MRI Highly Accelerated Wave-CAIPI T1-SPACE vs. Standard T1-SPACE to detect brain gadoliniumenhancing lesions at 3T Check for updates

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Running Title: Evaluation of Enhancing Lesions with Post-Contrast Wave-CAIPI T1-SPACE

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Background and Purpose: High-resolution three-dimensional (3D) post-contrast imaging of the brain is essential for comprehensive evaluation of inflammatory, neoplastic, and neurovascular diseases of the brain. 3D T1-weighted spin-echo-based sequences offer increased sensitivity for the detection of enhancing lesions but are relatively prolonged exams. We evaluated whether a highly accelerated Wave-controlled aliasing in parallel imaging (Wave-CAIPI) post-contrast 3D T1-sampling perfection with application-optimized contrasts using different flip angle evolutions (T1-SPACE) sequence (Wave-T1-SPACE) was noninferior to the standard high-resolution 3D T1-SPACE sequence for visualizing enhancing lesions with comparable diagnostic quality.

Methods: 103 consecutive patients were prospectively evaluated with a standard postcontrast 3D T1-SPACE sequence (acquisition time [TA] = 4min 19s) and an optimized Wave-CAIPI 3D T1-SPACE sequence (TA = 1min 40s) that was nearly three times faster than the standard sequence. Two blinded neuroradiologists performed a head-to-head comparison to evaluate the visualization of enhancing pathology, perception of artifacts, and overall diagnostic quality. A 15% margin was used to test whether post-contrast Wave-T1-SPACE was noninferior to standard T1-SPACE.

Results: Wave-T1-SPACE was noninferior to standard T1-SPACE for delineating parenchymal and meningeal enhancing pathology (P<0.01). Wave-T1-SPACE showed marginally higher background noise compared to the standard sequence and was noninferior in the overall diagnostic quality (P=0.03).

Conclusions: Our findings show that Wave-T1-SPACE was noninferior to standard T1-SPACE for visualization of enhancing pathology and overall diagnostic quality with a three-fold reduction in acquisition time compared to the standard sequence. Wave-T1-SPACE may be used to accelerate 3D post-contrast T1-weighted spin-echo imaging without loss of clinically important information.

Introduction

Three-dimensional (3D) post-contrast T1-weighted imaging (T1WI) of the brain is one of the essential techniques used in the routine clinical evaluation of the central nervous system pathology and is increasingly used for a broad range of inflammatory, tumoral and neurovascular diseases. It is well known that 3D spin-echo (SE) T1WI is preferred for detecting contrast-enhancing intracranial lesions.¹ However, these sequences have long scanning times and have been frequently replaced by other pulse sequences that offer similar images with shorter scan times and 3D multiplanar views, such as magnetization-prepared rapid gradient-echo (MPRAGE), axial MRI 3D brain volume and other fast gradient recalled-echo (GRE)-based sequences.

Several trade-offs need to be considered when choosing sequences for inclusion in any brain NR protocol, with acquisition time deemed as an important factor in that decision. While 3D THM GRE-based sequences have the advantage of generating isotropic datasets that can be used for treatment planning of neoplastic lesions, they are less sensitive for detecting small foci of enhancement without surrounding edema than 3D T1WI SE sequences,² which can be particularly important for the investigation of small intraparenchymal enhancing lesions.³ Moreover, the 3D T1WI SPACE (sampling perfection with application-optimized contrasts using different flip angle evolutions) sequence intrinsically suppresses the signal of vascular flow-related artifacts commonly encountered on 2D TSE sequences,⁴ thus providing higher contrast-to-noise ratio, which can improve the diagnostic accuracy for leptomeningeal disease.⁵ 3D T1WI SE-based sequences have been improved to permit the efficient application of T1WI in contrast enhanced exams within a reasonable scanning time,⁶ thereby offering the benefits of optimal image contrast and spatial resolution inherent to these techniques.⁷

