Super-resolution magnetic resonance imaging of the knee using 2-dimensional turbo spin echo imaging

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Super-Resolution MRI of the Knee Using 2D Turbo Spin Echo Imaging

Abstract

Objectives

The purpose of this study was to assess the technical feasibility of 3-dimensional (3D) super-resolution reconstruction (SRR) of 2D turbo spin echo (TSE) knee magnetic resonance imaging (MRI) and to compare its image quality to conventional 3D TSE sampling perfection with application optimized contrast using different flip angle evolutions (SPACE) MRI.

Materials and Methods

SRR 2D TSE MRI and 3D TSE SPACE images were acquired from a phantom and from the knee of 22 subjects (8 healthy volunteers and 14 patients) using a clinical 3T scanner. For SRR, seven anisotropic 2D TSE stacks (voxel size = $0.5 \times 0.5 \times 2.0$ mm^3, scan time per stack = 1:55 minutes, total scan time = 13:25 minutes) were acquired with the slice stack rotated around the phase-encoding axis. SRR was performed at an isotropic high-resolution grid with a voxel size of $0.5 \times 0.5 \times 0.5$ mm^3. Direct isotropic 3D image acquisition was performed with the conventional SPACE sequence (voxel size = $0.5 \times 0.5 \times 0.5$ mm^3, scan time = 12:42 minutes). For quantitative evaluation, perceptual blur metrics and edge response functions (ERFs) were obtained in the phantom image, and signal- (SNR) and contrast-to-noise ratios (CNR) were measured in the images from the healthy volunteers. Images were qualitatively evaluated by 2 independent radiologists in terms of overall image quality, edge blurring, anatomic visibility, and diagnostic confidence to assess normal and abnormal knee structures. Nonparametric statistical analysis was performed, and significance was defined for *P* values less than 0.05.

Results

In the phantom, perceptual blur metrics and ERFs demonstrated a clear improvement in spatial resolution for SRR compared to conventional 3D SPACE. In healthy subjects, SNR and CNR in clinically relevant structures were not significantly different between SRR and 3D SPACE. SRR provided better overall image quality and less edge blurring than conventional 3D SPACE, yet the perceived image contrast was better for 3D SPACE. SRR received significantly better visibility scores for the menisci, whereas the visibility of cartilage was significantly higher for 3D SPACE. Ligaments had high visibility on both SRR and 3D SPACE images. The diagnostic confidence for assessing menisci was significantly higher for SRR than for conventional 3D SPACE, while there were no significant differences between SRR and 3D SPACE for cartilage and ligaments. The interreader agreement for assessing menisci was substantial with 3D SPACE and almost perfect with SRR, and the agreement for assessing cartilage was almost perfect with 3D SPACE and moderate with SRR.

Conclusions

We demonstrated the technical feasibility of SRR for high-resolution isotropic knee MRI. Our SRR results showed superior image quality in terms of edge blurring, but lower image contrast and fluid brightness when compared with conventional 3D SPACE acquisitions. Current SRR results thus suggest that further contrast optimization and combination with state-of-the-art acceleration techniques are necessary for future clinical validation of SRR knee MRI.

Keywords

Knee, magnetic resonance imaging, 3-dimensional, TSE, SPACE, isotropic reconstruction, super-resolution

Introduction

Current knee magnetic resonance imaging (MRI) protocols typically consist of two-dimensional (2D) intermediate-weighted (IW) and fat-suppressed T2-weighted turbo spin echo (TSE) sequences. These sequences provide excellent tissue contrast and high in-plane resolution, but they are typically acquired with a large slice thickness, which results in partial volume averaging.[1,2]

As an alternative to multiple 2D TSE acquisitions, all major MRI vendors now offer three-dimensional (3D) TSE sequences. The primary advantage of these sequences lies in their ability to provide a single-slab isotropic 3D volume covering the whole knee joint, thereby reducing partial volume effects, and eliminating interslice gaps.[2] Some of the commercially available 3D TSE sequences are fast spin echo (FSE) Cube (GE Healthcare), volume isotropic TSE acquisition (VISTA, Philips Medical Systems), and sampling perfection with application optimized contrast using different flip angle evolutions (SPACE, Siemens Healthcare).[1] Typically, these 3D TSE techniques have integrated parallel imaging which allows for the use of large turbo factors (TF) and thus long echo train lengths (ETL > 40 echoes), as well as ultrashort echo spacing, decreased flip angles, and variable flip angle modulation along the echo train.[2,3] These characteristics allow to produce an IW contrast, which is commonly applied in clinical practice for comprehensive knee joint assessment. An additional benefit of the 3D TSE sequences is that the source data can subsequently be reformatted in any desired orientation, which facilitates the depiction of oblique complex knee structures (e.g. meniscal roots) and eliminates the need for multiplanar acquisitions.[1-3] Despite their advantages, current 3D TSE sequences still exhibit limitations regarding image quality due to the use of long ETLs.[4] In particular, image blurring caused by acquiring the high frequencies at the later echoes can be problematic as this decreases the visibility of low contrast structures, such as the menisci, which in turn may impede accurate diagnosis.[5-7] Compared to 2D TSE sequences, conventional 3D TSE sequences are also characterized by long acquisition times, which increases the probability of motion artifacts.[3,4] However, to reduce scan time, several new data sampling strategies for high-resolution isotropic 3D TSE MRI of the knee have been developed and are now available on clinical MR scanners, such as 3D SPACE with 2D controlled aliasing in parallel imaging results in higher acceleration (CAIPIRINHA)[8] and 3D TSE with compressed sensing (CS).[9-11] Yet, despite the optimization of 3D TSE acquisition parameters[12,13] and the fact that similar image quality and diagnostic performance have been observed for accelerated 3D TSE acquisitions,[14-17] these 3D TSE techniques are not widely adopted in routine knee MRI.

