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Research article

Diagnostic value of diffusion-weighted STEAM-MRI in ischemic stroke

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ABSTRACT

Introduction: Diffusion-weighted imaging in stimulated echo acquisition mode (STEAM-DWI) is an interesting alternative with less susceptibility artifacts compared to the most commonly used diffusion-weighted echo-planar imaging (EPI-DWI). Sensitivity and specificity of a novel STEAM-DWI, described by Merrem et al. 2017 [1], were assessed in patients with ischemic stroke.

Methods: EPI- and STEAM-DWIs were performed in patients with suspected subacute stroke between 01 July 2019 and 30 June 2020 using 3-T MRI. Three neuroradiologists independently and separately rated STEAM-DWI images with respect to (i) signs of an acute/subacute stroke, (ii) the number, size and localization of infarctions and, (iii) the presence of artifacts.

Results: In 55 (23 right, 23 left, 9 both hemispheres) of 85 patients a subacute stroke was confirmed using EPI-DWI. The cerebral vascular territories were affected as follows: anterior cerebral artery 8 %, middle cerebral artery 48 %, posterior cerebral artery 27 %, brainstem 7 %, cerebellum 10 %. In 53 of 55 (96 %) cases the stroke was detected by usage of STEAM-DWI, in 35 of 37 patients microembolic events were noticed (95 %). Results showed a sensitivity and specificity of 100 % (70/70) for major infarcts (>9 mm^2 in-plane) and a sensitivity of up to 94 % (121/129) for detecting subacute microembolic lesions. No susceptibility artifacts were noticed in STEAM-DWI.

Conclusion: Compared to standard EPI-DWI, STEAM-DWI offers a more robust alternative for diagnosing subacute strokes in areas affected by susceptibility artifacts.

1. Introduction

The basics of STEAM-DWI were introduced by Merboldt et al. in 1992 [2]. In contrast to EPI-DWI, which is routinely used in clinical practice, significantly fewer susceptibility artifacts were noticed, for example by Nolte [3]. Nevertheless, EPI-DWI has become the "gold standard" in everyday clinical practice with a high level of sensitivity, as described by Gonzalez in 1999 [4].

Further developments using numerical methods by Rieseberg et al. 2005 [5] ultimately led to the STEAM-DWI variant used in this study, which is based on nonlinear inverse reconstruction [1]. In 2016 Khalil et al. [6] evaluated a variant of the Rieseberg STEAM-DWI [5] for infratentorial strokes.

The STEAM sequence is rarely used due to its intrinsically low SNR [1]. Comparable to EPI-DWI, the acquisition time of STEAM-DWI takes between 2 and 3 min depending on slice thickness and number of slices. A novel STEAM technique, developed at the Max Planck Institute for Biophysical Chemistry in Göttingen, was performed and compared with EPI-DWI in order to increase the detection rate for pathologies. As described by Merrem [1], the formerly low image quality due to limited signal-to-noise ratio (SNR) is compensated (1) by radial undersampling to enhance the flip angle and thus the signal strength of stimulated echoes; (2) by defining the image reconstruction as a nonlinear inverse problem, solved by the iteratively regularized Gauss-Newton method; and (3) by denoising with use of a modified nonlocal means filter. An example of a subacute infarction is shown in Fig. 1. Artifacts - caused by implants or air located in the nasal sinuses or the tympanic cavity - can limit the assessment of the anterior skull base, the temporal lobes or the brain stem. The advantage of the STEAM technology is the absence of these susceptibility artifacts, as shown in Fig. 2. In our retrospective study, the capability of the new STEAM-DWI for detecting subacute supra- und infratentorial infarcts was analyzed.

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2. Methods

2.1. Study design and participants

We retrospectively analysed MRIs of patients with a suspected subacute stroke and tandem DWI (EPI- and STEAM-DWI) on our 3 T MRI scanner (Siemens MAGNETOM Prisma). Since a combination of non-enhanced computed tomography, computed tomography angiography and computed tomography perfusion imaging is the standard for acute stroke detection in our hospital, the MRI is typically carried out within the first three days after symptoms onset. The STARD 2015 protocol was followed [7].

We searched the database of our imaging archive (PACS) for the terms "STEAM-DWI" and "subacute infarction" for patients scanned between 01 October 2019 and 30 April 2020. The radiological and neurological reports of these patients were checked for "suspected stroke" or "subacute stroke". Patients with postoperative infarctions or tumor associated ischemias were excluded.

2.2. MRI protocol

A high-resolution axial T2 Turbospin Echo (TSE) sequence with 2.5 mm slice thickness and an EPI-DWI (3scan_trace_p2) with 4 mm slice thickness are part of our local standard stroke protocol. An additional STEAM-DWI (6 gradient directions) with 3 or 4 mm slice thickness was performed at the end of each MRI scan.

