-spatial excitation & | IDEAL                | - replaces time-consuming spectral encoding by conventional MRI readout | - requires good spectral separation and $\Delta B_0$ homogeneity | - $^{12}$C/$^{31}$P-MRSI; good spectral separation required |

Abbreviation: $\Delta B_1^+-$transmit field inhomogeneity.
FIGURE 6 2D-PEPSI in the human brain at 3 T using $T_\text{R}$ 2 s, spatial matrix $32 \times 32$, scan time 64 s. The anatomical reference image (A) and an additional water image (B; from a separate non-water-suppressed acquisition) show the location of the multi-voxel spectra (C).
3.2 Non-Cartesian SSE

Non-Cartesian SSE techniques accelerate in two k-space dimensions and the spectral dimension simultaneously with only a few exceptions.\textsuperscript{140} The most prominent examples are spirals,\textsuperscript{76} concentric ring trajectories (CRTs),\textsuperscript{80} rosettes\textsuperscript{81} and radial EPSI.\textsuperscript{96} The most common reconstruction approach for non-Cartesian trajectories is to perform a non-uniform fast Fourier transform (NUFFT) in the spatial domain and conventional fast Fourier transform (FFT) along the temporal domain.

3.2.1 Spirals

Historically, the first non-Cartesian SSE k-space trajectory was the spiral.\textsuperscript{76} This was motivated by the early application of spirals in MRI and the fact that nominally constant-density spirals are the most efficient trajectories, offering the best acquisition time and SBW benefit while sacrificing the least SNR, but they are also more susceptible to gradient infidelities than other SSE techniques.\textsuperscript{66} which requires corrections.\textsuperscript{67} For small matrix sizes and lower SBW (e.g. at 1.5 T), spirals can acquire spectroscopic data in a single shot, but single-shot approaches are usually not practical due to SBW limitations imposed by the time required to complete the spiral trajectory. In practice, spiral MRSI is, therefore achieved via spectral (Figure 7A) and spatial interleaves (Figure 7B) (i.e., acquiring only a fraction of the k-space or FID, respectively, per TR).\textsuperscript{141}

With these properties, spirals are ideal for application in hyperpolarized 13C studies, where speed is critical to minimize T1 relaxation-related SNR losses,\textsuperscript{37,142-146} but also more recently in dynamic 31P-MRSI in muscles,\textsuperscript{30,147} where a high temporal resolution is essential. Spiral SSE is also playing an increasingly important role in 1H-MRSI of the brain\textsuperscript{71,148-157} and prostate\textsuperscript{141,158,159} to reach clinically attractive scan times. At 3 T fully scanner-integrated solutions for spiral MRSI\textsuperscript{153,155} have recently facilitated a stronger clinical use for brain tumor,\textsuperscript{149,151,152} neurodegenerative\textsuperscript{150,160} and demyelinating disorders,\textsuperscript{161} as well as psychiatric research.\textsuperscript{148,162}

Since the evolution of 1H-MRSI towards whole-brain coverage\textsuperscript{76,163} there is an increased need for mitigation of extra-cranial lipid bleeding artifacts. This has led to the development of variable-density spirals, which improve the SRF during the acquisition in an SNR-efficient manner without the need for inefficient post-processing k-space filters.\textsuperscript{142,165-168} This is frequently augmented by preprocessing to remove (lipid) artifacts even further.\textsuperscript{166-170}

However, due to limitations imposed by common whole-body gradients the efficiency of spirals suffers with increasing spatial resolution and SBW, which is typical for high-field MRSI.\textsuperscript{5,41} For SSE the same trajectory must be repeated several hundred times to sample an FID, but gradient

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure7.png}
\caption{a: Two types of spiral-based k-space acquisition schemes illustrate the concept of spectral interleaves: Uniformly (top) and randomly (bottom) undersampled spiral k-space acquisition schemes. The blue vertical lines represent the time at which a sample is acquired. b: The projections of possible k-space trajectories onto the k_x-k_y plane illustrate the concept of spatial (angular) interleaves. The projection from fully sampled (all six spatial interleaves), uniformly undersampled (R = 3, only two of six spatial interleaves), and randomly undersampled (R = 3) acquisition are shown from left to right, respectively. Reproduced from Chatnuntawech et al.\textsuperscript{142}}
\end{figure}
slew rate limitations do not allow return to the k-space center after each spiral sufficiently fast. All data acquired during such gradient rewinders (i.e., similar to flyback-EPSI gradients) are unused, which lowers the SNR. This makes “closed loop” trajectories without such a deadtime attractive for SSE. In-out spirals feature such self-rewinding properties, but they are only efficient for strong animal gradient systems, not for whole-body systems, where additional limitations on maximum SBW would be imposed.

3.2.2 | Concentric rings

These problems have triggered the development of inherently closed SSE trajectories without deadtimes, which are not merely translations of existing MRI trajectories, but rather tailored for the needs of MRSI. CRTs are the best example of this. They were originally proposed for hyperpolarized 13C-MRSI, but were rapidly adapted for 1H-MRSI with high spatial resolution and SBW. Via CRTs an N×N matrix resulting from a kN×kN k-space is covered by kN/2 equidistant rings, which makes CRT-based SSE exactly twice as fast as EPSI (i.e., it requires kN lines). For equidistant CRTs the acquired k-space is inherently 1/k weighted, but the weighting can be optimized (e.g., Hanning weighting) at the expense of reduced acceleration. The constant-angular-velocity properties of CRTs make them robust to gradient timing imperfections and eddy current delays, and PI reconstruction is considerably simplified. A unique feature of CRTs is that scan time/SNR efficiency can be further improved by acquiring a variable number of temporal interleaves (one temporal interleave/circumnavigation is sufficient in the k-space center, while in the k-space periphery gradient slew rate limits demand two or three temporal interleaves). This makes high-resolution whole-brain 1H-MRSI clinically feasible even at UHF (Figure 8).