Wave-controlled aliasing in parallel imaging (Wave-CAIPI) is an acquisition and reconstruction approach that provides maximal efficiency for parallel imaging. Wave-CAIPI

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efficiently encodes 3D k-space by synergistically combining CAIPI shifts along k_y/k_z with a corkscrew k-space trajectory along the readout (k_x). This homogeneously spreads the voxel aliasing along all three spatial dimensions, thus allowing to take better advantage of the 3D coil sensitivity information and hence facilitating higher acceleration with negligible artifacts and g-factor penalty.⁸ The 3D T1WI SPACE sequence offers a robust and flexible approach for 3D T1WI SE-based imaging⁹ which is suitable for an aggressive acceleration strategy due to the intrinsically high contrast and the added advantage of multiplanar viewing for evaluating pathological enhancement in the complex CNS anatomy. The resulting decrease in acquisition time may facilitate broader clinical application of high-resolution contrast-enhanced imaging, especially in motion-prone populations.

The goal of this study was to compare a highly accelerated Wave-CAIPI postcontrast 3D T1-SPACE sequence (Wave-T1-SPACE) with the commonly used standard high-resolution 3D T1-SPACE sequence for routine clinical contrast-enhanced brain imaging at 3T. We hypothesized that Wave-T1-SPACE is noninferior to the standard sequence in visualizing enhancing lesions, providing equal diagnostic quality with the added benefit of considerable reduction of acquisition time.

Methods

Selection of participants and study design

A prospective comparative study was performed after Institutional Review Board approval, and all components were compliant to the Health Insurance Portability and Accountability Act. 103 consecutive adult patients undergoing clinical brain MRI with contrast at a single institution in both inpatient and outpatient settings were enrolled. Demographic information of the study participants and the clinical indications for MRI examination are shown in Table 1. Patients were scanned on a 3T MRI scanner (MAGNETOM Prisma, Siemens Healthcare, Erlangen, Germany) using a commercially available 20- or 32-channel receiver coil array. All MRI exams were acquired as part of the standard examination of the enrolled participants with less than 2 minutes of added imaging time per case. Given the minor increase in total scan time, the institution's IRB waived the need for written informed consent. Exclusion criteria followed the same routine clinical requirements for MR imaging with contrast. Patients were provided with an information sheet providing a succinct and clear description of the research study and could decline participation prior to initiating the scan.

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All batients had an accelerated 3D post-contrast Wave-T1-SPACE inserted in the standard contrast-enhanced MRI protocol for brain evaluation. Each scan included a standard 3D post-contrast T1-SPACE sequence (acquisition time [TA] = 4min 19s) and a Wave-T1-SPACE sequence (TA = 1min 40s). Contrast-enhanced images were obtained after intravenous administration of standard dose of 0.2 ml/kg (0.1 mmol/kg) of gadoterate meglumine (Dotarem[®], Guerbet; Paris, France) at a flow rate of approximately 2 ml/second. Of the total number of exams, 65 studies (63%) were performed with the standard post-contrast T1-SPACE sequence acquired before Wave-T1-SPACE, and 38 studies (37%) were performed with the Wave-T1-SPACE acquired before the standard T1-SPACE, to factor out potential differences related to the order of acquisition. Although we could not control precisely the time elapsed from contrast injection to the start of acquisition of each sequence in either order, we standardized that both sequences would be acquired after the acquisition of two immediately post-injection sequences (post-contrast axial TSE T2 and axial T1 blade). Consequently, we could estimate the approximate times, shown in Table 2, to initiate acquisition of each sequence after contrast administration.