In the acute setting, a computer tomography (CT) of the brain with CT perfusion is performed, followed by an MR in the coming days. In rare cases of an MRI for acute stroke, we perform a FLAIR to determine the FLAIR-DWI-mismatch. T2 TSE is less prone to artifacts than a FLAIR sequence.

2.2.1. Image analysis

Axial T2 TSE and STEAM-DWI scans of all included cases were pseudonymized and listed in a PACS folder. For every case a bookmark with T2 TSE, STEAM b1000 and STEAM Apparent Diffusion Coefficient (ADC) map was built.

Three independent neuroradiologists (>2 years experience in MRI diagnostics) with different levels of experience reading STEAM-DWI images (6, 3 and 0 months, in the following N1, N2 and N3) separately evaluated the scans for the occurrence and the number of subacute infarctions and micro-embolic lesions defined as T2-hyperintense diffusion restricted lesions ≤ 9 mm^2 in-plane. To assess the rater's diagnostic certainty of visual evaluation without EPI DWI the raters had to indicate their level of confidence on a 6-step scale (0 = complete guess, 1= very uncertain, 2= somewhat uncertain, 3= somewhat certain, 4= very certain, or 5= completely certain). Moreover, the raters evaluated the scans for susceptibility and movement artifacts on a visual analogue scale, VAS from 0 to 5; 0–100 % (0 = no artifacts, 1= small artifacts, not involving the parenchyma, 2= moderate to large artifacts, but not involving the parenchyma, 3= small artifacts involving the parenchyma, 4= moderate artifacts involving the parenchyma, or 5=large artifacts involving the parenchyma). Typical EPI phenomena, like eddy currents, image blurring, geometric distortion and ghosting [10] were only rated as artifacts, if they were unusually large. EPI-DWI ("gold standard") was finally evaluated together by all three neuroradiologists four weeks later.

2.2.1.1. Quantification of image contrast. SNR was calculated in 20 STEAM sequences (b1000) by dividing the mean values of healthy brain by the standard deviation of air in the unfiltered "b0" images. SNR is a function of the pixel location as the noise distribution is not Gaussian for magnitude MR images. Hence, SNR should not be stated as a number, but as a map. Therefore, the numbers given here are only raw estimates to enable a comparability with other studies. Contrast-to-noise ratio (CNR) was calculated for 20 randomized patients with subacute infarctions by dividing the mean values of infarct lesions minus mean values of normal brain tissue by the standard deviation of air in the unfiltered "b0" images. Contrast resolution was calculated by dividing the mean values of infarct lesions minus adjacent healthy brain by the mean values of infarct lesions plus adjacent healthy brain.

2.3. Statistical analysis

The program Statistica, version 13 (TIBCO Software Inc., Palo Alto, California, USA) was used for statistical analysis. P-values below 0.05 were defined as statistically significant. The sensitivity and specificity of STEAM-DWI to detect a stroke as compared to EPI-DWI was calculated