3.2.3 | Rosettes

Rosettes are the other class of closed non-Cartesian SSE trajectories. A main feature of rosettes is their design flexibility, which allows tailoring of the trajectories for desirable features such as speed, low-gradient performance, repeated sampling of the k-space center or adapting the k-space weighting. Depending on the parameter settings, rosettes can become identical to rings, in-out spirals or radial EPSI. The ability to tailor rosette trajectories for low-gradient performance and reduced acoustic noise could make them useful in the regime of very high SBW/spatial resolution. MRI results indicate that rosettes can be more incoherently undersampled than other non-Cartesian trajectories, which may be a benefit for CS reconstruction.

3.2.4 | Radial EPSI

Finally, MRSI based on radial EPSI (again originally proposed for hyperpolarized 13C-MRSI) is a fairly young field. Only recently have preliminary experimental reports in 1H-MRSI and 31P-MRSI been published. Like spirals, radial EPSI trajectories return to the k-space center, which offers in principle the possibility for self-navigation (i.e., correction by phase/magnitude alignment of consecutive trajectories). This can be used

![Sample maps of six major metabolites obtained in a brain tumor patient (30-year-old female; anaplastic astrocytoma grade 3 with suspected progression into glioblastoma) along with conventional T₁- and T₂-weighted MRI displayed in transversal, sagittal and coronal planes. Whole-brain FID-MRSI data were acquired at 7 T in 15 min using a 3D CRT sequence with variable temporal interleaves, T₁ 450 ms, acquisition delay 1.3 ms, spatial resolution 3.4 × 3.4 × 3.4 mm³, 64 × 64 × 39 matrix and SBW 2778 Hz. The T₂-weighted FLAIR image is strongly affected by B₁ inhomogeneities, while this is less of a problem for gradient-echo-based images such as the T₁-weighted MRI and metabolic maps. Courtesy of Gilbert Hangel](image)
to reduce instabilities (e.g., motion) between different $k$-space interleaves (Figure S2)\textsuperscript{182,183} while other SSE techniques (e.g., EPSI) require interleaved navigators for this.\textsuperscript{184}

4 | UNDERSAMPLED MRSI

$k$-space undersampling is the third major acceleration method for MRSI. For an unambiguous signal allocation by gradient encoding, the distance between all adjacent $k$-space points must be less than 1/object size (i.e., Nyquist criterion). Conventional phase-encoded MRSI at the Nyquist rate (i.e., full $k$-space sampling) is very time consuming. In undersampled MRSI, fewer $k$-space points are acquired below the Nyquist rate to speed up the acquisition using coherent and incoherent undersampling patterns (Figure 9). Complementary information other than gradient encoding, which includes sensitivity maps, spatial-spectral sparsity or prior knowledge, is employed to reconstruct the undersampled data sets without aliasing.

4.1 | Parallel imaging

A common group of methods for reconstruction of $k$-space undersampled MRI data is PI.\textsuperscript{185–187} In classic implementations, $k$-space undersampling is performed in a uniformly equidistant manner across $k$-space (i.e., regular pattern), yielding a larger distance between sampled $k$-space points. This in turn leads to a field-of-view reduction to below the dimensions of the object and thus to aliasing (folding) of image information. To reconstruct the missing $k$-space points or to unfold the aliased image additional information on the spatial signal origin is derived from sensitivity profiles of receive coil arrays. There are two major reconstruction approaches in PI that have found widespread application: (i) sensitivity encoding (SENSE)\textsuperscript{187} and (ii) generalized autocalibrating partially parallel acquisition (GRAPPA).\textsuperscript{186} SENSE solves the image reconstruction problem in the image domain by unfolding the aliased images, and requires explicit sensitivity maps of each coil element to form an over-determined system of linear equations. Both the $k$-space encoding trajectory and receiver coil sensitivity patterns are input to the algorithm. GRAPPA solves the same problem in $k$-space domain, and typically only undersamples the outer parts of the $k$-space to derive a reconstruction kernel that predicts the missing $k$-space points from the central fully sampled part of $k$-space. Both principles are widely applied in MRI and have been demonstrated for $^1$H-MRSI as well. PI is generally also compatible with SSE and incoherent $k$-space undersampling (see Section 5).

4.1.1 | SENSE

Sensitivity-encoded $^1$H-MRSI was introduced shortly after the invention of SENSE-MRI in 2001 and was combined with different localization schemes such as PRESS,\textsuperscript{188} slice-selective adiabatic SE localization,\textsuperscript{189} SE- or FID-MRSI with OVS\textsuperscript{190–193} or FID-MRSI without OVS.\textsuperscript{55} This pre-localization was necessary because the original SENSE-MRSI implementation suffered from residual lipid aliasing artifacts introduced by imperfections of the sensitivity maps and insufficient control of the SRF. The ESPRIT approach\textsuperscript{55,192,194,195} to derive reliable sensitivity maps enhanced the robustness and applicability of SENSE-MRSI since it is free of residual bias fields or image contrasts, is compatible with transceiver arrays and is free of interpolation errors towards the edge of the object of interest. Several methods to further reduce lipid aliasing were presented, and include direct optimization of the SRF, overdiscrete or superresolution reconstruction and retrospective lipid removal.\textsuperscript{55,193,196–198} SENSE was also utilized for an overdiscrete $B_0$-correction that enhances the SNR of MRSI data.\textsuperscript{55,192} Figure 10 illustrates controls of SRF, resulting lipid

