Comparison of 3D Cube FLAIR with 2D FLAIR for Multiple Sclerosis Imaging at 3 Tesla

Vergleich von 3-D-Cube-FLAIR und 2-D-FLAIR bei der Bildgebung der multiplen Sklerose bei 3 Tesla

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Key points
- MR imaging
- multiple sclerosis
- 3 D imaging
- FLAIR

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Zusammenfassung
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Ziel: Dreidimensionale MRT-Sequenzen erlauben sowohl eine verbesserte räumliche Auflösung bei guten Signal- und Kontrasteigenschaften als auch multiplanare Rekonstruktionen. Wir verglichen Cube, eine 3-D-FLAIR-Sequenz, mit einer Standard-2 D-FLAIR-Sequenz bei der Bildgebung der multiplen Sklerose (MS).

Material und Methoden: Die Untersuchungen wurden an einem 3-Tesla-Scanner in der klinischen Routine durchgeführt. 12 Patienten mit gesicherter MS wurden eingeschlossen. Läsionen mit MS-typischen Eigenschaften wurden gezählt und verschiedenen Hirnregionen zugeordnet. Signal-Rausch-(SNR) und Kontrast-Rausch-Verhältnisse (CNR) wurden berechnet.

Ergebnisse: Die Anzahl der insgesamt detektierten Läsionen war mit 384 mit der Cube-FLAIR-Sequenz signifikant höher als mit der 2-D-FLAIR-Sequenz (N = 221). Der Unterschied kam hauptsächlich durch supratentorielle Läsionen zustande (N = 372 gegenüber N = 216), während die Anzahl gefundener infratentorieller Läsionen mit beiden Sequenzen gering war. Die berechneten SNR und CNR lagen bei der Cube-FLAIR signifikant höher als bei der 2-D-FLAIR, mit Ausnahme der CNR von Läsion zu grauer Substanz, welche sich nicht signifikant unterschied.

Schlussfolgerung: Die Cube-FLAIR-Sequenz zeigte eine höhere Sensitivität für MS-Läsionen gegenüber einer 2-D-FLAIR-Sequenz. 3-D-FLAIR- könnten 2-D-FLAIR-Sequenzen in Zukunft ersetzen.

Kernaussagen:
1. MRT-Befunde sind ein wichtiger Bestandteil der Diagnosekriterien für multiple Sklerose.
2. Mit 3-D-Cube-FLAIR wurden mehr Läsionen nachgewiesen als mit der 2-D-FLAIR.
3. Signal- und Kontrasteigenschaften der 3-D-Cube-FLAIR waren größtenteils signifikant besser gegenüber der 2-D-FLAIR.

Abstract
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Purpose: Three-dimensional (3 D) MRI sequences allow improved spatial resolution with good signal and contrast properties as well as multiplanar reconstruction. We sought to compare Cube, a 3 D FLAIR sequence, to a standard 2 D FLAIR sequence in multiple sclerosis (MS) imaging.

Materials and Methods: Examinations were performed in the clinical routine on a 3.0 Tesla scanner. 12 patients with definite MS were included. Lesions with MS-typical properties on the images of Cube FLAIR and 2 D FLAIR sequences were counted and allocated to different brain regions. Signal-to-noise ratios (SNR) and contrast-to-noise ratios (CNR) were calculated.

Results: With 384 the overall number of lesions found with Cube FLAIR was significantly higher than with 2 D FLAIR (N = 221). The difference was mostly accounted for by supratentorial lesions (N = 372 vs. N = 216) while the infratentorial lesion counts were low in both sequences. SNRs and CNRs were significantly higher in CUBE FLAIR with the exception of the CNR of lesion to gray matter, which was not significantly different.

Conclusion: Cube FLAIR showed a higher sensitivity for MS lesions compared to a 2 D FLAIR sequence. 3 D FLAIR might replace 2 D FLAIR sequences in MS imaging in the future.

