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22nd December 2020

JoVE62142:
Magnetic Resonance Imaging of Multiple Sclerosis at 7.0 Tesla

Dear Dr. Nguyen:

Thank you for reviewing the above manuscript and providing your feedback. We have made the changes that you and the reviewers have requested.

Please find uploaded a point-by-point response to the peer review comments and a revised version of the above manuscript.

Changes in the manuscript can be identified as colored text. Blue and green text reflects changes made in response to review 1 and review 2, respectively, and purple text reflects other changes following the editorial comments.

Approximately 3 pages of protocol text is highlighted in yellow for inclusion in the protocol section of the video.

We look forward to the next steps.

Yours sincerely,

Sonia Waiczies, Antje Els, Joseph Kuchling, Karin Markenroth Bloch, Anna Pankowska, Helmar Waiczies, Carl Herrmann, Claudia Chien, Carsten Finke, Friedemann Paul, Thoralf Niendorf

Reviewer #1

Major Concerns:

1. The manuscript is very detailed, to the point of excluding non-Siemens users. I feel that not all the details on adjustments and user interface are relevant, and they risk confusing other users (for example, but not limited to, 4.5-4.16). The large amount of detail also hides the important and more specific information regarding the UHF scanning and/or MS protocol. It would improve the accessibility of the paper if some of details were pruned away. I think you can refer the reader to the scanners user manual, for example. I think the manuscript would gain from focusing on the details that are UHF and/or MS specific and not the ones that are valid for all MR scanning.

   In order to avoid excluding non-Siemens MR users, we removed detail that was too specific to this MR system. We specify where the operation of a 7.0 T MR scanner might be different between different vendors. We also refer the reader to the operator manuals of their specific system. In addition, we include more detail specific to the MS pathology, particularly in the introduction of each MR acquisition method.

2. The manuscript discusses how to ask for and document contraindications and implants (Table 1, sections 1.1-2, 1.7) but gives no clear information on how to handle the information if a patient has an implant/device/tattoo. For example, Table 1 lists "Some tattoos" as contraindications, without any reference to in which circumstances tattoos are deemed safe or not. Overly conservative risk assessments are serious hindrance for patients to get potentially treatment changing UHF examinations, and it is important to in addition to discussing the serious risks of implants talk about what implants can be scanned without increased risk. At the least, a few references to recent published safety papers and guidelines should be included.

   We agree that overly conservative approaches might ultimately hinder the benefits that patient would otherwise gain from the examination. We have now added a note in the introduction of section 1. Subjects.

3. Regarding dedicated MR sequences; The rest of the manuscript is very detailed to the point of not changing angles of images stacks, but the sequences are as far as I understand just a list of sequences that can be used. The study protocol should define which sequences that are used (in 4.12 it says not to change anything as it will make data in longitudinal studies difficult to use - it would be even worse not to use the same scans?). How is it decided which sequences should be run?

   The sequences are run depending on the scientific or clinical question of the study e.g. the subtype or form of multiple sclerosis being studied. The sequences that we list in our protocol are the most commonly used in our MS clinical studies at 7.0 T. We have now sorted the sequences according to their contrast and have also included an informative section in the introduction of each sequence, indicating the significance and relevance of each specific sequence to the MS pathology.

4. Several of the MR sequences seem to give similar contrasts; 3D MPRAGE, 3D MP2RAGE and the four T2*-weighted sequences. It would add to the understanding if more information was added on why one sequence would be choosen over the other or how they give complementing information. it would also be interesting to see a list of the standard study protocol, which I assume will not contain all of the listed sequences.

We have now added more detail about each MR acquisition method in the opening section of each sequence, indicating the benefits of using one sequence over the others.

Minor Concerns:

5. P3 L69-70: Suggest to change to: "... resembling morphology at lower field strengths." to avoid the vague definition of "clinical field strength" as "typically =<3T.

   We changed the wording as suggested.

6. P4 L 82: Add a reference to parametric T2 mapping.

   We have added the reference from Shepherd and colleagues on T_2 qunatification to detect pathology in normal-appearing brain matter in relapsing-remitting MS patients.

7. P7 L164: I assume that I misunderstand this but; what is the point of locking valuables in a locker if the key is left in the locker? (Is this information even needed, it also seems like a detail which is not UHF specific)

   We removed this sentence.