An alternative to direct 3D MRI is super-resolution reconstruction (SRR) of 2D MRI which has been shown to improve the MRI trade-off between signal-to-noise ratio (SNR), spatial resolution and scan time.[18-20] Among the various SRR frameworks described in the image reconstruction literature, a group of SRR methods developed for structural MRI combines multiple low through-plane resolution acquisitions with high SNR to obtain a single high-resolution image using a variety of algorithms.[18] An SRR scheme based on rotation around the phase-encoding axis ensures that each low-resolution image covers a different part of the k-space and thus adds information in the slice-selection direction.[19-21]

SRR has been applied to structural MRI of adult[18,19] and fetal brain[22], and to diffusion-weighted imaging (DWI) of the brain[20,21] and the breast[23]. Furthermore, it holds applications in functional and dynamic MRI, e.g. cardiac[24] and thoracic[25]. However, SRR has not yet been reported for routine MRI of the knee. Therefore, the purpose of the present study was to assess the technical feasibility of SRR of 2D TSE knee MRI and to compare its image quality to conventional 3D SPACE MRI. Our hypothesis was that SRR can be applied to 2D TSE MRI to obtain high-resolution isotropic 3D knee MRI, yielding better image quality in terms of edge blurring when compared with conventional 3D SPACE acquisitions.

Materials and Methods

Study Design

This prospective single-center study was approved by our institutional ethics committee and included MRI of both a phantom and human subjects. The adopted study design is depicted in **Figure 1**. All subjects provided written informed consent for study inclusion and prospective data collection.

Phantom and Subjects

First, a phantom experiment was performed using the American College of Radiology (ACR) MRI Phantom (Newmatic Medical, MI, USA). Second, 23 volunteers were recruited between December 2016 and January 2019. Among these, 22 subjects were included in the main study: 8 healthy volunteers (5 men, 3 women; mean age, 26.4 years; age range, 24-29 years; mean BMI, 22.8 kg/m^2; BMI range, 21.1-25.2 kg/m^2; right knee, n = 7) with no known history of prior knee symptoms and 14 patient-volunteers (9 men, 5 women; mean age, 40.1 years; age range, 18-62 years; mean BMI, 23.7 kg/m^2; BMI range, 20.1-28.0 kg/m^2; right knee, n = 11) with a history of knee symptoms within the last 12 months. One additional patient-volunteer (male; age, 20 years; BMI, 22.1 kg/m^2; right knee) was recruited for a high-resolution SRR experiment. Exclusion criteria included prior knee surgery, age < 18 years old, and the general contraindications for MRI, such as pregnancy, a pacemaker or other implanted electronic devices. All MRI examinations were obtained for research purposes only. Two groups of outcome variables were defined prospectively. The first quantitative group comprised the perceptual blur metric,[26] the edge response function (ERF)[27] and the SNR and contrast-to-noise (CNR) measurements. The second group included the qualitative variables of technical image quality, anatomic visibility and diagnostic confidence to assess normal and abnormal knee structures.

MRI Technique

Phantom and in vivo experiments were performed on a commercially available, clinical whole-body 3T MRI system (Magnetom PrismaFit, Siemens Healthcare, Erlangen, Germany) with VE11B software, a maximum gradient amplitude of 80 mT/m and maximum slew rate of 200 T/m/s. A dedicated phased-array knee-coil with 15 receiver channels and 1 transmission channel (Quality Electrodynamics, Mayfield Village, OH, USA) was used.

Twenty-two subjects, as well as the phantom, were imaged with a 2D TSE-based SRR protocol and the commercially available conventional 3D SPACE sequence (Siemens Healthcare, Erlangen, Germany). The imaging parameters of these MRI pulse sequences are summarized in **Table 1**. The parameter values used for the sequences were based on the standard recommendations from the manufacturer for software version VE11B. The phantom and the healthy volunteers (n = 8) were scanned twice to assess SNR and CNR.

For the SRR, 7 repetitions of a 2D TSE sequence with a low through-plane resolution (voxel size = $0.5 \times 0.5 \times 2.0$ mm^3) were acquired. Each acquisition was characterized by a specific rotation around the phase-encoding axis (*i.e.* 0°, 26°, 51°, 77°, 103°, 129°, 154°). The scan time per anisotropic 2D slice stack was 1:55 minutes, resulting in a total scan time of 13:25 minutes. SRR was performed at an isotropic high-resolution grid with a voxel size of $0.5 \times 0.5 \times 0.5$ mm^3 **(Fig. 2)**. For comparison, the conventional 3D SPACE sequence used the same high resolution while keeping a similar scan time (12:42 minutes).

To surpass the spatial resolution that is routinely obtained with the currently available 3D sequences, the additional patient-volunteer was scanned using a 2D TSE sequence with a resolution of $0.3 \times 0.3 \times 1.2$ mm^3 and with a scan time of 8:55 minutes per anisotropic slice stack. Seven repetitions were acquired using the same rotations as for the $0.5 \times 0.5 \times 0.5$ mm^3 SRR, which resulted in a total scan time of 62:25 minutes. For this patient, SRR was performed at an isotropic high-resolution grid with a voxel size of $0.3 \times 0.3 \times 0.3$ mm^3.