Wave-CAIPI Post-contrast T1-SPACE Sequence and Reconstruction

Wave-T1-SPACE was implemented using a prototype single slab 3D T1-SPACE sequence.⁸ On-line reconstruction was performed using an auto-calibrated procedure in which the true gradient trajectory is estimated during the reconstruction without the need for additional calibration scans.¹⁰ This allowed for simultaneous estimation of the parallel imaging reconstruction and the true k-space trajectory, with a reconstruction time of approximately 60 seconds. We sought to match the TR, TE, and flip angle as those are the main sequence parameters that contribute to T1WI contrast between the Wave and standard T1-SPACE sequences. Although SPACE is inherently a variable flip angle technique, we set the user-selectable flip angle of 120 degrees, which relates to the maximum flip angle of the range of variable flip angles used during acquisition. The standard T1-SPACE sequence used in our institution's routine clinical protocol employs the default vendor reconstruction filter that introduces a small degree of spatial smoothing. Therefore, to provide comparable effective spatial resolution using the prototype Wave-T1-SPACE sequence, a marginally larger isotropic voxel size was used in the Wave-T1-SPACE compared to the standard T1-SPACE acquisitions (1.0 mm vs 0.9 mm). This strategy ensured comparable visual spatial resolution as evaluated by the study neuroradiologists (Figure 1). Detailed sequence parameters are presented in Table 2.

Image Evaluation

Two neuroradiologists with 15 and 5 years of post-fellowship experience, respectively (O.R. and S.Y.H.), performed a blinded and randomized independent review of all images. The scales set for previously published clinical validation studies of Wave-CAIPI sequences¹¹ were adapted for the evaluation of abnormal enhancement. The reviewers used a predetermined 5-point grading scale to compare Wave-T1-SPACE with the standard T1-SPACE and evaluated only the post-contrast images of the anonymized DICOM datasets on an independent workstation. Adjustments of the window width and level settings were permitted for optimal visualization of each image series.

Reviewers undertook several head-to-head analysis sessions in which they evaluated the detection of pathological enhancement in the parenchyma, leptomeninges, pachymeninges (dura), and ependymal surface. They also evaluated the presence of artifacts related to motion, the grade of background noise, and the overall diagnostic quality of the image series. The order of the cases and the position of each sequence on the screen were randomized.

All cases were rated for each feature with the 5-point grading scale, where positive numbers favored the sequence on the right, and negative numbers favored the sequence on the left of the screen (Table 3). A third neuroradiologist with over 20 years of experience (P.W.S.) adjudicated disagreements between the reviewers.

Statistical Analysis

We tested for noninferiority of Wave-T1-SPACE compared to standard T1-SPACE in the head to head analysis. The standard sequence could not be considered the gold standard for traditional diagnostic performance testing for sensitivity, specificity, and accuracy given that in some instances it presented with inferior quality than Wave-T1-SPACE. Therefore, a non-inferiority margin (Δ) of 15% was chosen with the null hypothesis (H₀) that the proportion of cases where standard T1-SPACE was preferred over Wave-T1-SPACE was > 15%.¹² The noninferiority margin was chosen after a careful review of similar imaging-based noninferiority publications and consensus among our group of neuroradiologists.^{11,13} We used the Z statistic to calculate the probability of the standard sequence being preferred over the Wave-T1-SPACE sequence in more than 15% of cases (H₀> Δ), with a type 1 error rate (α) of 0.05. Other descriptive data were summarized by the calculation of percentile proportions, means and standard deviations. We also calculated the upper bound of the 95% confidence interval for the proportion of cases where standard T1-SPACE was preferred over Wave-T1-SPACE, i.e., the critical value, P_{critical}. The interrater agreement was reported using the quadratically weighted Cohen κ to disproportionately

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penalize larger disagreements. The agreement of categorical variables was interpreted according to Landis and Koch.¹⁴ All statistical calculations were performed using R version

3.6.3.