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure9.png}
\caption{Illustration of different 2D $k$-space undersampling schemas for two-fold acceleration ($R = 2$) and four-fold acceleration ($R = 4$). GRAPPA/SENSE can reconstruct coherently sampled $k$-space data (e.g., entire rows or columns are not acquired), while CAIPIRINA can reconstruct even coherently undersampled data with any other patter and benefits from controlled aliasing. All of them use information about sensitivity profiles of the individual receive channels to remove spatial aliasing either in the image (e.g., SENSE) or $k$-space domain (e.g. g GRAPPA, CAIPIRINA). This translates into better reconstruction with lower $g$-factors (e.g. g less lipid aliasing and higher SNR). In contrast, CS can reconstruct incoherently (e.g., random-like) undersampled $k$-space data without knowledge about the coil receive profiles of the individual receive channels. Courtesy of Lukas Hingerl}
\end{figure}
artifacts, and SNR increase. SENSE-MRSI was combined with alternative acceleration methods such as elliptical k-space sampling,\textsuperscript{199} multi-echo MRSI,\textsuperscript{20,21} EPSI,\textsuperscript{190,191,200} spiral MRSI,\textsuperscript{142} CS,\textsuperscript{57} low-rank reconstruction\textsuperscript{58} and partial Fourier imaging.\textsuperscript{201} SENSE-MRSI was also used to accelerate the acquisition of unsuppressed water maps for internal water referencing\textsuperscript{202} and a phantom-based external referencing for quantitative SENSE-MRSI compatible with receive arrays.\textsuperscript{203} SENSE-MRSI was applied to clinical studies in brain tumor patients,\textsuperscript{196,204} and shortly after its introduction SENSE-MRSI was also implemented as a commercial option by a major vendor and is utilized in clinical diagnostics today on a regular basis.

SENSE-MRSI is not easily applicable to $^3$P-, $^{13}$C- and $^2$H-MRSI due to the lack of a high-SNR reference standard (e.g., water in $^1$H-MRI/MRSI) that allows for generation of high-quality sensitivity maps. Nevertheless, applications of SENSE to hyperpolarized $^{13}$C-MRSI have been demonstrated\textsuperscript{201,205} sensitivity maps have been derived either by self-calibration exploiting the high SNR of in vivo pyruvate and a fully sampled k-space center\textsuperscript{205} or by using an oil phantom.\textsuperscript{201,206}

### 4.1.2 GRAPPA

The earliest description of GRAPPA-accelerated $^1$H-MRSI stems from 2006.\textsuperscript{207} Implementations have been demonstrated that relied on PRESS pre-localization,\textsuperscript{204,207} slice-selective or volumetric SE,\textsuperscript{65,208} and FID-MRSI.\textsuperscript{52,56,64,209} To reduce lipid aliasing in SE- or FID-MRSI, lipid suppression by either OVS or double inversion recovery were presented,\textsuperscript{190,209} but both options limit the acquisition speed by demanding higher T\textsubscript{R} values due to SAR. Controlled aliasing in parallel imaging results in higher acceleration (CAIPIRINHA)-MRSI encoding in combination with retrospective lipid removal yielded significantly better metabolite maps.\textsuperscript{202,167} Finally, training neural networks for GRAPPA reconstruction on MRI data\textsuperscript{56} or acquiring the reference data for GRAPPA reconstruction interleaved\textsuperscript{64} reduced lipid aliasing to a negligible level. GRAPPA-MRSI was combined with alternative acceleration methods such as elliptical k-space sampling,\textsuperscript{210} EPSI,\textsuperscript{65,208,211} CRT,\textsuperscript{64} and spirals.\textsuperscript{212} Recently, through-time/through-k-space GRAPPA was presented, which simultaneously yields an unsuppressed water reference scan.\textsuperscript{64} The impact of GRAPPA-accelerated EPSI on diagnostic sensitivity in traumatic brain injury patients was investigated and identical metabolic changes were found.\textsuperscript{211} GRAPPA is generally compatible with non-proton MRI, but preliminary $^{31}$P-MRSI implementations were limited by low SNR.\textsuperscript{213} A simultaneous auto-calibrating and k-space estimation (SAKE) variant was applied to hyperpolarized $^{13}$C-MRSI\textsuperscript{195,214,215}

Early implementations of SENSE-MRSI and GRAPPA-MRSI have been compared, and favorable results have been obtained for conventional GRAPPA due to SNR advantages and lower lipid aliasing.\textsuperscript{204} SENSE-MRSI was also compared against elliptical k-space shuttering and EPSI, and it was concluded that all three methods are applicable to clinical diagnostics of brain tumors with individual advantages and disadvantages.\textsuperscript{216} However, the full potentials of neither SENSE nor GRAPPA have been exploited in these studies, and a more thorough comparison of state-of-the-art SENSE and GRAPPA reconstruction algorithms and alternative sampling schemes has yet to be performed.