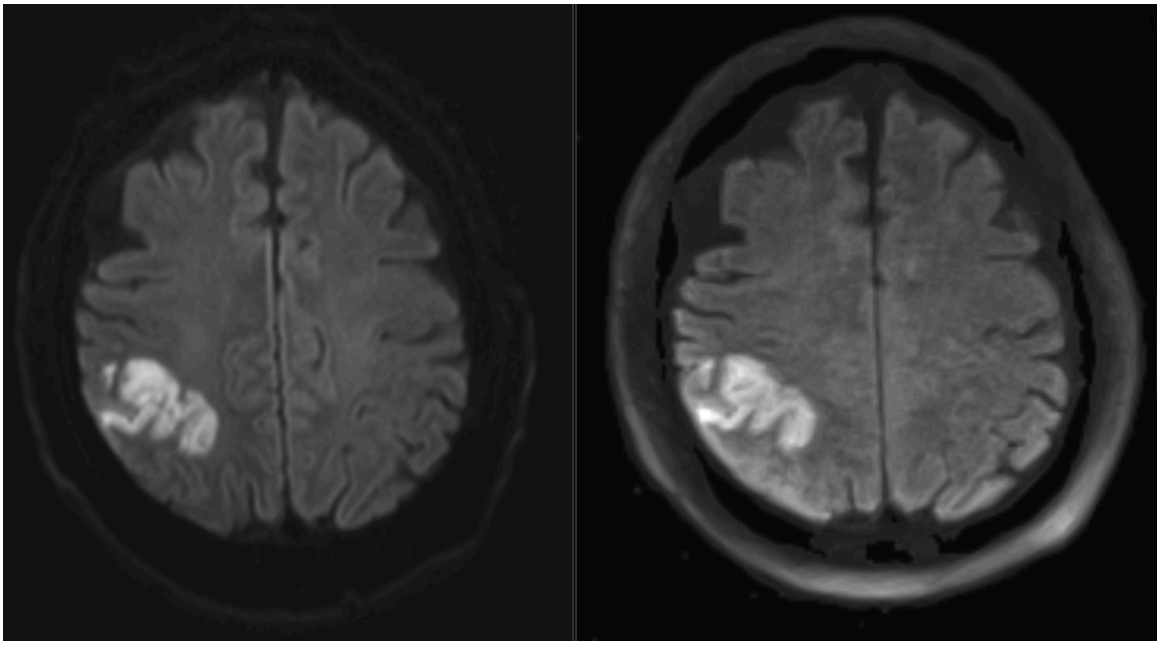

Fig. 1. Axial EPI-DWI (b = 1000s/mm2) (left) and STEAM-DWI (b = 1000s/mm2) (right), both demonstrating a subacute infarction in the right middle cerebral artery (MCA) territory.

for every individual neuroradiologist as well as for all readers. A sum of all ratings was built to estimate the maximal detection rate, called "virtual summarized judgement". Fleiss' kappa [8] for the overall raw agreement between the three raters (STEAM-DWI) and EPI-DWI was calculated.

3. Results

3.1. Participants

99 patients were collected using the database query. 14 patients were excluded. Of these, 8 patients demonstrated postoperative, iatrogenic infarctions at the resection margins after brain surgery) and 6 patients showed newly diagnosed symptomatic brain tumors. 85 patients (44 males, 40 females) were included. A female patient with subacute infarctions in different territories within 5 months was included twice. A flow chart depicting the patient acquisition is shown in Fig. 3. Mean age was 66.9 ± 16.7 years (mean ± standard deviation) and ranged between 8 and 94 years. In 55 cases the symptoms matched the localization of the brain lesions in EPI-DWI. A correlating subacute infarct lesion was not found in 30 patients with symptoms. The average time between symptom onset and MRI was 71 ± 53 h (mean ± standard deviation, median 51 h).

3.2. Test results

3.2.1. Infarction areas

In 55 (23 right, 23 left, 9 both hemispheres) out of 85 patients a subacute stroke was confirmed using the EPI-DWI. The following territories were affected (mean values of all observers): ACA territory 4 %, anterior border zone 8 %, MCA territory 37 %, posterior border zone 13 %, PCA territory 21 %, brainstem 7 %, cerebellum 10 %.

3.2.2. Sensitivity and specificity

Ischemic strokes were detected in 53/55 patients (N1, sensitivity 96.4 %), 52/55 (N2, sensitivity 94.6 %) and in 51/55 (N3, sensitivity 92.7 %) patients using STEAM-DWI. No false positive cases occurred (specificity 100 %, 30/30 for N1, N2 and N3). Negative predictive values were 30/32 (N1, 94 %), 30/33 (N2, 91 %) and 30/34 (N3, 88 %).

Larger infarct lesions (>9 mm^2 in-plane) were detected in 70/70 cases by the experienced (N1/N2), and in 65/70 cases (92.9 %) by the non-experienced neuroradiology fellow. No false positive cases occurred.

Smaller lesions were detected in 114/129 (N1, 88.4 %), 105/129 (N2, 81.4 %), 80/129 (N3, 62.1 %) cases. The ratios of false to positive detections were 1.8 % (2/114), 12.4 % (13/105) and 1.3 % (1/80), respectively. 121 lesions (93.8 %) were detected calculating a virtual summarized judgement of all three neuroradiologists. A scheme of all detected large and small lesions is shown in Fig. 4 above.

The overall sensitivity for small and large subacute ischemic lesions was 92.5 % for N1, 86.5 % for N2, 73 % for N3, and 96 % (191/199) for the total of all three raters.

An estimated learning curve for the detection of subacute infarctions is shown in Fig. 5 below.

3.2.3. Onset dependent sensitivity and specificity

Onset dependent analysis shows a slightly better sensitivity and less false positive for small subacute infarctions within 72 h after symptom onset, as demonstrated in Table 1.

3.2.4. Influence of slice thickness and infarct location

In 47 patients with 35 confirmed subacute infarctions a 3 mm STEAM-DWI was performed. A slice thickness of 4 mm was applied in 38 patients with 20 subacute infarctions.

Overall sensitivity (3 mm, 4 mm) was for N1 (93 %, 92 %), N2 (90 %, 84 %), N3 (79 %, 63 %), summarized maximal sensitivity (96 %, 96 %), respectively.

The following sensitivities resulted for the division into supra-(40 cases) and infratentorial (15 cases) strokes: N1 (95 %, 86 %), N2 (87 %, 89 %), N3 (73 %, 71 %), summarized maximal sensitivity (98 %, 89 %), respectively. Table 2 provides a detailed cross tabulation of the raters.