The core of the SRR is the forward transformation from high-resolution images to low-resolution images with rotated slice stacks, which is performed efficiently using shear transformations.[19] To improve the conditioning without losing fine details, the inverse operation (SRR) is performed using total variation regularization.[28] Furthermore, rigid registration is incorporated into the reconstruction algorithm to correct for inter-scan motion.[29]

Quantitative Image Analysis

Images of the ACR phantom were used to quantitatively assess image quality in terms of spatial resolution, image intensities and image contrast. First, high-contrast spatial resolution was assessed in all three image dimensions by means of the ERF. Thus, per anatomical direction, a line-of-interest, comprising 100 pixels, was drawn along sharp signal discontinuities (i.e. edges) across a specific phantom insert **(Fig. 3)**. The corresponding ERFs were normalized and plotted in terms of the distance in millimeters along the edge profile. As the derivation of quantitative measures from the ERF is sensitive to a number of factors such as the presence of noise, the perceptual blur metric was used to quantify the amount of blurring along the three anatomical directions (i.e. superior-inferior, anterior-posterior and left-right) in the phantom images.[26] This normalized metric, that takes on a value of 1 for maximum sharpness and 0 for maximum blurriness, does not require any high-resolution reference image to evaluate the blur annoyance. Instead, signal intensity variations between neighboring pixels are compared before and after convolution with a low-pass filter. Sharp images thus produce large differences between the original and filtered images, while the differences are smaller for blurrier images. Since the blur factor relies on filter kernels which can be decoupled into different directions, the blurring was calculated for all three anatomical directions.

In addition to the assessment of the spatial resolution, SNR and CNR were obtained using the repeated acquisitions of the phantom and the healthy volunteers. First, volumes-of-interest (VOIs) were defined in the healthy volunteers' data. More specifically, VOIs were manually delineated in the central femoral cartilage at the medial femoral condyle, in the synovial fluid, in the cancellous bone marrow of the distal femoral epiphysis, in the posterior horn of the medial meniscus, and in the posterior cruciate ligament (PCL) near the tibial attachment. VOIs were placed in anatomically similar locations among the subjects, except for the synovial fluid which was variably present in the volunteers' knees. The VOIs had mean volumes between 10.20 mm^3 and 449.05 mm^3 (22.06 mm^3 for cartilage, 30.27 mm^3 for meniscus, 449.05 mm^3 for bone marrow, 10.20 mm^3 for fluid and 21.81 mm^3 for ligament). Subsequently, the SNR was calculated for each anatomical structure by means of the difference method:[30]

$$SNR_{VOI} = \frac{m_{sum,VOI}}{\sqrt{2} \cdot SD_{diff,\ VOI}}$$

where $m_{sum,VOI}$ represents the mean signal intensity value of the VOI in the sum image and $SD_{diff,VOI}$ the standard deviation (SD) of the VOI signal in the difference image.

Finally, CNR calculations were performed for the following tissue contrasts: cartilage/fluid, medial meniscus/fluid, PCL/fluid, and bone marrow/fluid. The CNR was defined as $|SNR_{tissue1} - SNR_{tissue2}|$. The above calculations were also applied to a single VOI in the phantom, comprising a region with fluid and a region with solid material. All measurements were performed by a biomedical engineer (reader A) with 3 years of experience in MRI.

Qualitative Image Analysis

The image quality of the phantom was visually assessed. The image data sets for all subjects were independently evaluated in terms of technical image quality, anatomic visibility, and diagnostic confidence during separate sessions by two musculoskeletal radiologists, with 17 years ([*blinded*], reader B) and 2 years ([*blinded*], reader C) of experience in musculoskeletal radiology, respectively. Additionally, the biomedical engineer ([*blinded*], reader A) performed the technical image quality evaluations in all subjects. Readings were carried out in a standardized fashion at our institution on a PACS monitor with 5-megapixel resolution (Barco®, Kortrijk, Belgium). At the time of the evaluations, the readers were blinded to the subject's clinical history and findings, and to whether the image data set was acquired with the SRR or conventional 3D SPACE method. Furthermore, each of the 44 anonymized data sets (i.e. 2 data sets per subject for a total of 22 study subjects) was normalized using min – max normalization and presented in a random order to the readers in two separate review sessions of about 48 hours each. Three weeks after the first session, all readers evaluated the images again. The readers could choose their preferred window and level settings, magnification and scrolling mode, as well as the interactive multiplanar reconstruction mode to view the data sets. The technical image quality and the possibility to evaluate specific anatomic structures were subjectively assessed using a 5-point Likert scale[5,31] (1 = poor quality; 2 = moderate quality; 3 = adequate quality; 4 = good quality; 5 = very good quality). The images were evaluated in terms of the following technical characteristics: overall image quality and noise, presence of artifacts (i.e. motion, parallel imaging artifacts such as aliasing and disproportional central increase of noise, chemical shift, and pulsatile flow-related artifacts), degree of edge blurring, image contrast, and partial volume effects. For the visibility assessment, the following anatomical structures were considered: the patellofemoral and femorotibial cartilage, the medial and lateral menisci, the anterior cruciate ligament (ACL) and the PCL, the medial collateral (MCL) and lateral collateral (LCL) ligaments, the extensor apparatus, muscle, and bone. The 2 radiologists (readers B and C) additionally noted the presence and location of cartilage defects, meniscal tears, ligament and muscle/tendon tears, as well as bone injuries. Each reader was hereby asked to assign a confidence level to their diagnosis with the use of an additional Likert scale (1 = definitely normal, 2 = probably normal, 3 = equivocal, 4 = probably abnormal, and 5 = definitely abnormal). The modified Noyes classification system[32] was used to categorize cartilage defects and only high-grade defects (grade 2B and 3) were counted. In the presence of multiple cartilage defects, only the dominant lesion was taken into account. Meniscus abnormalities were graded according to the classification system established by Lotysch et al.:[33] grade 1 = low intrameniscal signal; grade 2 = high meniscal signal not extending to the articular surface; grade 3 = high meniscal signal definitely breaching the lower and/or upper meniscal surface. Ligamentous and musculotendinous tears were taken into consideration if more than 50% of the fibers were disrupted. A bone injury was defined for one or a combination of the following findings: bone marrow edema pattern, subchondral linear signal abnormality, and cortical depression. The standard of reference for the MR abnormalities was based on a consensus reading between the 2 radiologists after the study readings were finalized. To this end, all available MR data, including the 2D TSE images obtained for SRR, as well as the clinical findings were used.