Key points:
1. MRI findings are an important part of multiple sclerosis diagnostic criteria.
2. Significantly more lesions were detected with 3 D Cube FLAIR compared to 2 D FLAIR.
3. Signal and contrast properties of 3 D Cube FLAIR were mostly superior to 2 D FLAIR.
4. 3 D FLAIR might replace 2 D FLAIR in the future

Introduction

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Magnetic resonance imaging (MRI) has become an important pillar in diagnostic concepts for multiple sclerosis (MS). Consequently, MRI was included in the widely used McDonald criteria of 2001 as well as in their 2005 and 2010 revised versions [1, 2]. MS-like lesions visible on MRI help to predict the probability of developing clinically definite MS in patients with clinically isolated syndromes [3]. Likewise, patients with "positive" MRI develop MS earlier than those without [4]. It has been demonstrated that patients selected with the aid of MRI for immunomodulatory therapy benefit from this treatment [5, 6]. Therefore, there is a need for a high sensitivity in lesion detection in MR imaging.

An improvement in lesion detection is likely possible by increasing the field strength which leads to higher signal-to-noise ratios (SNR). Additionally, the choice of the sequences is of obvious importance. MS lesions typically present with a high T2 signal. The fluid attenuated inversion recovery (FLAIR) is a T2-weighted sequence with nullified cerebrospinal fluid (CSF) signal, thus increasing contrast between lesions and CSF and improving white matter lesion detection [7]. For these properties it has become a standard sequence for MS imaging. More recently, three-dimensional sequences have become available. These allow high spatial resolution with good SNR as well as multiplanar reconstruction. "Cube" (previously "XETA") is a 3 D single-slab fast spin echo (FSE) sequence. To improve scanning efficiency and generate a large isotropic image volume in feasible time, Cube features autocalibrating reconstruction for Cartesian imaging (ARC), a 2 D-accelerated autocalibrating parallel imaging reconstruction method [8, 9].

Cube has already been evaluated for imaging of the knee and ankle, yielding positive results [10, 11]. Moreover, Cube FLAIR was shown to produce almost no CSF flow artifacts when applied in brain imaging [12]. We sought to test the Cube FLAIR sequence for parenchymal brain imaging in the field of multiple sclerosis at 3 Tesla. For this purpose we compared Cube to a standard 2 D FLAIR sequence regarding MS lesion detection and signal/contrast properties in the brain.

Materials and Methods

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Patients

The MR images of the first twelve patients with clinically definite MS examined with the Cube FLAIR sequence at University of Munich, Department of Neuroradiology were retrospectively analyzed in this study. Seven of the patients were female. The mean patient age was 43.7 (range 27 – 70) years. All patients agreed to the MRI examination including the additional sequence.

Imaging

Measurements were performed on a 3.0 Tesla scanner (Signa HDxt, GE Healthcare, Milwaukee, Wisconsin, USA). An eight-channel head coil was used. The patients were examined in the clinical routine with a standard MS diagnosis protocol including the 2 D FLAIR sequence and additionally the Cube FLAIR sequence in the same session.

Cube FLAIR is a single-slab 3 D fast spin echo (FSE) T2 FLAIR sequence. Modulated flip angle refocusing radiofrequency pulses are used to create long echo trains. This results in slower signal decay as compared to conventional FSE sequences with constant flip angles of 180°. In this way many more echoes can be used to generate the T2 image without causing extensive blurring and artifacts [13]. Moreover, the specific absorption rate (SAR) of the Cube sequence is rather low as the flip angles are mostly much less than 180°.

Half-Fourier reconstruction and ARC are used to lower TE and echo train length and reduce scanning time.

2 D FLAIR was acquired in the axial plane, Cube FLAIR sagitally. The slice thicknesses were 5 mm (2 D) and 1.4 mm (Cube). The acquisition time of the 2 D sequence was 3:24 minutes while the measurement with the Cube sequence took 6:09 minutes. For further sequence parameters see ❍ **Table 1**.

Image analysis

The Cube images were reformatted into axial slices of 1.0 mm with the positioning of slices as similar as possible to the images acquired with the 2 D FLAIR sequence. Two observers analyzed the axial images of both sequences, counted hyperintense lesions in consensus and allocated them to the following brain regions: Periventricular, deep white matter (WM), juxtacortical and cortical, basal ganglia, brain stem, cerebellum and corpus callosum.

Signal and contrast properties were determined as follows: Signal intensities (SI) were measured in both sequences for lesions, white matter, gray matter (GM) and CSF by two regions of interest (ROI) for each tissue type in each patient's images. The standard deviation of the noise (SD noise) was evaluated by placing four ROIs outside of the head in each patient, avoiding artifacts. The signal-to-noise ratio (SNR) was calculated as SI tissue/SD noise, the contrast-to-noise ratio as (SI tissue1 – SI tissue2)/SD noise.