3.2.5. Interrater agreement

Overall Fleiss' kappa (4 raters; three neuroradiologists and EPI-DWI)

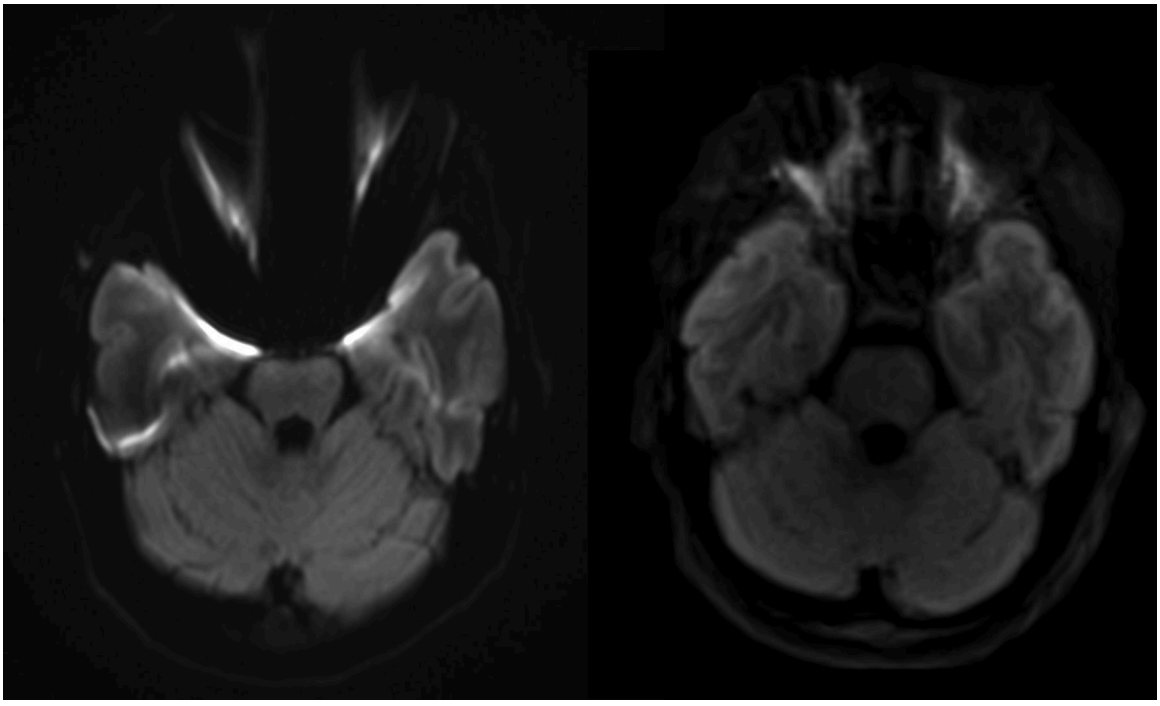

Fig. 2. Axial EPI-DWI (b = 1000s/mm2) (left) and STEAM-DWI (b = 1000s/mm2) (right), susceptibility artifacts of metallic braces, which limit the assessment of temporal lobes and brain stem.

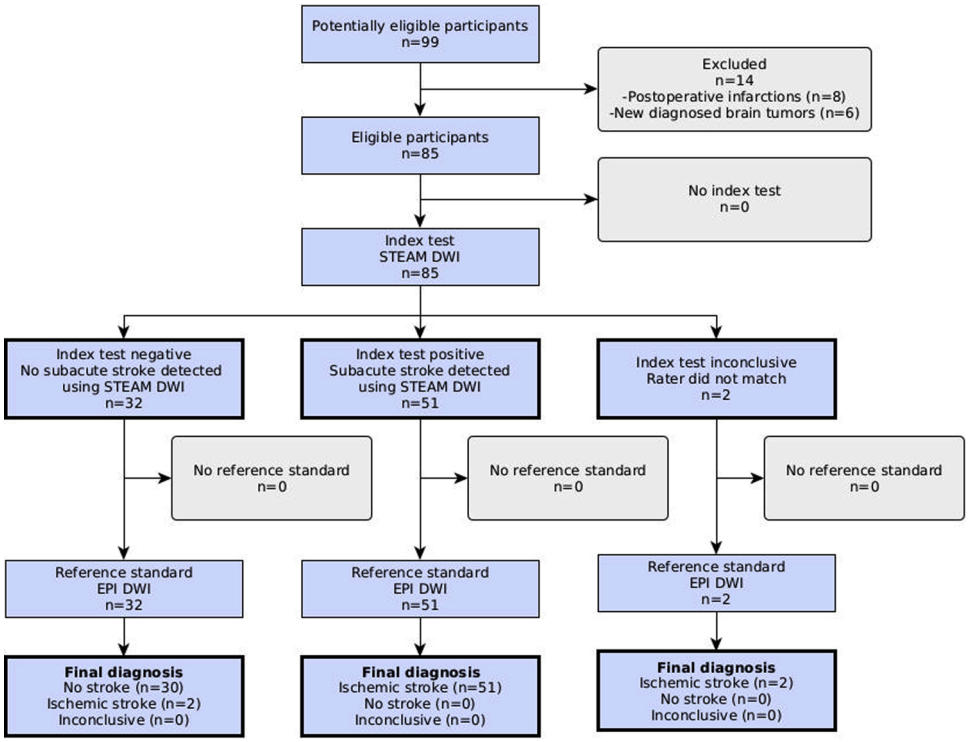

Fig. 3. Participant flow chart.