### 4.2 Multi-band/simultaneous multi-slice

Another possibility to exploit the sensitivity profiles of multi-channel receive coils for MRI acceleration is simultaneous multi-slice (SMS) imaging.\textsuperscript{217} SMS makes efficient use of simultaneous excitation of several slices by one multi-band RF pulse\textsuperscript{218} in combination with controlled aliasing\textsuperscript{219} and reconstructs the individual slices using the PI concept (Figure 11). The achievable acceleration factors are fairly low (~2 to 4) and
can therefore only be used as an add-on to either undersampling\textsuperscript{52} or SSE techniques,\textsuperscript{82,220} as shown for preliminary \textsuperscript{1}H-MRSI\textsuperscript{82,220} studies. The excitation of multiple slices via SMS should be not confused with multi-band spectral-spatial excitation (ie exciting different frequency bands simultaneously), which has been employed for rapid \textsuperscript{13}C-MRSI.\textsuperscript{38,92,221,222}

4.3 Compressed sensing

CS-MRI relies on a combination of non-uniform \textit{k}-space undersampling and the assumption of spatial and/or spectral sparsity.\textsuperscript{223} Spatial or spectral sparsity means that there are relatively few significant voxels or spectral points with non-zero values. During the image reconstruction, a wavelet and/or other compression transformation such as total variation or principal component analysis is performed to yield a sparse representation of the data similar to data compression in JPEG. \textit{k}-space undersampling must be incoherent to yield a noise-like distribution of nuisance signals, which can be removed by a non-linear reconstruction algorithm that enforces sparsity in the transformation domain (e.g., wavelet space) and is consistent with the acquired data.

The first implementation of CS-MRSI was demonstrated in 2008 with application in hyperpolarized \textsuperscript{13}C-MRSI,\textsuperscript{36} which still yields the majority of publications utilizing this MRSI acceleration method.\textsuperscript{35,36,38,85,224-231} CS is ideal for hyperpolarized \textsuperscript{13}C-MRSI due to its intrinsic spectral sparsity, which allows for additional acceleration along the spectral dimension. CS can be combined with SSE to further accelerate the metabolic imaging readout for hyperpolarized \textsuperscript{13}C-MRSI to reach sufficient coverage and resolution in the presence of strict time limits,\textsuperscript{35,36,85,228,231} and was demonstrated for flyback-EPSI, a custom designed incoherent spatial-spectral undersampling scheme and EPI with frequency selective excitation. Other acceleration methods that have been combined with CS for hyperpolarized \textsuperscript{13}C-MRSI are multi-band encoding,\textsuperscript{38} multi-point Dixon encoding\textsuperscript{227,230} and balanced SSFP.\textsuperscript{229} Applications of CS in \textsuperscript{13}C-hyperpolarization studies have focused mainly on cancer imaging.\textsuperscript{35,224-226}

Similarly, \textsuperscript{31}P-MRSI is well suited for this acceleration approach due to well separated spectral lines and the absence of large nuisance signals. The first CS \textsuperscript{31}P-MRSI implementation was shown in 2012 and was based on simulated 2D-MRSI data.\textsuperscript{232} An actual 2D implementation for human brain \textsuperscript{31}P-MRSI was shown in 2017.\textsuperscript{148,233,234} CS has been recently combined with flyback-EPSI for highly accelerated \textsuperscript{31}P-MRSI,\textsuperscript{62} and two distinct reconstruction schemes—L1-norm minimization and low-rank Hankel matrix completion—have been compared.\textsuperscript{138}

The application of CS to \textsuperscript{1}H-MRSI is complicated due to large water and lipid nuisance signals, which can mislead the reconstruction algorithm to exclude the lower-intensity metabolite peaks by misadjusted thresholding. In addition, \textsuperscript{1}H spectra are not sparse (short-\textit{T}_E MRS in particular), making acceleration along the spectral dimension more challenging. The first CS \textsuperscript{1}H-MRSI implementation was shown in 2009 in vitro\textsuperscript{235} and 2012 in vivo via retrospective undersampling.\textsuperscript{236} Several studies investigated the dependence of the SRF on the SNR and sampling pattern in CS-accelerated \textsuperscript{1}H-MRSI using phantom data.\textsuperscript{237-239} In vivo applications of CS \textsuperscript{1}H-MRSI were combined with either PRESS\textsuperscript{164,236,240,241} or semi-LASER\textsuperscript{85} pre-localization or slice-selective \textsuperscript{1}H-FID-MRSI\textsuperscript{57,58} (Figure 12). CS was used to further accelerate 3D \textit{J}-resolved EPSI for \textsuperscript{1}H-MRSI prostate applications.\textsuperscript{240,241} In addition the combination of CS with SENSE,\textsuperscript{57} CS with SENSE and incoherently undersampled spiral trajectories\textsuperscript{142} as well as CS and a low-rank constrained reconstruction scheme have been demonstrated for \textsuperscript{1}H-MRSI.\textsuperscript{58}
Even though SSE by itself can provide up to two magnitudes of acceleration compared with pure phase encoding, this is often not sufficient for reaching the desired target temporal resolution or volume coverage (e.g., whole brain) with sufficiently high spatial resolution. In such cases, SSE techniques can be combined with PI, CS or a mixture of the two techniques. Such undersampling can be performed in spatial ($k_x$, $k_y$), spectral ($t$) and dynamic (frame) dimensions. The possibility to undersample in multiple dimensions in an entangled fashion (e.g., both $k$-space and time domain) is highly beneficial for reconstruction efficiency.

5.1 | Cartesian

EPSI techniques simultaneously encode one spatial dimension and the spectral dimension, but the other spatial dimensions are still acquired using conventional phase encoding, and thus the scan time increases proportionally. PI can be used to regularly undersample the phase-encoding dimensions of EPSI and exploit differences in coil sensitivities to reconstruct unaliased spectroscopic images. 1D-SENSE and 1D-GRAPPA were employed to accelerate 2D-EPSI in the brain twofold for an 8-channel coil array and threefold for a 32-channel array, resulting in acquisition times below 1 min for a 32 $\times$ 32 spatial matrix and TR of 2 s. Acceleration in PI is limited by noise amplification due to a reduced number of phase-encoding points and instability in the inverse reconstruction produced by overlapping coil sensitivities (the so-called $g$-factor). Higher accelerations are feasible with the use of 2D undersampling for 3D imaging and a coil array with a large number of elements to enable 2D-SENSE, which reduce the $g$-factor. For example, 2D-SENSE using a 32-channel soccer ball head coil array enabled an acceleration factor of 2 $\times$ 2 for 3D-PEPSI with no additional degradation in spatial-spectral quality beyond the expected SNR decrease of $\sqrt{R}$, resulting in acquisition times of 2 min for a 32 $\times$ 32 $\times$ 8 spatial matrix (Figure S3).