Statistics

The software package SPSS 19.0 was used for statistical calculations. As data was not normally distributed, the Wilcoxon signed-rank test was applied for comparisons of the results of the two sequences.

Table 1 Sequence parameters.

Tab. 1 Sequenzparameter.

	TR (ms)	TE (ms)	TI (ms)	FOV (mm)	matrix	acquisition	slice thickness (mm)	acquisition time (min)
2 D FLAIR	8502	124.0	2250	220 × 220	320 × 320	axial	5	03:24
Cube FLAIR	6000	116.1	1885.0	240 × 240	224 × 224	sagittal	1.4	06:09

TR: Repetition time; TE: Echo time; TI: Inversion time; FOV: Field of view
TR: Repetitionszeit (repetition time); TE: Echozeit (echo time); TI: Inversionszeit (inversion time); FOV: Bildbereich (field of view)

	Peri-ventricular	Deep WM	Juxtacortical/cortical	Corpus callosum	Basalganglia/Thal.	Brainstem	Cerebellum	Total	P-value (total)[1]
2 D FLAIR	87	101	19	4	5	2	3	221	0.002
Cube FLAIR	136	153	54	21	8	8	4	384	

Table 2 Number of detected lesions in all patients, total and per brain region.

Tab. 2 Anzahl der bei allen Patienten detektierten Läsionen, insgesamt und pro Hirnregion.

[1] Wilcoxon signed-rank test
WM: White matter
Thal.: Thalamus
Wilcoxon-Vorzeichen-Rang-Test

Results
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With 384 MS lesions overall a significantly higher number was found with Cube FLAIR compared to the standard 2 D FLAIR sequence (p-value 0.002). In both sequences mostly supratentorial lesions were detected: 372 with Cube FLAIR and 216 with 2 D FLAIR. Only 12 (Cube) and 5 (2 D) infratentorial lesions were scored. The relative difference between lesion counts was particularly high in the corpus callosum and the juxtacortical regions (○ **Table 2**).

With the exception of the CNR lesion GM (not statistically significant), all SNRs and CNRs were significantly higher in Cube FLAIR than in 2 D FLAIR (○ **Table 3, 4**).

Discussion
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Early studies on 3 D FLAIR described the feasibility of these sequences as well as their superiority in the detection of MS lesions compared to 2 D sequences [14, 15]. In the beginning, however, 3 D sequences were acquired in a multi-slab mode which had several disadvantages including the occurrence of so-called venetian blind effects and long acquisition times. These drawbacks were extinguished by the introduction of single-slab sequences [16]. More recently, single-slab 3 D FLAIR sequences were tested and compared to 2 D sequences in MS imaging and were shown to be highly sensitive in lesion detection [17, 18]. To our knowledge, the 3 D "Cube" sequence has not yet been tested for this purpose and there is only one study comparing 3 D and 2 D FLAIR sequences regarding MS lesions at 3 T [18].

In our setup, 74 % more lesions could be detected by implementing the three-dimensional Cube FLAIR sequence than by using the standard two-dimensional FLAIR sequence. This finding confirms the subjective impression of better delineation and a distinctive "pop-out" effect of MS lesions in Cube FLAIR images. The higher lesion count of the Cube sequence was particularly due to the detection of small lesions which were not visible on the 2 D images. Moreover, many lesions which appeared to be one lesion or confluating lesions on 2 D FLAIR were found to actually be several distinct lesions when using Cube FLAIR.

3 D sequences allow thin slices without intersectional gaps. It has been demonstrated that a decrease in slice thickness in 3 D FLAIR sequences improves lesion detection [19, 20]. The axially reformatted slices of the Cube sequence were contiguous and had a thickness of 1.0 mm, compared to a thickness of 5 mm and a gap of 0.5 mm in the 2 D sequence. This improvement in spatial resolution as well as the decrease in partial volume effects likely contributed substantially to the increase in sensitivity. ○ **Fig. 1** shows two lesions visible with Cube FLAIR which cannot be clearly identified on the thicker slices of the 2 D se-

Table 3 Signal-to-noise ratios.

Tab. 3 Signal-Rausch-Verhältnisse.