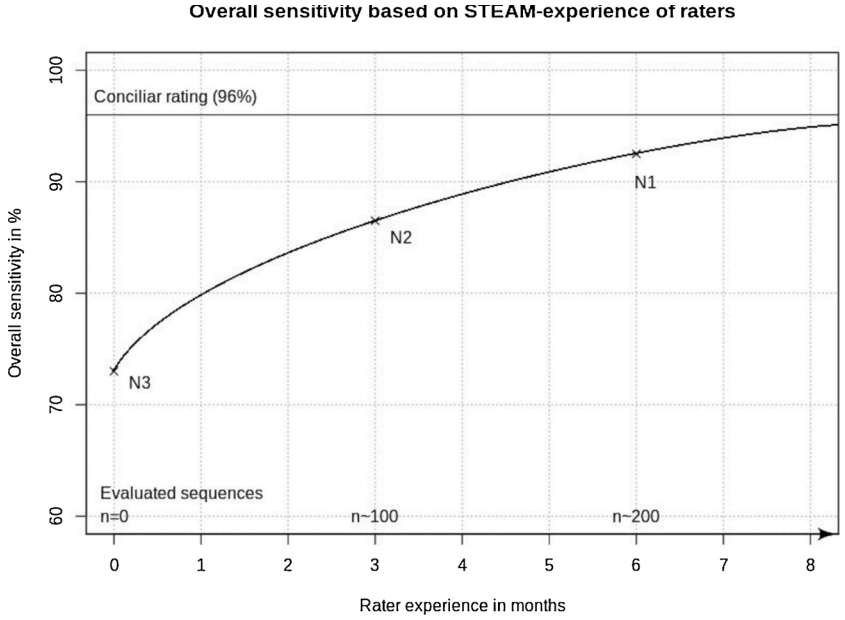

Fig. 4. Estimated learning curve for detecting micro lesions.

was 0.77 ($p > 0.001$) and 0.96 ($p < 0.001$, excellent agreement) for larger infarctions but only 0.55 for microlesions ($p < 0.001$, moderate agreement).

Excluding the unexperienced N3, overall Fleiss' kappa was 0.83 (for N1, N2 and EPI-DWI, 3 raters) and 0.80 ($p < 0.001$, good agreement) only for N1 and N2 (2 raters).

3.2.6. Sequences

The acquisition times were 96 s for the EPI-DWI and 144 (3 mm slice thickness) and 108 s (4 mm slice thickness) for the STEAM-DWI.

3.2.7. Artifacts

Artifacts occurred in 12.9 % of all cases. In the four (partially) non-detected strokes, noticed artifacts were increased to 30 % in VAS. Artificial microlesions (lesions with artificial diffusion restriction, but no "T2 shine through effect", [9]) were less often found in STEAM-DWI (31 vs. 52 in EPI-DWI). Susceptibility artifacts (air, dentures, shunt catheters) were not noticed in STEAM-DWI (0/85 STEAM-DWI vs. 6/85 in EPI-DWI). However, since many of the patients were restless and the STEAM sequence was scanned last in our stroke protocol, more severe movement artifacts were registered (5/85 in EPI vs. 17/85 in STEAM-DWI). We observed new elongated cortical artifacts in case of an