Statistical Analysis

Statistical analysis was carried out using the R programming environment (version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism (version 8.00 for Windows, GraphPad Software, La Jolla, California, USA). *P* values less than 0.05 were considered statistically significant. Non-parametric Wilcoxon signed-rank tests were used to compare SNR and CNR values between conventional 3D SPACE and SRR data of the healthy volunteers. The corresponding values were represented by means of boxplots that depict the median value, the interquartile range, and the minimum and maximum values observed. The second readings of all readers were used for data presentation. The individual Likert scores for the technical image quality and anatomic visibility assessments were analyzed using the Wilcoxon signed-rank test. The diagnostic confidence scores were analyzed using McNemar tests to compare the degree of certainty. The weighted Cohen kappa (κ) statistic with 95%

confidence intervals (upper and lower range values) was used to assess the inter- and intrareader agreement. The κ-values were interpreted according to the recommendations by Landis and Koch.[34]

Results

Quantitative Image Analysis

Phantom blur metric values were higher for conventional 3D SPACE than for SRR in all anatomical directions. Blur factors of 0.41 (A-P), 0.26 (H-F) and 0.31 (L-R, i.e. through-plane) were obtained for 3D SPACE, while for SRR the calculated blur factors were 0.28 (A-P), 0.24 (H-F) and 0.26 (L-R). Furthermore, the improvement in resolution achieved by SRR was confirmed by the ERFs. In all directions and for both repetitions of the 3D SPACE and SRR, sharper signal discontinuities were observed for SRR **(Fig. 3)**. In the phantom, the SNR of fluid was 165.71 for 3D SPACE and 160.22 for SRR; and for material, the SNR was 4.56 for 3D SPACE and 4.85 for SRR. The CNR values were 161.15 for 3D SPACE and 155.37 for SRR. The SNR and CNR analyses of the in vivo data are shown in **Figure 4**. There were no significant differences in SNR between 3D SPACE and SRR for cartilage, synovial fluid, cancellous bone marrow, and the medial meniscus. Only for the PCL, the SNR value was significantly higher ($P < 0.01$) for 3D SPACE. In terms of CNR, no significant differences could be observed between 3D SPACE and SRR for any of the evaluated tissue contrasts.

Qualitative Image Analysis

In the ACR phantom, image blurring and ghosting artifacts were visibly present in the conventional 3D SPACE acquisition, resulting in a reduction in spatial resolution and poor low-contrast object detectability **(Fig. 3)**. An example illustrating the visual quality in human subjects is given in **Figure 5**. For all 3 readers, the overall technical image quality was significantly better with SRR than with conventional 3D SPACE ($P < 0.05$). The 3D SPACE images scored significantly lower for edge blurring compared with SRR ($P < 0.01$). However, 3D SPACE performed better than SRR in terms of image contrast ($P < 0.001$). Motion, aliasing, and partial volume effects were either absent or only mildly present with no significant differences between 3D SPACE and SRR for all readers. 3D SPACE performed better than SRR for chemical shift effects for reader B, and performed better than SRR for flow artifacts for reader A ($P < 0.05$). The scores of the technical image quality evaluations are shown in **Table 2**.

When considering the anatomic visibility, the menisci were significantly better visible with SRR than with conventional 3D SPACE for both reader B and reader C ($P < 0.001$) **(Fig. 5)**. The visibility of cartilage was higher for 3D SPACE ($P < 0.05$), while there were no significant differences between SRR and 3D SPACE for the visualization of ligaments, tendons, muscle, and bone. The scores of the readers' evaluation of anatomic structures are summarized in **Table 3**.

The readers' diagnostic confidence scores to assess normal and abnormal knee structures are listed in **Table 4**. Among the 14 patients with knee pain, 6 meniscus lesions (medial meniscus, n = 4 and lateral meniscus, n = 2), 7 cartilage lesions, 6 ligamentous lesions (MCL, n = 4; LCL, n = 1; ACL, n = 1), 1 muscle tear, and 2 bone injuries were recorded. Both radiologists felt more confident assessing the medial and lateral menisci with SRR than with conventional 3D SPACE, reaching statistical significance for reader B ($P < 0.05$). Although 5 of the 6 meniscus tears were correctly identified on both SRR and 3D SPACE images by both readers, SRR provided better visualization of the tear extension **(Fig. 6)**. One lateral meniscus tear was missed on 3D SPACE and identified on SRR images by reader B, and missed on both SRR and 3D SPACE images by reader C **(Fig. 7)**. In contrast, the readers felt more confident assessing cartilage with 3D SPACE than with SRR, but this was not statistically significant for either reader. Of the 7 cartilage defects, 3 were correctly identified on both SRR and 3D SPACE images and 1 was missed on either sequence by both readers. Two cartilage defects were identified with 3D SPACE by both readers and missed with SRR by one reader **(Fig. 8)**. One cartilage defect was identified with 3D SPACE and SRR by 1 reader and missed in both by the other one. There were no significant differences in the diagnostic confidence scores for evaluating ligaments, tendons, muscle and bone for both radiologists.