103 cases were successfully acquired and included in the comparison evaluation. In the head-to-head analysis, abnormal enhancement was detected in 69 cases (67%) (Figure 2). Of the 69 cases that showed abnormal enhancement, 44 (64%) had parenchymal enhancement, 48 (70%) had dural enhancement, 26 (38%) had leptomeningeal enhancement, and 15 (22%) had ependymal enhancement, with 33 (48%) showing more than one type of enhancing lesion. Interrater agreement was considered moderate ($\kappa = 0.52$ for parenchymal enhancement, 0.57 for dural enhancement, 0.50 for leptomeningeal enhancement, 0.41 for noise, 0.47 for motion artifacts, and 0.58 for the overall diagnostic quality). For ependymal enhancement, Cohen κ was zero (κ = 0) despite a high proportion of agreement – both raters agreed on a score of '0' in the majority of cases (80%), a known paradoxical result that can occur when the study population is highly unbalanced¹⁵ (in this case, a much higher proportion of '0' than non-zero scores). Wave-T1-SPACE was noninferior to standard T1-SPACE for delineating parenchymal, dural and leptomeningeal enhancing pathology (P<0.01). The results of the head-to-head comparison and the noninferiority testing are depicted in Figure 3. Of the 44 cases with parenchymal enhancement, 41 (93.2%) were rated as equivalent, while in one (2.3%) the standard sequence was preferred and in two cases (4.5%) the Wave-T1-SPACE sequence was preferred. In the evaluation of dural enhancement, 46 (95.8%) were considered equivalent, one (2.1%) had the standard sequence preferred and one (2.1%) had Wave-T1-SPACE preferred. In the leptomeningeal enhancement evaluation, 24 (92.4%) were graded as equivalent, one (3.8%) had the standard sequence preferred and one (3.8%) had Wave-T1-

SPACE preferred. The evaluation of ependymal enhancement also showed that 93.3% were considered equivalent (14 cases out of 15), and in one (6.7%) the standard sequence was preferred. This last category of enhancing pathology failed the noninferiority test (P=0.09), likely due to the small number of cases showing ependymal enhancement.

Of the total cohort, most cases were considered equivalent for the evaluation of motion artifacts (76 cases, 73.8%), with 24 cases (23.3%) showing less motion in the standard sequence, and three (2.9%) showing less motion in the Wave-T1-SPACE. The assessment of background noise showed that approximately half of the exams (55 cases, 53.4%) had the standard sequence rated with less noise artifacts when compared to the Wave-T1-SPACE sequence, 45 cases (43.7%) were considered equivalent and in three cases (2.9%) the Wave-T1-SPACE was preferred for showing less noise. Based in those results, Wave-T1-SPACE failed the noninferiority test for motion (P=0.97), and for noise (P=1). Nevertheless, Wave-T1-SPACE was considered noninferior for the overall diagnostic quality (P=0.03), with nearly all exams (91 cases, 88.3%) rated as equivalent. Ten cases (9.7%) had the standard sequence preferred for diagnostic quality, of which 8 were preferred without affecting the final clinical diagnosis, and two would affect the final clinical diagnosis. One of those cases had extensive motion artifacts in the Wave-T1-SPACE sequence and the other had a metallic CSF-shunt valve over the skull causing susceptibility artifacts that became allased in the Wave-T1-SPACE and could be mistakenly interpreted as additional enhancing lesions in the axial plane, although they were easily interpreted as artifacts in other planes. Two cases (2%) had Wave-T1-SPACE preferred for diagnostic quality, one of which would not affect the final clinical diagnosis, whereas in the other the Wave-T1-SPACE sequence was preferred to the extent that it would affect the final clinical diagnosis due to the presence of extensive motion artifact on the standard sequence. There was no difference in results when comparing the two sequences by the subgroup according to the

coil array used during scanning (57 participants (55%) used the 32-channel coil; 46 participants (45%) used the 20-channel coil).