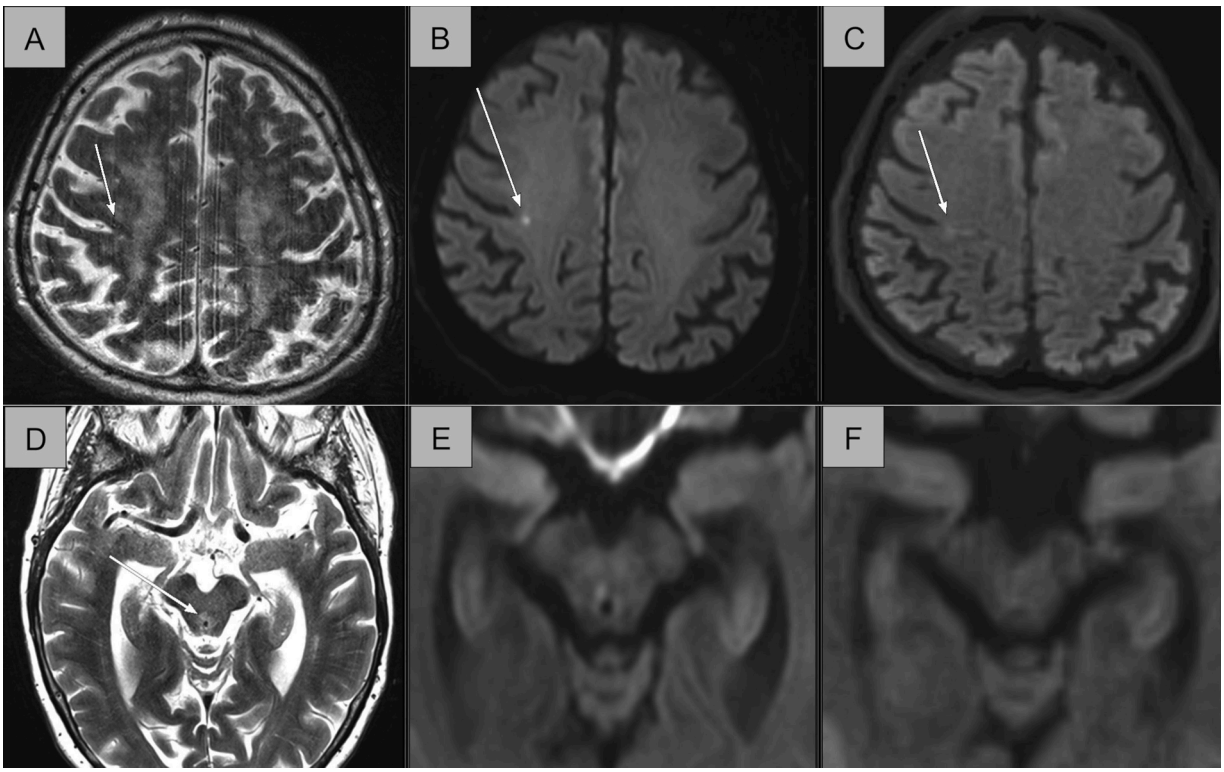

Fig. 5. Detection of stroke completely failed with usage of STEAM-DWI in these two cases (2/55): Case 1, a right precentral subcortical microembolic infarction: (A) T2 TSE, (B) EPI-DWI b1000, (C) STEAM-DWI b1000. Case 2, a right mesencephalic periventricular microembolic infarction: (D) T2 TSE, (E) EPI-DWI b1000, (F) STEAM-DWI b1000.

Table 1
Onset dependent sensitivity for microembolic lesions.

Time between symptom onset and MRI t	Sensitivity (all)	Sensitivity (N1 + N2)	False positive (all)
<72 h	79 %	87 %	4 % (7/173)
>72 h	77 %	84 %	7 % (8/111)

inclined head position in the STEAM DWI, which were not severe and easy to distinguish from real lesions and infarcts. A detailed listing of artifacts is provided in Table 2.

3.2.8. Diagnostic confidence

Overall confidence in the diagnostic rating was high (median, "completely certain", mean (96 %, median 5 on VAS). In the controversial four cases in which most mistakes occurred, the confidence was significantly decreased (82 %, median 4 on VAS).

3.2.9. Quantification of image contrast

Contrast resolution was 28 ± 8 % (mean ± standard deviation, n = 20) for STEAM-DWI. SNR and CNR are less meaningful in noise-filtered sequences, but show good results for STEAM-DWI (SNR 49 ± 28; CNR 39 ± 20) in the few cases (8/20) with residual noise due to air. In most cases, the standard deviation of air was zero (in b0 and b1000) and so far no SNR or CNR could be calculated.

3.2.10. Selected examples

The four cases, in which the ischemic lesion was not confirmed using the STEAM-DWI by at least one neuroradiologist are shown in Figs. 5 and 6.

Table 2
STEAM vs. EPI DWI.

Category	STEAM DWI					EPI DWI		Ratio	
	N1	N2	N3	opt	sum	N1, N2, N3	sum	sum	opt
Infarct lesion correctly detected	184	175	145	**191**	**504**	199	**597**	84 %	96 %
-macrolesion	70	70	65	**70**	**205**	70	**210**	98 %	100 %
-false positive macrolesion	0	0	0	**0**	**0**	0	**0**	%	0
-microlesion	116	118	81	**121**	**315**	129	**387**	81 %	94 %
-false positive microlesions	2	13	1	**0**	**16**	0	**0**	–	–
-true positive microlesions	114	105	80	**121**	**299**	129	**387**	77 %	94 %
Artifacts	25	21	29	–	**75**	34	**102**	74 %	
-motion	20	14	18	–	**52**	5	**15**	347 %	
-susceptibility	0	0	0	–	**0**	6	**18**	0 %	
-geometric distorsion of parenchyma	0	0	0	–	**2**	15	**45**	0 %	
Image blurring									
-inclined head artifacts	5	5	10		**20**	0	**0**	–	
-other	0	2	1	–	**3**	23	**69**	4 %	

N1, N2, N3 – raters; opt - virtual summarized judgement; sum - N1 + N2+N3; Ratio – detections in STEAM divided by detections in EPI DWI.