An alternative approach to undersample the phase-encoding dimensions of EPSI is CS, which can exploit the natural sparsity along the spectral dimension in long-$T_E$ acquisitions or transform sparsity for short-$T_E$ acquisitions. The application of typical sparsifying transforms, such as wavelets and principal component analysis, along the spectral dimension can lead to combined spatial-spectral sparse representations of short-$T_E$ data. For 2D-EPSI, spatial-spectral incoherent sampling can be achieved by using phase-encoding blips, which result in a different $k_y$-undersampling pattern for each time point (Figure 13). To increase the acceleration rate, CS can be combined with PI to enforce joint coil sensitivity sparsity in the reconstruction. SPARSE-SENSE, which combines CS and SENSE, was applied to 2D-PEPSI to achieve fourfold acceleration with significant improvements compared with standard SENSE.

5.2 | Non-Cartesian

It is well known from MRI that non-Cartesian trajectories, such as those also used for radial EPSI, spirals and CRTs, can be more efficiently accelerated via PI than Cartesian trajectories, meaning that the $g$-factor-related SNR penalty is lower. This is a consequence of the less structured...
aliasing artifacts that are obtained via non-Cartesian sampling, which translates into more efficient reconstruction compared with Cartesian counterparts.\(^{242}\) This has also been suggested experimentally for MRSI using spirals\(^ {212,247}\) and CRTs (non-Cartesian \(k\)-space undersampling and reconstruction approaches illustrated in Figure 14).\(^ {64,80}\) SMS, which exploits sensitivity profiles as well, can therefore also be more efficiently combined with non-Cartesian SSE (e.g., CRTs).\(^ {220}\) Additionally, CS reconstruction benefits from variable-density \(k\)-space sampling,\(^ {223}\) which can be easily achieved via non-Cartesian spatial encoding.

Despite this evidence, the number of reports that have combined non-Cartesian SSE with undersampling is still limited compared with Cartesian SSE. This is partially related to the more complicated and often time-consuming reconstructions (e.g., iterative).\(^ {246,248}\) With its excess SNR, hyperpolarized MRSI is a prime candidate to benefit from undersampled non-Cartesian MRSI. On the other hand, there is a lack of good multi-

**FIGURE 13** A, CS acquisition scheme for 2D-PEPSI, based on random \(k_y\)-\(t\) undersampling using phase-encoding blips. Each time point is undersampled with a different random \(k_y\) pattern to achieve spatial-spectral incoherence. B, Comparison of real spectra obtained with fourfold acceleration for 2D-EPPI using SENSE (PI) and SPARSE-SENSE (combination of CS and PI). SPARSE-SENSE jointly exploits sparsity in the spectral wavelet domain and coil SENSE by enforcing joint multi-coil sparsity in the reconstruction to achieve significantly higher spectral quality and noise reduction compared with standard SENSE due to regularization. Reproduced from the work of Otazo et al.\(^ {243}\)

**FIGURE 14** A schematic diagram of the through-time/through-\(k\)-space GRAPPA method applied to concentric-ring MRSI. The figure shows a fully sampled calibration dataset on the left and a two-fold variable-density undersampled MRSI \(k\)-space on the right: the center of the \(k\)-space is fully sampled (solid points), followed by constant two-fold undersampling (empty points). For calibration, a segment (shaded area) was used around each target point for the through-\(k\)-space GRAPPA part with a kernel size of \(3 \times 2\) (red dotted lines), i.e., six source points. The kernel was slid through the segment of the calibration data to gather all the through-\(k\)-space kernel repetitions. Twenty-one calibration time points (through-time kernel repetitions) were used. After calculating the GRAPPA weights using the calibration data, the weights are used to reconstruct missing \(k\)-space points in the undersampled MRSI data (right). Reproduced from the work of Moser et al.\(^ {64}\)
channel multi-nuclear coils that would be necessary to perform PI efficiently for hyperpolarized 13C-MRSI, leaving CS—in particular in the spectral domain—the only option for further acceleration. In fact, spectral aliasing due to undersampling may not necessarily have to be undone for hyperpolarized 13C-MRSI as long as it does not cause major spectral overlap of important metabolite resonances.249 In this context, it should be noted that spectral aliasing due to undersampling is more problematic for 1H-MRSI data. Short-TE MR spectra are far less sparse (i.e., many strongly overlapping resonances) and there can be strong contamination by large nuisance signals (i.e., unsuppressed water or extra-cranial lipids). This is not a problem for 13C- or 31P-MRSI.148,234 Nevertheless, highly efficient combination of variable density spirals and an entangled SENSE and CS reconstruction has so far been shown only for 1H-MRSI at 3 T using PRESS.142 However, with an increasing number of better rapid non-Cartesian reconstruction algorithms emerging for MRI,250 the interest in undersampled non-Cartesian SSE for 1H-MRSI is increasing.

6 | USING PRIOR KNOWLEDGE

A promising approach to improve the results of highly accelerated MRSI is the incorporation of spatial (e.g., from high-resolution anatomical MRI) and spectral (e.g., spectral components and their relaxation times) prior knowledge as well as bias field maps (B₀ maps, B₁⁺ maps) to reconstruct data with incoherent k-space undersampling. More recently, low-rank reconstruction schemes were combined with corresponding prior knowledge. The following paragraphs review the evolution of acquisition and reconstruction approaches based on prior knowledge.