Discussion

This study compared an ultrafast 3D post-contrast Wave-T1-SPACE to the standard 3D T1-SPACE sequence in the diagnostic evaluation of abnormal intracranial enhancement. In addition to providing a three-fold reduction in acquisition time, Wave-T1-SPACE was noninferior in the delineation of enhancing parenchymal, leptomeningeal and dural abnormalities. Wave-T1-SPACE images were slightly more susceptible to noise artifacts compared to the standard T1- SPACE sequence, but this difference did not interfere with the diagnostic quality needed for a final clinical diagnosis. Our results support the advantages of lesion detection using an accelerated thin-slice 3D SE-based pulse sequence, and the gains in saved acquisition time were projected to improve patient comfort and throughput. Therefore, our findings support the idea that Wave-T1-SPACE could replace standard T1-SPACE for the clinical evaluation of enhancing brain lesions.

In addition to providing equivalent high-resolution evaluation of enhancing lesions as compared to the standard sequence, the adoption of Wave-T1-SPACE enables more efficient use of intrinsic advantages of this technique, such as the magnetization transfer effect obtained by the multiple refocusing pulses that cause off-resonance saturation and reduces the signal intensity in the background white matter.¹⁶ This effect allows contrast-enhancing lesions stand out in the homogeneously suppressed signal intensity of the background parenchyma on SPACE. Moreover, 3D Wave-T1-SPACE presents an inherent black blood effect that improve the specificity for the detection of enhancing lesions near the venous sinuses, as well as optimizing the characterization of intralesional flow-voids by removing the signal coming from vascular flow-related artifacts⁴ (Figure 4).

The Wave-CAIPI encoding approach has been successfully applied to other imaging sequences providing complementary contrasts such as susceptibility weighted imaging (SWI) ^{11,47} and non-enhanced T1 MPRAGE for volumetric brain measurement.¹⁸ The savings in acquisition time could be improved with the combined use of multiple accelerated sequences that shorten the overall exam time without loss of clinically relevant information. We believe the integration of multiple Wave-CAIPI-based 3D acquisitions could directly benefit patients and their providers by synergistically reducing acquisition times and increasing scan throughput. As a practical note, we have fully replaced the standard T1 SPACE sequence with the Wave-T1-SPACE sequence in all our clinical protocols that use a T1 SPACE sequence, achieving improvements in patient turnaround times and operational capacity.

Our study has several limitations. First, we observed slightly greater artifacts with Wave-T1-SPACE than standard T1-SPACE. Artifacts in 3D SE-based sequences, including SPACE, onginate from a variety of mechanisms, including bulk patient motion, vascular and CSF flow-related artifacts, signal evolution during the variable flip-angle echo-train, B1 inhomogeneity, free-induction-decay (FID) related artifacts, and any artifacts that may arise due to restdual issues with the calibration and the parallel imaging method employed.⁹ Because it can be difficult for the radiologist to be certain of the mechanism of a given artifact, we considered that the perception of motion and the background image noise would put together these different causes of artifact in more realistic categories. Possible explanations for the increased artifacts observed in Wave-T1-SPACE include interactions between the Wave-CAIPI approach and motion/flow-related artifacts, conceivably exacerbated by high vascular signal in the presence of gadolinium contrast, FID and other 3D SE related artifacts, or imperfections in the Wave-CAIPI acquisition and reconstruction procedure itself. Even though these factors did not result in the obscuration of any enhancing lesions and did not alter the radiologists' overall assessment of diagnostic quality,

further evaluation of the underlying causes and strategies for artifact mitigation is desirable to provide a more general application of Wave-T1-SPACE in the clinical setting.

Second, although we sought to acquire an equal number of cases with post-contrast Wave-T1-SPACE before standard T1-SPACE and vice versa to control for potential differences in the conspicuity of enhancing lesions related to the elapsed time for image acquisition after contrast injection, more studies had standard T1-SPACE acquired before Wave-T1-SPACE (65 [63%] versus 38 [37%] cases).