	2 D FLAIR	Cube FLAIR	P-value[1]
Lesion	78.2 (24.1)	184.4 (69.3)	0.003
White matter	48.7 (16.4)	104.0 (30.2)	0.003
Gray matter	58.8 (15.7)	144.58 (40.22)	0.002
CSF	12.1 (6.7)	21.2 (9.3)	0.028

[1] Wilcoxon signed-rank test
CSF: cerebrospinal fluid
Wilcoxon – Vorzeichen – Rang –Test
CSF: Liquor (cerebrospinal fluid)

Table 4 Contrast-to-noise ratios.

Tab. 4 Kontrast-Rausch-Verhältnisse.

	2 D FLAIR	Cube FLAIR	P-value[1]
White matter to lesion	29.5 (12.3)	80.40 (39.5)	0.004
Gray matter to lesion	19.5 (8.8)	40.3 (36.0)	0.117
CSF to lesion	66.1 (18.8)	159.8 (60.7)	0.002

[1] Wilcoxon signed-rank test
CSF: cerebrospinal fluid
Wilcoxon-Vorzeichen-Rang-Test
CSF: Liquor (cerebrospinal fluid)

quence and would likely be overlooked. ○ **Fig. 2** illustrates the superior differentiability of lesions with Cube FLAIR and gives an impression of the differences in signal intensity and contrast between lesions, white matter and CSF.

3 D sequences have the advantage of good signal and contrast properties despite the small voxels. High SNRs and CNRs have been described for 3 D FLAIR sequences [17, 18]. These findings are confirmed by our measurements, which showed higher values for all calculated ratios except for the CNR lesion GM.

Another reason for the improved lesion detection with Cube FLAIR could be the superior CSF suppression and absence of CSF flow artifacts, which has been demonstrated before [12]. This is because no inflow of unsuppressed CSF from outside the imaging volume can occur due to the large volume excited using 3 D techniques.

We detected lesions mainly in the deep white matter, periventricular and juxtacortical regions. In both sequences only a few lesions were found in the brainstem and cerebellum. This could be a coincidental finding due to the limited number of patients. However, it has been stated before that FLAIR sequences might not be ideally suited for the detection of infratentorial lesions as a result of lower lesion-white matter contrast compared to supratentorial regions [21, 22].

Cortical and juxtacortical MS lesions have recently received more attention in pathological and imaging studies as they occur more
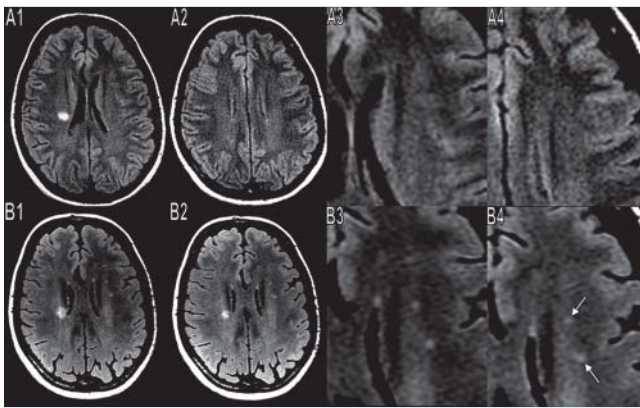
Fig. 1 A1, A2: Successive 5-mm slices of the 2 D FLAIR sequence; A3, A4: Detail enlargements of A1, A2; B1, B2: Successive 1-mm slices of the Cube FLAIR sequence, approximately corresponding to A1, A2; B3, B4: Detail enlargements of B1, B2;
On the Cube images, two white matter lesions (marked with arrows in B4) are visible, which cannot be detected on the 2 D FLAIR images.

Abb. 1 A1, A2: Aufeinanderfolgende 5 mm – Schichten der 2-D-FLAIR-Sequenz; A3, A4: Ausschnittvergrößerungen von A1, A2; B1, B2: Aufeinanderfolgende 1mm-Schichten der Cube-FLAIR-Sequenz, etwa entsprechend zu A1, A2; B3, B4: Ausschnittvergrößerungen von B1, B2; Auf den Cube-Bildern sind zwei Marklagerläsionen sichtbar (in B4 mit Pfeilen markiert), welche auf den 2-D-FLAIR Bildern nicht nachgewiesen werden können.
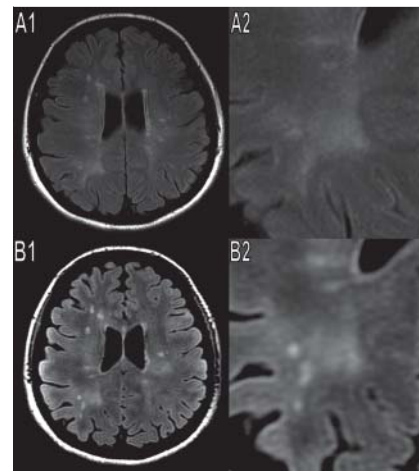