8. P10 L235: "Walk slowly to the 7.0T examination table." - this requires an explanation of why you have to walk slowly.

   This protocol was written for a passively shielded magnet. We have added a sentence about passive versus active shielding (point 3.5).

9. P10 L237: "woolen blanket" - why does it have to be woolen?

   We have replaced “woolen blanket” with “blanket”

10. P13 4.12: This comment seems out of place - it concerns study design in general and is not specific to UHF (or MR in general) or MS.

    We removed this point.

11. P14 3D MPRAGE: Is the 1x1x1 mm3 acquisition really over 9 minutes? Why is no acceleration used?

    We have altered the protocol accordingly.

12. P14 4.20, 44: Why cant the angle be changed?

    While a strict sagittal setting is not absolutely necessary, it is recommended during longitudinal studies. One could alter the angle during planning and use anatomical structures as guides; these would then need to be implemented in the next examinations. Since it is a 3D sequence, the images can however still be registered onto the baseline scan. We have reworded this and introduced a sentence at the end of the MPRAGE sequence.

Reviewer #2

Major Concerns:

1. There is very little content both in the manuscript and protocol addressing B0 and B1 inhomogeneity and its impact on the scan quality and diagnostic accuracy. Attempts to mitigate these problems are not included in sufficient detail.

   We agree with the reviewer and now address B_1 inhomogeneities in "Representative Results" (see next points) and B_0 inhomogeneities in the section "Adjustments and scout images":

   4.4: "…. These include a correction (shimming) of the inhomogeneous static magnetic (B_0) field. B_0 inhomogeneities occur because of the large magnet and due to susceptibilities within the body (e.g. air, bone, blood) and their distribution. Inhomogeneities broaden the frequency distribution of the spins and can also cause significant intravoxel dephasing; this is not an issue in RF-refocused (spin-echo) sequences but can reduce signal amplitude considerably in most of the following sequences, particularly the T_2*-weighted acquisitions."

   4.6: "…. this includes frequency and transmitter adjustments to set the basic frequency and the voltage required for the RF coil and amplifier power used, as well as 3D shimming to correct the inhomogeneity of the static magnetic field…. "

2. Figure 12 shows the signal loss due to B1 very clearly. Some mention should be made of this.

   We have included the following section in the section "Representative Results":

   "…. Some distortions in the B_1^+ profile can be observed in the MR images. This is anticipated when moving to higher resonance frequencies [1]; the shorter wavelengths increase destructive and constructive interferences [2,3]. ….."

3. Figure 14: There is almost complete loss of signal due to B1 below the cortex. Appropriate use and placement of **dielectric pads** could improve this substantially.

   We continue the "Representative Results" section with the following text:

   "…. While the B_1^+ pattern cannot be modified for a single transmit element of a given coil, the electromagnetic properties of the surrounding environment may be altered, as has been shown with dielectric padding filled with water [4] or calcium titanate suspensions [5] used at 7.0 T. Geometrically tailored dielectric pads have been shown to be effective at imaging the brain [6,7] and particularly the inner ear [8], a challenging place to image due to inhomogeneities from susceptibility differences between inner ear fluids and bone."

4. Figure 15: 3D SWI seems to be much more B1 sensitive than it should be. There is major signal loss in the center of the brain. There may be a wrong setting for transmit amplitude that is causing this.

   All the representative MR images of the MS case report were acquired using a single channel transmit RF coil on an Siemens 7.0 T MR system. Although this single-channel transmit coil is split into two channels by a power splitter and driven in quadrature mode (0° and 90°), the fixed phase offset between these two channels cannot be adjusted, since this is hardwired to the coil by the manufacturer. Reference power settings are also assigned by the MR system following the adjustments. On Philips and GE scanners, 2-channel transmit coils may be employed, in this case phase and amplitude could be manually adjusted to offset the inhomogeneities.

Apart from pointing out the distortions in the B1+ profile in the "Representative Results" section we also add the following text:

"….To acquire the MR images (Figures 11-14), we used a single channel transmit volume coil on a Siemens 7.0 T MR system in which a manual adjustment of phase and amplitude was not possible to offset the B_1^+ inhomogeneities. Multi-transmit technologies offer the degrees of freedom of parallel transmission required to dynamically modulate the B_1^+ field distribution [9] …"

5. The purpose of each sequence, as it relates to MS pathology should be explained. How does 2D FLASH-ME provide new and different information compared to SWI? QSM is included to capture iron deposition and microbleeds. The importance to MS diagnosis and treatment needs to be better explained. Also, the necessity for both QSM and SWI should be explained. If SWI is being used to detect the central vein sign, this should be stated in the introduction for the sequence.