4. Discussion

The new STEAM-DWI with enhanced CNR showed excellent results for detecting subacute infarctions in the whole brain. Our study demonstrated a good sensitivity and specificity of STEAM-DWI for (acute and) subacute infarctions.

Diffusion weighted imaging is the gold standard for the detection of acute and subacute strokes [10–13]. Due to the poor CNR, STEAM-DWI was neglected in favor of the EPI-DWI [14].

A handful of STEAM sequences exist, developed by Merboldt et al. [2], Nolte et al. [3], and Rieseberg et al. [5]. Shrestha et al. [15] showed similar results with a related technique called HASTEAM. The novel STEAM sequence is based on the results from Merrem et al. [1] and offers an improved resolution and less acquisition time. An increase of the CNR and a good contrast resolution lead to a better detection rate compared to the older variants in the literature [5,6].

Specificity of STEAM-DWI for detecting subacute infarctions was 100 % in our work, even for unexperienced neuroradiologists.

Since CNR of older STEAM versions was not sufficient [1], STEAM DWI was to our knowledge not tested for the detection of supratentorial subacute strokes. In contrast to the study from Khalil [6], in which the STEAM-DWI was only used in infratentorial strokes, we also applied the STEAM-DWI to detect supratentorial infarctions and the new technique showed excellent results for both.

Our study confirmed no metal and air artifacts of the STEAM-DWI [1, 6]. Therefore, STEAM-DWI may be used for decision making in false positive cases based on EPI-DWI [6]. Another area of application could be in diagnostics after neurosurgical operations, if blood and air make diagnostics difficult.

4.1. Limitations

The evaluation was partly carried out by neuroradiology fellows without experience with STEAM-DWI. However, all investigators were well trained in reading EPI-DWI. This could also have a negative impact on the assessment of STEAM against EPI-DWI.

Since STEAM-DWI was the last sequence in our MRI protocol, we noticed more movement artifacts then in the other sequences, which might be regarded as a small systemic error in the measurements favoring EPI-DWI. Due to the retrospective nature of our study, we were not able to avoid this error.

A prospective study with a randomized order of the tandem DWIs is needed for an equal distribution of the movement artifacts. The newly developed STEAM sequence seems to be an even greater challenge for EPI standard technology.

4.2. Error sources

Despite of less susceptibility artifacts, the fuzzy character of the STEAM-DWI requires experience. Especially very small lesions or older subacute lesions with a weak signal in the EPI-DWI are sometimes hard to detect using the STEAM-DWI, because they seem to disappear in the noise. A correlation with the T2 sequence, which was allowed in our setup, enables a safe differentiation between artifact and lesion in many