Fig. 2 A1: 2 D FLAIR image; A2: Detail enlargement of A1; B1: Cube FLAIR image, approximately corresponding to A1; B2: Detail enlargement of B1; White matter lesions can be more clearly distinguished on the Cube FLAIR image.

Abb. 2 A1: Bild der 2-D-FLAIR; A2: Ausschnittvergrößerung von A1; B1: Bild der Cube FLAIR; B2: Ausschnittvergrößerung von B1; Die Marklagerläsionen können auf dem Bild der Cube-FLAIR deutlich besser abgegrenzt werden.

frequently and seem to affect clinical disability to a larger extent than primarily assumed [23 – 25]. The much higher number of detected lesions in these regions in our study was mostly accounted for by juxtacortical lesions. Analyzing the Cube images, only four lesions were described as mixed gray/white matter (one in the 2 D FLAIR) and none was located clearly intracortically. Again a definite conclusion cannot be drawn from this small study, yet these findings are in accordance with the results of Moraal et al. who found significantly lower numbers of intracortical lesions with a 3 D FLAIR sequence than with a 3 D double inversion recovery (DIR) sequence [17, 18]. It may well be possible that Cube FLAIR improves detection of supratentorial white matter lesions while different sequences are necessary for optimized imaging of the infratentorial and cortical regions.

With 6:09 minutes, Cube FLAIR has a longer acquisition time than 2 D FLAIR (3:24 min). However, the 3 D sequence permits multiplanar reconstruction in virtually no time. Obviously, different planes can be highly useful for the detection and location of lesions. Cube can replace several 2 D sequences of different orientation and effectively reduce the time required for imaging in multiple sclerosis. We believe that a routine diagnostic set consisting of Cube FLAIR, a T2-weighted sequence optimized for infratentorial imaging and a 3 D T1-weighted sequence pre- and post-gadolinium are highly sensitive and efficient for MS imaging.

It is well conceivable that improvements in MR imaging techniques will have an impact on the diagnostic criteria for multiple sclerosis. The current MR criteria included in the McDonald criteria are based on 1.5 T imaging studies. It has been shown that examinations performed at 3 T yield higher numbers of patients positive for dissemination in space than at 1.5 T, although the influence on the number of diagnoses of definite MS is low [26 – 28]. The combination of 3 T MRI with 3 D sequences, as in our study, might raise the sensitivity for MS-like lesions even more.

Applying the new McDonald criteria, dissemination in space can be diagnosed on the grounds of only two lesions. It will have to be evaluated whether optimized imaging with high-field MRI and 3 D sequences will improve early detection of MS patients or lead to overdiagnosis, making adjustments to diagnostic criteria necessary.

The two sequences were compared as they are used in the clinical routine. Thus, they were applied in a way that was considered to optimally utilize the individual properties of each sequence. A reformation of the thin slices of Cube FLAIR into 5-mm axial slices to fit the 2 D FLAIR images and an adaptation of the scanning times was not chosen, because this would have compromised the qualities of the 3 D sequence. Therefore, Cube FLAIR in itself has the disadvantage of a longer scanning time. Included in a diagnostic set of sequences, however, we believe it to be able to reduce MRI scanning time, as stated above.

In conclusion, Cube FLAIR is superior to the 2 D FLAIR sequence used in our study regarding multiple sclerosis imaging. The role of 3 D sequences in MS diagnosis has yet to be determined and their effectiveness remains to be proven by larger studies. Because of their intrinsic advantages, however, it seems likely that 3 D will replace 2 D sequences in the future.

Clinical Relevance:
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▶ The study suggests that 3 D Cube FLAIR is superior to standard 2 D FLAIR in MS imaging.
▶ 3 D FLAIR could replace 2 D FLAIR in MS imaging in the future.
▶ The combination of high-field MRI with 3 D sequences might lead to more and earlier diagnoses of MS.
▶ It is possible that revisions of MS diagnostic criteria will be necessary because of new MRI techniques.

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