The κ-statistic test for interreader agreement for assessing menisci was substantial with conventional 3D SPACE and almost perfect with SRR (κ-values of 0.61-0.77 and 0.98-0.99, respectively). In addition, the agreement between readers for grading meniscal signal was substantial with 3D SPACE and perfect with SRR (κ-values of 0.65-0.74 and 1.00, respectively). For cartilage, the interreader agreement was almost perfect with 3D SPACE and moderate with SRR (κ-values of 0.86 and 0.60, respectively). Intrareader agreement for assessing menisci was higher for SRR for reader B (κ-values of 0.96-1.00 and 0.85-0.93, respectively). The κ-values are summarized in **Table 5**.

Finally, although the acquisition time was long (62:25 minutes), the SRR data set with $0.3 \times 0.3 \times 0.3$ mm^3 resolution yielded excellent image quality and allowed for comprehensive knee joint assessment **(Fig. 9)**.

Discussion

Our study has demonstrated the technical feasibility of SRR for highly-resolved isotropic 3D IW MRI of the knee at 3T. We showed that SRR was superior to conventional 3D SPACE in terms of overall technical image quality and edge blurring and, as such, greater diagnostic confidence was achieved with SRR for assessing the menisci of the knee joint. However, image contrast and fluid brightness were better for 3D SPACE. We also demonstrated the capability of SRR to surpass the spatial resolution of that routinely obtained with conventional 3D SPACE for clinical knee imaging.

Currently, most institutions continue using 2D TSE sequences as part of their standard knee MRI protocol, while the clinical application of 3D TSE acquisitions has been typically limited to cartilage imaging.[35,36] A major limitation of the first-generation 3D TSE MRI sequences, such as the conventional 3D SPACE, is image blurring. This occurs when the high spatial frequency data, representing edge information in the image, is attenuated late in the echo train compared with data in the central region of the k-space.[1,4] Blurring is of particular concern for the detection of meniscal injury, which is still the most common indication for knee arthroscopy, as it hampers accurate grading of the meniscal signal.[37] In various studies, blurring resulted in a lower diagnostic performance of 3D TSE acquisitions for detecting meniscal injuries.[6,7,38-42] In our study, the readers were more confident to diagnose meniscal injuries with SRR than with conventional 3D SPACE and showed higher agreement for grading meniscal signal with SRR than with 3D SPACE. One peripheral vertical tear of the posterior horn of the lateral meniscus was correctly identified on SRR images and missed on conventional 3D SPACE images by one reader (reader B), and was missed on both SRR and 3D SPACE images by the other reader (reader C). Classically, this type of meniscal tear, which frequently occurs in the ACL-deficient knee, is readily missed on MRI due to the complex anatomy of the posterior lateral meniscal root.[5,40] Of note, reader C had a low intrareader agreement for evaluating the lateral meniscus (κ-value of -0.12). We believe that this is related to the so-called 'prevalence effect',[43] as we had a proportion of agreement of Likert 1 ratings of 16 out of 22 compared to a zero proportion of agreement of Likert 5 ratings. This resulted in a high observed agreement, but also in a high chance agreement, which led to the reduced κ-value. Nevertheless, our preliminary findings are promising given the lower diagnostic performance of conventional 3D SPACE for evaluating meniscal injuries.

To achieve high isotropic resolution, an SRR scheme based on rotated slice stacks was used in this study (rather than translated slice stacks). This scheme allows us to effectively cover the k-space by rotating each acquisition over a predefined angle increment around the phase-encoding direction.[18] The application of this scheme on our low-resolution 2D TSE data resulted in a 4-fold resolution increase in the slice-encoding direction. For comparison, we used the clinically available conventional 3D SPACE sequence with a linear k-space reordering scheme and standard parameter settings, as recommended by the manufacturer. To avoid bias from personal alterations of the conventional 3D SPACE protocol, these settings were preferred as a more objective parametrization. We used a small isotropic voxel size (0.5 mm^3), full Fourier sampling and a high TF of 76, as reported by previous studies.[5-7] A receiver bandwidth of 391 Hz/pixel was used to preserve edge sharpness and minimize chemical shift effects. In addition, a 15-channel knee-coil was used to improve image homogeneity.[13] Despite these parameter settings, our study results show that SRR compares favorably to conventional 3D TSE acquisitions in terms of image quality and edge blurring.

Our findings are in line with recent studies by Chaudhari et al.,[44,45] where the authors used a deep-learning-based SRR neural network (entitled DeepResolve) for evaluating knee osteoarthritis. They found that SRR minimally affected the perceived global image blurring, without biasing cartilage and osteophyte quantitative biomarkers. As such, they concluded that SRR may become a more promising technique than simple interpolation for accelerated image acquisition by converting rapidly-acquired low-resolution images into higher-resolution images.[45] However, as the diagnostic power of this stochastic deep-learning SRR approach is inherently limited by the data used to train the neural network, a comparative benefit of our SRR method lies in the fact that all information is directly derived from the subject-specific input data, which increases the probability of correctly detecting subtle and/or rare abnormalities.