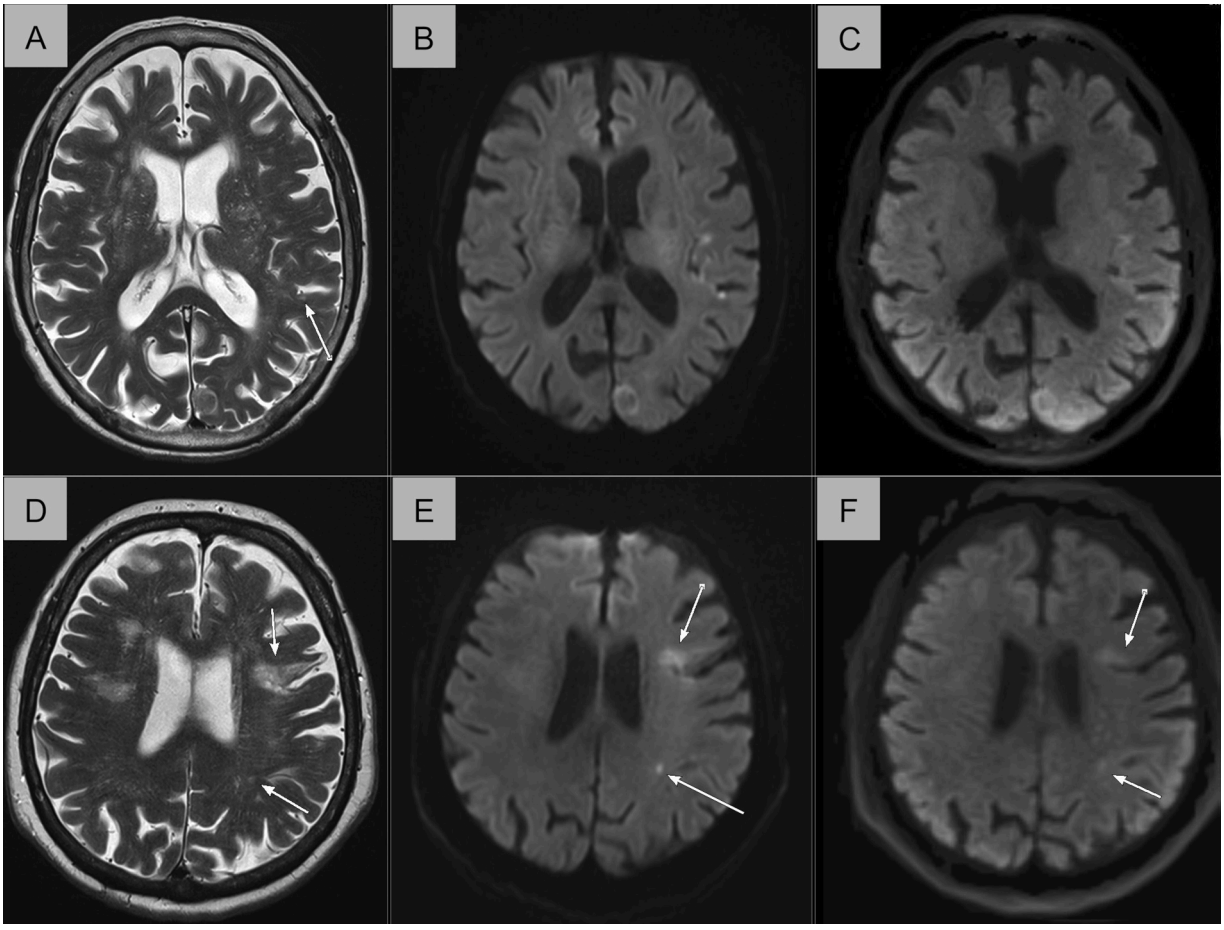

Fig. 6. In two cases (2/55) the detection of a stroke using STEAM-DWI was not unanimous. Case 1 (detected by 2/3 neuroradiologists), a left temporal cortical microembolic infarction: (A) T2 TSE, (B) EPI-DWI b1000, (C) STEAM-DWI b1000. Left occipital falcine meningioma also shown. Case 2 (detected by 1/3 neuroradiologist), a large left frontoopercular defect zone and a small microembolic ischemia in the left parietal white matter: (D) T2 TSE, (E) EPI-DWI b1000, (F) STEAM-DWI b1000.

cases.

Interestingly, the sensitivity of all three neuroradiology fellows decreased in the STEAM-DWI with 4 mm slice thickness while summarized maximal sensitivity remained the same.

4.3. Conclusion

Compared to previous approaches, the CNR, SNR, contrast resolution and thus the sensitivity of the STEAM-DWI has improved significantly, which allows a rational use in clinical practice for the first time. Especially in cases with many metal or air artifacts the STEAM-DWI is imaginable as a replacement for the EPI-DWI. Additionally, STEAM-DWI showed similar excellent results in both supra- and infratentorial infarctions. We will continue to develop STEAM-DWI to ensure an even higher in-plane resolution and, as far as possible, a better CNR.

CRediT authorship contribution statement

The study was conceived and designed by **Sebastian Johannes Müller**, **Eya Khadhraoui**, **Christian Heiner Riedel**, and **Jens Frahm**. Material preparation, data collection, and analysis were performed by **Sebastian Johannes Müller**, **Eya Khadhraoui**, **Julia My Van Kube**, **Philip Langer**, **Dirk Voit**. **Marielle Ernst** analyzed the data, and revised the draft of the manuscript. The neuroradiologists were **Sebastian Johannes Müller** (N1), **Eya Khadhraoui** (N2) and **Julia My Van Kube** (N3). The first draft of the manuscript was written by **Sebastian Johannes Müller** and **Jens Frahm**, and **Sebastian Johannes Müller**, **Eya Khadhraoui**, **Julia My Van Kube**, **Philip Langer**, **Christian Heiner Riedel**, **Dirk Voit**, **Marielle Ernst**, **Jens Frahm** commented on previous versions of the manuscript. **Sebastian Johannes Müller**, **Eya Khadhraoui**, **Julia My Van Kube**, **Philip Langer**, **Christian Heiner Riedel**, **Dirk Voit**, **Marielle Ernst**, **Jens Frahm** read and approved the final manuscript.

Ethical approval

The study was ethically approved by the institutional review board ("Ethikkommission der Universitätsmedizin Göttingen", Göttingen, Germany, No. 12/06/20) and registered in the German clinical trials register (drks.de, DRKS00022965). The full study protocol can be accessed in the supplementary materials.

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No funding was received for the conduct of this study.

Declaration of Competing Interest

The authors report no declarations of interest.

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