   In the opening section of each sequence we added more detail regarding the purpose of the acquisition method, as it relates to the MS pathology. As shown in one of the representative results (**Figure 15b**) of our case report, SWI delineates the hypointense rim structure around the lesion that suggests the presence of iron-laden macrophages. We have also included an explanation for using QSM in addition to SWI.

6. The spatial resolution of the DW-EPI does not seem to leverage the SNR of the 7T at 1.95x1.95x2 mm3. A higher resolution should be achievable. Also, the word isotropic spatial resolution is used when it should be specified as in-slice.

   Although compelling, the feasibility of performing in vivo high-resolution diffusion MRI is still limited in practice, especially for clinical studies at 7.0 T. The increased scan time required to compensate for the reduced SNR because of the increased spatial resolution to [1×1×1]mm^3 [10] is not compatible with patient examinations that might include other equally important sequences. While increased power deposition (SAR) is a significant challenge at higher resolutions, the shorter T_2^* and stronger B_0 inhomogeneity at 7.0 T that are already a cause of image blurring and distortion artefacts for EPI, an increase in the matrix size is likely to increase the propensity to distortion artefacts due to lengthening in the echo train length. Reducing the voxel size at 7.0 T is not always beneficial and artefacts could be an additional source of bias [11]. We believe that the benefit of increasing spatial resolution of the DW-EPI at 7.0 T does not outweigh the risk of introducing bias in the data due to blurring and distortion artefacts.

   We changed "isotropic spatial resolution" to "spatial resolution".

Minor Concerns:

7. In the introduction and discussion, some mention of how MS imaging could be improved with greater coverage afforded by the parallel transmit (pTx) Nova Medical coil would be good to include.

   As mentioned in point 4 we have included the advantage of parallel transmission in the "Representative Results" section. We have also included the following text in the introduction:

   "Transmission field (B_1^+) inhomogeneities that are an adverse attribute of the ^1H radio-frequency used at ultrahigh magnetic fields [1] would benefit from multichannel transmission using parallel transmit (pTx) RF coils and RF pulse design approaches that enhance B_1^+ homogeneity and thus facilitate uniform coverage of the brain [9]."

8. Much of the detail provided for the scan protocol is for any standard MRI scan. Perhaps some of the steps may not be necessary to include.

   We have reduced some of the steps that were redundant or those too specific to Siemens MR systems.

9. It would be good to make some mention in the discussion of extending coverage into the brain stem and spinal cord through new coils and pTx. For MS it would be a very important future direction given prevalence of MS lesions in these regions.

   As mentioned in point 7 we now include the advantage of parallel transmission in the introduction and in the representative results section. Additionally, we add a sentence on the benefits of parallel transmission for spinal cord imaging within a new concluding paragraph in this section:

   "…. Aside from brain lesions, lesions in the spinal cord frequently affect MS patients causing motor, sensory and autonomic dysfunction. However spinal cord imaging, particularly at 7.0 T, is technically challenging [12]. Further developments in parallel transmission and parallel imaging are warranted to overcome the hurdles of distorted B_1 field profiles [13]. …"

10. MP2RAGE may be a work in progress sequence. Might be good to cite the developer.

    We had already cited the original publication on MP2RAGE by Jose Marques and colleagues [14]. We now also included that: ***"The open-source MP2RAGE code is available from the developer: https://github.com/JosePMarques/MP2RAGE-related-scripts"***

11. 4.52: The fact that the b value is set to 0 here is confusing. Perhaps the purpose of each of these acquisitions (e.g. B0 correction) needs to be stated.

    We agree with the reviewer that an explanation is necessary. We have added the following sentences to the introduction of this sequence:

    "DW-EPI is commonly associated with geometric distortions that appear as stretched or compressed pixels in the acquired image. In order to compensate for this, reversed phase gradient approaches have been introduced, in which the same slice is acquired twice using opposite phase encoding (PE) polarities [15,16]. The opposite spatial distortion patterns can be aligned and the images combined using registration tools. For distortion correction, the same image is acquired with a reversed PE direction but without diffusion weighting, hence a reduction in acquisition time."

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