Another advantage of the current SRR framework is its ability to deal with motion. A distinction can be made between inter- and intra-scan motion. If a patient moves in the time between 2D TSE acquisitions, the SRR's built-in registration step will correct for the inter-scan motion. In contrast, this type of 'low-frequency' motion cannot be corrected for in a direct 3D scan. Moreover, as the likelihood of motion is positively correlated with the acquisition time, the individual 2D TSE scans of the SRR protocol are less prone to motion artifacts than the longer conventional 3D SPACE acquisition. Nevertheless, if motion occurs during a 2D TSE scan, it is possible to repeat only the specific 2D TSE acquisition(s) that is/are corrupted by motion. If the same intra-scan motion occurs during a direct 3D acquisition, the 3D sequence needs to be repeated, which would be time-consuming and impractical. Thus, SRR allows for more time-efficient management of observable intra-scan motion artifacts.

Recently, optimized versions of the conventional 3D SPACE sequence have become available for clinical use. The optimization typically resides in the acceleration of the 3D SPACE protocol by using either parallel multi-slice techniques such as CAIPIRINHA[8] or k-space undersampling concepts such as CS[9,46-48], and thus allows to significantly reduce the scan time of the 3D TSE acquisition. These approaches also obviate the use of other acceleration strategies, such as the choice of a high TF (*i.e.* > 80), thereby contributing to the preservation of edge sharpness.[8,9]

For the future, we see great potential for further optimization of the SRR acquisition protocol and the reconstruction framework. First, the optimal acquisition parameters need to be determined to further improve image contrast and fluid brightness with SRR. This is of particular importance for the assessment of the articular cartilage.[35,36] Although we found no significant differences in the quantitative measures of SNR and CNR for cartilage, the perceived image contrast and fluid brightness were higher for conventional 3D SPACE than for SRR, which affected the diagnostic assessment of articular cartilage in our study. In general, the observers' preference to assess cartilage was higher for 3D SPACE than for SRR. Also, confidence scores were higher for 3D SPACE than for SRR, but differences were not significant. These findings are in line with previous studies reporting high performance in the detection of cartilage defects for 3D SPACE.[4,5,14,35]

With respect to the reconstruction process, a practical question is the optimal adjustment of the regularization parameter for SRR images, being a compromise between denoising (for suppression of noise amplification) and sharpness. In our study, we heuristically chose a regularization factor. While it is based on individual practice preferences, this choice depends on the gross signal level of the data to be reconstructed and is primarily chosen to preserve edge sharpness and decrease the perceived noise.

Our study has shown that SRR can significantly surpass the spatial resolution that is routinely obtained with conventional 3D TSE sequences. However, despite the excellent image quality of the 0.3-mm^3 isotropic resolution SRR data set, the acquisition time (62:25 minutes) is unacceptably long for routine clinical use.

To enable clinical validation in the future, the time-efficiency of the SRR protocol needs to be improved. The present study used 7 slice stack rotations consisting of 2-mm thick slices with 0.5 x 0.5 mm^2 in-plane resolution in order to create 0.5-mm^3 isotropic resolution images. Alternatively, a 2D TSE acquisition with 1.5-mm thick slices would only require 5 slice stack rotations and the increase in acquisition time due to a larger number of thin slices that is necessary to cover the FOV could then be compensated for by using, for example, the Simultaneous Multi-Slice (SMS) technique.[49,50] The implementation of SMS in TSE would reduce the scan time of the 2D TSE sequence, and thus further decrease the total acquisition time of the SRR method. The desired SMS acceleration could practically be achieved via shortening of the repetition time (TR), possibly reducing image contrast and fluid brightness of the SRR protocol, or by increasing the TF while keeping the TR constant. Increasing the TF would increase blurring, but when comparing our 2D TSE parameter settings to previous publications,[9,14] we note that TFs reported in this literature are significantly higher than the TF value of 5 used in the present study. Further investigation is required to define the optimal trade-off between increasing TF and reducing the TR when utilizing SMS for 2D knee imaging. In addition, comparison between 2D SMS TSE and the state-of-the-art 3D

CAIPIRINHA SPACE would be of great interest. Finally, the introduction of 7T magnet systems in the clinical practice will allow to further speed up routine knee MRI.[51-53]

In this proof-of-concept study, we did not use fat suppression (FS), which is essential for the assessment of bone marrow edema.[5,14,15] However, FS is not expected to pose a technical difficulty to SRR and therefore future work will explore the use of FS.

There were several limitations to this study. First, since 3D CAIPIRINHA SPACE and 3D CS SPACE sequences were not clinically available at the time that we started this research study, we used a first-generation 3D SPACE sequence for comparison with our SRR protocol. Also, we did not compare our SRR protocol against a 2D TSE clinical standard, as this would have substantially increased the duration of the MRI exams. Secondly, the sample size was relatively small. Yet, primary outcome variables (*i.e.* image quality and edge blurring) were significantly different between SRR and 3D SPACE in this feasibility study. Thirdly, the readers were familiar with the 3D SPACE sequence and the interpretation of the sequences may thus have been biased to a certain extent, despite the normalized, anonymized and randomized presentation of the data to the readers. Furthermore, we did not determine the optimal acquisition parameters for SRR imaging to maximize SNR and tissue contrast. We chose to compare the commercially available conventional 3D SPACE sequence with SRR from commonly used 2D TSE sequences. Finally, while this study provides suggestive evidence of the SRR performance, the diagnostic potential of SRR for the detection of internal derangement is currently unknown and requires stricter evaluation criteria, particularly for cartilage, as well as a larger patient study with arthroscopic correlation to confirm our preliminary results.