6.1 | Spatial prior knowledge and bias field maps: SLIM, SLOOP and SLAM

The utilization of prior knowledge derived from high-resolution anatomical images for reconstruction of MRSI data with substantial k-space undersampling was suggested as early as 1988, when the concept of spectral localization by imaging (SLIM)251 was introduced by Hu et al. The basic idea behind SLIM is to use a structural image to identify several compartments, each of which is assumed to be spatially uniform with regard to its metabolism. Hence, SLIM was originally used to derive spectra from a few arbitrarily shaped spatial compartments. For instance, a 1H-MR image of a limb may show three regions containing muscle, fat and bone marrow.251 In principle, only three phase encoding steps are required to reconstruct three spectra from these three compartments. Applications of SLIM were reported for 1H and 31P-MRS of tissue samples,252 perfused organs253 and in vivo skeletal muscle.251,254 In 1991 spectral localization with optimal pointspread function (SLOOP) as an improvement to SLIM was suggested, which minimizes contaminations from other compartments by optimizing the k-space sampling scheme.255 SLOOP was developed further to include additional prior knowledge on B₁⁺, T₁ and sequence parameters to optimize the SNR for human application of 3D-encoded 31P-MRS in the human myocardium.256 A further development step was the utilization of additional non-linear gradients for the encoding of the SLOOP compartments.257 In vivo 31P-SLOOP was mainly performed to characterize human cardiac muscle metabolism.257–263

SLIM developed into a metabolic imaging method, with the first report being the generalized series approach to MR spectroscopic imaging (GSLIM).264,265 GSLIM allows for spatial variations inside the compartments (e.g., metabolite concentrations and B₀ inhomogeneity), which are estimated from the data itself, the ill-posedness of the problem is dealt with by using regularization techniques. GSLIM and natural linewidth chemical shift imaging (NL-CSI) compensate for the sensitivity of SLIM to B₀ inhomogeneity across the predefined compartments by incorporating prior knowledge from additional B₀ maps into the reconstruction.266,267 Static and radiofrequency-compensated SLIM (STARS-LIM) even incorporates prior knowledge about B₀ and B₁⁺ inhomogeneity.268 B₀-adjusted and sensitivity-encoded spectral localization by imaging (BASE-SLIM) incorporates B₀ and sensitivity maps into the SLIM reconstruction.269 Finally, spectroscopy with linear algebraic modeling (SLAM)270,271 was introduced, which substitutes the compartments in SLIM by a set of coalesced MRSI voxels with the same concentrations. Similar to SLOOP, SLAM chooses an optimized set of the same number of low-gradient k-space vectors as final compartments to maximize SNR and to minimize signal bleeding. SLAM has been combined with SENSE. Initial applications are 31P-MRS in human skeletal muscle and myocardium271 and hyperpolarized 13C-MRSI.272 A recent review paper gives a more comprehensive overview of all derivatives of SLIM and its applications in brain MRSI.273

An alternative reconstruction approach unrelated to SLIM incorporates B₀ inhomogeneity as an additional encoding process together with the use of anatomical prior knowledge in a regularization term274 to improve MRSI reconstruction of undersampled data. Finally, the consideration of image prior knowledge as a direct constraint of the SRF along with B₀ inhomogeneity correction has also been demonstrated for SENSE-MRSI to better control lipid artifacts.275

6.2 | Spatial-spectral prior knowledge and low-rank reconstruction: toward SPICE

In addition to spatial prior knowledge, spectral prior knowledge has been used to reconstruct accelerated MRSI data. The first reported use of spectral priors in MRSI reconstruction relates to B₀ inhomogeneity correction by reference deconvolution using a spectral line shape model
reflecting the $B_0$ inhomogeneity distribution and aims at the improvement of the spectral linewidth. Early spatial-spectral modeling in MRSI reconstruction combined the conventional gradient encoding data consistency term with additional regularization terms considering a combined spectral and baseline model term as well as a total variation term and considered $B_0$ inhomogeneity as an encoding mechanism. Another spatial-spectral reconstruction approach aimed at controlling lipid spread and combined the usual consistency term that minimizes the difference between the gradient encoding data model and the data with a regularization or penalty term that includes a spatial-spectral lipid model.

Another important development step was the use of low-rank approximation approaches in MRSI reconstruction, the main idea of which is to remove basis vectors related to noise to yield higher-SNR spectroscopic images. Following an initial application in denoising of MRSI data, low-rank filtering was integrated with $B_0$ inhomogeneity correction and additional image prior knowledge on tissue type boundaries for a more robust reconstruction of fully sampled Cartesian MRSI. Shortly afterwards, low-rank approximation was combined with balanced-SSFP or dynamic spiral hyperpolarized $^{13}$C-MRSI with incoherent $k$-space sampling and $^1$H-FID-MRSI accelerated by short $T_R$ and a combined SENSE and CS acceleration. Low-rank reconstruction was also used together with a spatiotemporal lipid prior that assumes orthogonality of spatiotemporal metabolite versus lipid signals and applied to lipid-unsuppressed dual-density spiral $^1$H-MRSI.