In conclusion, we demonstrated that SRR is technically feasible for 3D high-resolution isotropic IW knee MRI. Our results showed that SRR was superior to conventional 3D SPACE in terms of overall technical image quality and edge blurring, resulting in higher confidence to assess the knee menisci. However, image contrast and fluid brightness were better for conventional 3D SPACE. These results thus suggest that further contrast optimization and combination of SRR with state-of-the-art acceleration techniques are necessary. Future studies with arthroscopic correlation will assess the diagnostic performance of optimized SRR MRI (including FS) and draw a comparison with 3D CAIPIRINHA SPACE and standard 2D TSE protocols.

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Figure Legends

Figure 1. Flow diagram of the study design.

Figure 2. Super-resolution reconstruction (SRR) of the knee. Seven 2D TSE images were acquired with large slice thickness (as schematically indicated by the dashed lines in the colored field-of-view boxes) and a high in-plane resolution as illustrated for angles 0° and 77° in the bottom-right corner of this figure. The slice orientation was consecutively altered by rotation over a specified angle (0°, 26°, 51°, 77°, 103°, 129°, 154°) around the phase-encoding direction. After the SRR, a single high-resolution (HR) isotropic 3D volume was obtained. The central and bottom-right axial views display the high resolution achieved in the slice-encoding direction.

Figure 3. Image quality assessment by means of the ACR phantom. A) SRR (top) versus the direct 3D acquisition (conventional 3D SPACE, bottom) of the ACR phantom's resolution insert. Image blurring and ghosting artifacts are visibly present in the direct 3D acquisition. Moreover, poor low-contrast object detectability is observed in the bottom image. Finally, note the reduction in spatial resolution at the level of the hole arrays, where the distance between the holes appears to decrease. B) High-contrast spatial resolution assessment by means of the edge response function (ERF). The left-hand SRR phantom images display the three lines-of-interest, drawn across different phantom inserts (a, b, c). The corresponding ERFs, shown on the right-hand side, represent the min-max normalized intensities in terms of the distance in millimeters along with the edge profile for two repetitions of the SRR (solid lines) and 3D SPACE acquisition (dashed lines).

Figure 4. Signal-to-noise (SNR) and contrast-to-noise (CNR) values of SRR and conventional 3D SPACE data computed for eight healthy volunteers. A) Box-and-whisker plots of the SRR (light gray) and 3D SPACE (dark gray) SNR represent the median value, interquartile range and the highest and lowest measurements for 5 anatomical structures: articular cartilage, synovial fluid, cancellous bone marrow of the distal femoral epiphysis (BM), medial meniscus (MM) and posterior cruciate ligament (PCL). For the PCL, a significant difference in SNR value between both methods could be observed ($P < 0.01$), while all other structures showed no significant difference (ns). B) Box-and-whisker plots of the SRR (light gray) and 3D SPACE (dark gray) CNR indicate that there are no significant differences (ns) in CNR between both methods for any of the 4 studied tissue contrasts: synovial fluid – articular cartilage, synovial fluid - medial meniscus (MM), synovial fluid - posterior cruciate ligament (PCL) and cancellous bone marrow of the distal femoral epiphysis (BM) – synovial fluid.

Figure 5. Right knee of a 25-year-old healthy male volunteer. The central coronal and axial views show a clear improvement in resolution achievable by SRR compared to the reference anisotropic low-resolution 2D TSE images shown in the left panel. SRR also provides superior delineation of normal knee structures such as cartilage and meniscus when compared with the direct 3D acquisition shown in the right panel (large arrows). Image blurring is seen on the conventional 3D SPACE images, especially at the posterior aspect of the medial femoral condyle (large arrows) and at the anterolateral capsular structures (small arrows).

Figure 6. A) Right knee of a 48-year-old female patient and B) right knee of a 57-year-old male patient. Sagittal images of both patients show a tear of the posterior horn of the medial meniscus (large arrows) that is better depicted with SRR than with conventional 3D SPACE. Coronal images of patient B (rightmost column) show tear extension at the posterior meniscal

root that is better displayed with SRR than with 3D SPACE (small arrows). A meniscal cyst can also be seen (*). Finally, note that the SRR image better depicts the lateral meniscal root than the 3D SPACE image (circle).

Figure 7. Left knee of a 23-year-old male patient sustaining an acute pivot-shift injury. The sagittal views on the left show a complete tear of the anterior cruciate ligament (*), which is equally well seen on SRR and conventional 3D SPACE images. The sagittal images on the right depict a peripheral vertical tear of the posterior horn of the lateral meniscus that is readily apparent on the SRR image, whereas it has a blurred appearance on the 3D SPACE image (arrows).

Figure 8. A 41-year-old male patient with right anterior knee pain. The conventional 3D SPACE image clearly displays the articular cartilage defect (arrow), while the same cartilage region appears blurrier on the SRR image due to the lower signal intensity of the synovial fluid.

Figure 9. A 20-year-old male patient with right lateral knee pain. For every orientation, three different slices of the SRR image volume with an isotropic resolution of $0.3 \times 0.3 \times 0.3$ mm^3 are shown. Note the excellent depiction of cartilage, menisci, and ligaments. In particular, the structures of the anterolateral complex, including the Kaplan fibers (long arrow) and the anterolateral ligament (short arrow) are clearly visible on the midcoronal image. Also, note a tear of the lateral meniscus (large arrows).

Tables

Table 1 MRI Parameters for 2D TSE and Conventional 3D SPACE Sequences

Parameter	2D TSE	3D SPACE
Orientation	Sagittal	Sagittal
Repetition time, ms	3080	1300
Echo time, ms	36	38
Acceleration factor*	3	2
Turbo factor	5	76
Receiver bandwidth, Hz/pixel	256	391
Flip angle, degree	160	120**
Field of view, mm	160 x 160	160 x 160
Matrix size	320 x 320	320 x 320
Slice thickness/gap, mm	2/0	0.5/0
Voxel size, mm	0.5 x 0.5 x 2.0	0.5 x 0.5 x 0.5
No. excitations	1	1
Echo spacing, ms	8.93	5.76
No. slices	53	192
Phase encoding direction	Head to feet	Anterior to posterior
Phase sampling, %	100	100
Number of repetitions	7	1
Angles of rotation, °	0, 26, 51, 77, 103, 129, 154	NA
Total scan time	13:25 min	12:42 min

**, Parallel imaging technique: GRAPPA (generalized autocalibrating partial parallel acquisition); **, constant flip angle mode; TSE*, turbo spin echo; *SPACE*, sampling perfection with application optimized contrast using different flip angle evolutions; NA, not applicable.

Table 2 Technical Image Quality Scores

	Method	Image Contrast	Motion	Aliasing	Chemical Shift	Flow	Partial Volume Effect	Edge Blurring	Overall Image Quality
Reader A	3D SPACE	102***	84	106	87	86*	87	77	82
	SRR	72	86	103	86	76	84	92**	89*
Reader B	3D SPACE	103***	106	110	110*	102	104	83	95
	SRR	89	108	108	104	108	104	110***	104**
Reader C	3D SPACE	105***	107	110	110	110	110	87	92
	SRR	82	110	110	110	110	110	106***	104**

Data are the summed ratings for technical image quality by means of a 5-point Likert scale with the maximum achievable score of 110 for a total of 22 patients. Statistically significant *P* values are indicated with asterisk(s) (*, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$). conventional 3D *SPACE*, sampling perfection with application optimized contrast using different flip angle evolutions; *SRR*, super-resolution reconstruction.

Table 3 Anatomical Structure Visibility Scores

	Method	Menisci	Cartilage	Ligaments	Tendons	Muscle	Bone
Reader B	3D SPACE	86	99*	94	94	95	97
	SRR	110***	92	92	95	95	98
Reader C	3D SPACE	88	107***	105	108	109	110
	SRR	106***	91	106	110	110	109

Data are the summed ratings for anatomical visibility by means of a 5-point Likert scale with the maximum achievable score of 110 for a total of 22 patients. Statistically significant *P* values are indicated with asterisk(s) (*, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$). conventional 3D *SPACE*, sampling perfection with application optimized contrast using different flip angle evolutions; *SRR*, super-resolution reconstruction.

Table 4 Diagnostic Confidence Scores

	Reader B		Reader C	
Structure	**% Certainty 3D SPACE**	**% Certainty SRR**	**% Certainty 3D SPACE**	**% Certainty SRR**
Cartilage	86	73	95	73
MM	68	100*	82	95
LM	55	100**	91	95
MCL	77	68	86	86
LCL	100	100	100	100
ACL	95	91	100	100
PCL	100	100	100	100
Tendon	95	95	100	100
Muscle	95	100	100	100
Bone	95	95	100	95

Data are dichotomized in definite (scores 1 and 5) versus probable (scores 2, 3 and 4) diagnoses and the percentages of definite scores (% certainty) are reported. Statistically significant *P* values are indicated with asterisk(s) (*, $P < 0.05$; **, $P < 0.01$; and ***, $P < 0.001$). The readers assigned a confidence level to their diagnosis by means of a 5-point grading scale. MM, medial meniscus; LM, lateral meniscus; MCL, medial collateral ligament; LCL, lateral collateral ligament; ACL, anterior cruciate ligament; PCL, posterior cruciate ligament; conventional 3D *SPACE*, sampling perfection with application optimized contrast using different flip angle evolutions; *SRR*, super-resolution reconstruction.

Table 5 Intra- and Interreader Agreement for Assessment of Knee Structures

	Interreader Agreement				**Intrareader Agreement - Reader B**				**Intrareader Agreement - Reader C**			
	3D SPACE		**SRR**		**3D SPACE**		**SRR**		**3D SPACE**		**SRR**	
Structure	**κ**	**CI**	**κ**	**CI**	**κ**	**CI**	**κ**	**CI**	**κ**	**CI**	**κ**	**CI**
Cartilage	0.86	0.62 – 1.00	0.60	0.21 – 0.98	0.96	0.92 – 1.00	0.93	0.87 – 1.00	0.91	0.76 – 1.00	0.41	-0.08 – 0.89
MM	0.77	0.52 – 1.00	0.99	0.97 – 1.00	0.93	0.86 – 1.00	0.96	0.88 – 1.00	0.60	0.23 – 0.96	0.41	0.00 – 0.81
MM Lotysch	0.74	0.42 – 1.00	1.00	1.00 – 1.00	0.96	0.88 – 1.00	0.96	0.88 – 1.00	0.33	-0.10 – 0.76	0.49	0.08 – 0.91
LM	0.61	0.19 – 1.00	0.98	0.94 – 1.00	0.85	0.62 – 1.00	1.00	1.00 – 1.00	0.61	0.10 – 1.00	-0.12	-0.22 – (-0.02)
LM Lotysch	0.65	0.01 – 1.00	1.00	1.00 – 1.00	0.88	0.60 – 1.00	1.00	1.00 – 1.00	0.41	-0.22 – 1.00	-0.04	-0.12 – 0.03

Data are κ-values. *CI*, 95% confidence intervals; conventional 3D *SPACE*, sampling perfection with application optimized contrast using different flip angle evolutions; *SRR*, super-resolution reconstruction.