A recent approach to reach very high acceleration factors and SNR in MRSI is the combination of the idea of “spatiotemporal imaging with partially separable functions” that separates temporal and spatial basis vectors with spectral prior knowledge and low-rank approximation. The resulting MRSI acceleration method SPICE (spectroscopic imaging by exploiting spatiotemporal correlation) represents the high-dimensional spectroscopic imaging data as a union or superposition of subspaces (Figure 15). In practice, four subspaces are used, including metabolites, lipids, water and macromolecules. The premise of SPICE is that the existence of spatial and temporal correlations will result in a low-dimensional representation given by the union of subspaces. Each subspace is represented using a low-rank tensor, whose basis is estimated from training data given by a fully sampled high-spectral-resolution and low-spatial-resolution acquisition to capture spectral correlations (Figure S4). Once the basis sets have been determined, undersampled data acquired with high spatial and spectral resolution can be reconstructed by enforcing the pre-computed union of subspaces model, which will remove aliasing artifacts and separate the spectroscopic imaging data into metabolites, lipids, water and macromolecules. The main advantage of SPICE is to learn an efficient model to represent spectroscopic images using training data, which goes beyond the handcrafted models used in CS and can enable access to higher spatial resolution and direct separation of nuisance signals. Recent implementations have eliminated the need for subject-specific navigator data to facilitate practical application. Initial applications were shown for $^1$H-MRSI of the human brain. Simultaneous readouts of SPICE-accelerated $^1$H-MRSI with QSM and functional MRI of the human brain have been demonstrated. Other applications include mapping of brain macromolecules and dynamic $^3$P-MRSI in skeletal muscle and hyperpolarized $^{13}$C-MRSI. The development of using prior knowledge in image reconstruction from SLIM to SPICE is described in a recent book chapter.

### 6.3 Super-resolution reconstruction

Another acceleration approach is the use of interpolation to yield higher-resolution metabolite maps from lower-resolution MRSI data. The most simple approach is $k$-space zero filling. Alternatively, the SENSE reconstruction framework uses additional spatial information on coil

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**FIGURE 15** An illustration of the SPICE approach. Each voxel spectra in the high-dimensional spatiotemporal function of interest $\rho(x,f)$, the image on the left) is modeled as a linear combination of a small number of spectral basis functions $\left\{\phi_l(f)\right\}_{l=1}^L$, rightmost column). This implies that the high-dimensional signals reside in a low-dimensional subspace (spanned by $\left\{\phi_l(f)\right\}$). With the subspace predetermined (from training data), the imaging problem is transformed into the estimation of a set of spatial coefficients $\left\{c_l(x)\right\}_{l=1}^L$ with much lower dimensions than the original spatiotemporal function. Different subspaces can be constructed for different signal components, i.e., water, lipids and metabolites.
A recently presented sophisticated interpolation method is the patch-based super-resolution approach that uses image prior knowledge to enforce smooth transitions inside a tissue compartment and sharp tissue boundaries in interpolated metabolite images. It assumes the existence of image redundancy in the form of metabolically identical patches of voxels and thus compartments. It was applied to enhance $^1$H-MRSI of multiple sclerosis$^{60}$ and glioma patients. For hyperpolarized $^{13}$C-MRSI super-resolution reconstruction in the spatiotemporal dimension was proposed in combination with an alternative spatial encoding without the necessity for time-varying SSE gradients. $^{297-299}$ Finally, deep learning in combination with semi-synthetic training data is utilized to yield super-resolution MRSI data. $^{200}$

### 6.4 Spectral-spatial excitation

Finally, another common strategy to accelerate metabolic imaging is to use prior knowledge about the resonance frequency of spectrally well-separated signals for frequency-selective excitation. This is applied especially to hyperpolarized $^{13}$C-MRI by combining spectral-spatial pulses with fast MRI readouts$^{286,301-309}$ but has been shown also for $^{31}$P-MRI.$^{310,311}$ Using a narrow-band spectral-spatial pulse to excite only a single metabolite resonance line makes the need for chemical shift encoding obsolete and enables conventional fast MRI readouts such as SSFP, echo-planar or spiral MRI that can be further accelerated via coherent/incoherent undersampling. The application of spectral-spatial pulses to different offset frequencies in successive MRI readouts enables fast hyperpolarized $^{13}$C-MRI of multiple resonance lines and even dynamic readouts for all metabolites if applied in an interleaved manner.

### 7 SUMMARY AND OUTLOOK ON EMERGING TECHNOLOGIES

In the long history of MRSI, time-efficient data acquisition was quickly identified as one of the main obstacles to high-spatial-resolution whole-organ metabolic mapping. Although a number of alternative approaches to SSE have been proposed, SSE will certainly remain the workhorse of different SSE strategies, it is increasingly challenged by other means of acceleration especially at UHF, where the increased SBW and spatial resolution demands have led to performance limitations for SSE with respect to speed and SNR efficiency. $^{63,83}$ These have complicated the use of purely SSE-based MRSI on common whole-body gradient systems, especially since the targeted spatial resolutions have gradually increased over time.$^{5,41}$ To make efficient use of the excess SNR available at UHF (e.g., by either shortening scans or increasing resolution) and to benefit from high-resolution strategies to minimize intra-voxel $B_0$ inhomogeneities, $^{312-314}$ it will become critical to not only adapt SSE strategies, but also combine them efficiently with other means of acceleration and reconstruction algorithms. This will allow the benefits of high fields to be fully exploited.$^{64,147,164,190,234}$ As the performance of $k$-space undersampling increases (i.e., $g$-factors improve with higher $B_0$ and short-$T_R$ FID-MRSI remains efficient (i.e., negligible SAR and CSDE at high $B_0$) while the efficiency of SSE (i.e., increasing SBW and spatial resolution demand for higher gradient slew rates) decrease with increasing $B_0$, we can expect to find an optimal balance between such combinations to slowly shift away from SSE alone to additional undersampling in the future. Depending on the application, such an efficient balance will include a reasonable compromise between short $T_R$ (increased relaxation weighting and possibly reduced spectral resolution), undersampling (increased lipid artifacts and motion sensitivity) and SSE (increased gradient imperfections and scanner drift).$^{184}$

The addition of spatial-spectral prior knowledge in the reconstruction algorithm appears to be another promising way to circumvent these limits.$^{290,295}$ New reconstruction algorithms with more complex models have recently become feasible due to the constant increase in performance of computational hardware and software. However, critically questioning what kind of prior knowledge and how much regularization is truly justified to avoid bias remains an important concern. In this respect, it is also expected that deep-learning-based reconstruction, which has shown promising results for MRSI/MRI,$^{45,56,315-318}$ will play an increasingly important role in the near future with the potential to substantially speed up the time-demanding reconstruction process of large multi-channel whole-brain MRSI datasets.

Another important step in the dissemination of fast MRSI techniques will therefore also be the progress in rapid automated spectral analysis tools tailored for whole-brain MRSI.$^{219}$ A number of well-established and freely available MRSI processing pipelines already exist for application studies (e.g., MIDAS package for whole-brain EPSI+GRAPPA; a comprehensive list of open-source MRSI processing software is provided in the appendix). However, by no means all MRSI acceleration and reconstruction approaches described herein are available as user friendly freeware tools and hence are not yet ready for larger application studies. We anticipate that it is just a matter of time for a larger number of open-source MRSI packages and full scanner integration of advanced MRSI methods to become available. To accelerate this process the developer community is encouraged to make MRSI sequences, reconstruction pipelines, and processing and visualization tools freely available to the scientific community. A more widespread dissemination of state-of-the-art MRSI methodology is also needed for cross-validation of different approaches.

Although several attempts to compare different SSE acceleration strategies—mostly via simulations rather than experimental validation—are documented,$^{74,83,216,320-323}$ a comprehensive comparison of all major SSE trajectories and undersampling techniques is not straightforward and has so far not been performed.
Considering the different and frequently hardware-specific artifact behavior of different encoding approaches, simulations alone can only give rough guidelines. In addition, the choice of specific reconstruction pipelines and parameters have a major influence on the resulting data quality and novel forms of reconstruction (e.g., based on neuronal networks or comprehensive low-rank models) may shift advantages/disadvantages in favor of currently more artifact-prone, but otherwise more efficient, acquisition schemes. Hence only a qualitative comparison of the major categories of MRSI acceleration methods is provided in Table 1. It includes important considerations such as acceleration factor, SNR efficiency, typical artifacts and limitations, and suggests typical applications for each method. It is important to mention that the maximum possible acceleration factors that a particular acceleration method can achieve (Table 1) cannot be fully exploited in the case of SNR limitations. Another important factor to consider is the SRF that describes the source of the signal displayed in a given voxel. In particular, non-Cartesian k-space undersampling and incoherent k-space undersampling easily allow tailoring of the k-space sampling density pattern (compare Table 1) and thus shaping of the SRF already during the acquisition. This allows trading the effective spatial resolution against higher SNR and better nuisance signal suppression (i.e., lipids in 1H-MRSI). SRF optimization is still possible during the reconstruction, but comes at the cost of SNR efficiency.

In line with the approach taken herein, a recent consensus effort on 1H-MRSI of the human brain324 also includes only qualitative guidelines on the application-dependent choice of MRSI sequence parameters and describes minimal standards for a wide range of influence factors including calibration, data acquisition, quantification and visualization. This is in contrast to a recent consensus on the standardized use of semi-LASER for clinical single-voxel MRS at 3 T, where the benefits over PRESS are unquestionable.325 For MRSI, currently well-established Cartesian SSE methods with standard k-space undersampling and multi-slice/3D options are strongly encouraged for clinical application.324 However, this is certainly only the most practical short-term solution, since multi-vendor scanner integration is already available for these methods, which is critical for clinical acceptance. The application of different encoding strategies on standardized MRSI phantoms or the same group of people in multicenter trials is needed to provide valuable experimental evidence that will help to come up with a true consensus on which MRSI acceleration methods should be implemented by manufacturers for future clinical use.

The development of methods with both time-efficient acquisition and reconstruction is, therefore, still ongoing and equally important for enabling clinical implementation of high-resolution whole-brain MRSI (or large-organ coverage), and possibly time-resolved MRSI such as for hyperpolarized and functional MRSI.
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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APPENDIX A

Open-source MRS/MRSI processing tools (in alphabetical order).

BrICS (https://brainimaging.emory.edu/brics/)—mainly display of metabolic maps and spectra.
CSItools (https://hci.iwr.uni-heidelberg.de/hci/softwares/csitools)—MRSI processing and display.
FID-A (https://github.com/CIC-methods/FID-A)—simulation and processing of MRS(I) data.
Gannet (http://www.gabamrs.com/)—edited MRS processing.
INSPECTOR (http://innovation.columbia.edu/technologies/cu17130_inspector)—simulation and processing of MRS(I) data.
jMRUI (http://www.jmrui.eu/)—simulation, processing and display of MRS(I) data.
jSIPRO (https://www.sites.google.com/site/jsiprotool/)—processing and display of MRSI data.
MIDAS (http://mrir.med.miami.edu:8000/midas/)—acquisition, processing and display of whole-brain MRSI data.
MRSIToolbox (https://cds-quamri.eu/index.php)—processing and display of MRSI data.
OXSA (https://github.com/oxsatoolbox/oxsa)—processing of MRS(I) data.
ProFit (https://mrtm.ethz.ch/research/mr-spectroscopy/physiological-projects/profit.html)—quantification of MRS(I) data.
SIVIC (http://sourceforge.net/projects/sivic/)—processing and display of MRS(I) data.
TARQUIN (http://tarquin.sourceforge.net/)—processing and display of MRSI data.