Third, while readers were blinded to the acquisition protocol, some aspects of the images might have allowed the readers to identify the pulse sequence being evaluated, which could introduce bias. We sought to minimize this possibility by matching the most important parameters that determine image quality and image contrast between acquisitions, including TR, TE flip angle, and spatial resolution. Lastly, the selection of a proper noninferiority margin for diagnostic imaging studies is often challenging. Our choice was advised by a review of similar imaging-based noninferiority publications and consensus among our group of neuroradiologists that the new sequence could be considered noninferior if the standard sequence were preferred in fewer than 15% of cases. Since this threshold is subjective, we also reported the critical value ($P_{critical}$), equivalent to the upper bound of a 95% confidence interval, for the proportion of cases in which the standard sequence was preferred.

In conclusion, contrast-enhanced Wave-CAIPI 3D T1-SPACE was noninferior to the standard 3D T1-SPACE sequence in the visualization of enhancing lesions and overall diagnostic quality while providing three-fold reduction in scan time compared to a standard post-contrast 3D T1-SPACE sequence. The clinical application of the Wave-CAIPI approach to T1WI spin-echo based contrast-enhanced imaging may enable more efficient utilization of MR resources without loss of clinically important information, while preserving the advantages of SE-based sequences in the evaluation of pathological enhancement.

anuscri Acknowledgments and Disclosure

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 Table 1: Clinical characteristics of the patients





Acq	Acquisition time			4min 19s	1min 40s
GRA	PPA = generalized autoca seconds; mm = millimeters	librating partial parallel acc ; min = minutes; s = second	juisition; TR ds.	= repetition time; TE = ec	sho time; msec =
Tab cont seq	le 3. Semiquantitativ trast Standard uences were randoml	e scoring criteria use T1-SPACE y positioned on either	ed for the vs. the right	head-to-head comp Wave-T1-SPA or left side of the s	arison of post- CE. The screen, labeled
Parameter	Favors Image A			Favors Image B	
	Score -2	Score -1	0	Score +1	Score +2
Visualization of Enhancement Noise	Visualization of enhancement is superior on Image A; lesions are missed on Image B Background noise of the image B is perceptibly greater than the image A and affects the visualization of underlying structures	Visualization of enhancement is prefer ed on Image A, but lesions are still visualized on Image B e Background noise of the image B is perceptibly greater than the image A and does not affects the visualization of underlying structures	r Equivalent Equivalent	Visualization of enhancement is preferred on Image B, but lesions are still visualized on Image A Background noise of the image A is perceptibly greater than the image B and does not affects the visualization of underlying structures	Visualization of enhancement is superior on Image B; lesions are missed on Image A Background noise of the image A is perceptibly greater than the image B and affects the visualization of underlying structures
Motion Artifact	Image B has more motion artifact that obscure small lesions	Image B has more motion artifact, but it does not obscure small lesions	n Equivalent	Image A has more motion artifact, but it does not obscure small lesions	Image A has more motion artifact that obscure small lesions
Overall Diagnostic Quality	Image B has poorer image quality, and the difference affects the final clinical diagnosis	Image B is of lower quality, but the difference does not alter the clinical diagnosis	Equivalent	Image A is of lower quality, but the difference does not alte the clinical diagnosis	Image A has poorer image quality, and the difference raffects the final clinical diagnosis

'Image A' and 'Image B'.



Figure 1. Magnified images of Standard T1-SPACE **(A)** and Wave-T1-SPACE **(B)** reveal comparable effective spatial resolution (sharpness) in delineating thin anatomic structures like the interface between the cortical surface and the adjacent sulci (arrows).



Figure 2. Representative images comparing the post-contrast Standard T1-SPACE and Wave-T1-SPACE sequences. (A) A 40-year-old male with a glioblastoma before treatment, presenting as a large heterogeneously enhancing mass in the right temporoparietal parenchyma. (B) A 55-year-old male with lymphoma presenting as multiple nodular foci of leptomeningeal enhancement throughout the bilateral cerebellar hemispheres. (C) A 73-year-old female with a parietal dural-based mass consistent with a meningioma. (D) A 74-year-old male with a previously treated glioblastoma in the right occipital lobe and splenium of the corpus callosum with involvement of the ependymal surfaces of the posterior lateral ventricles R = Acceleration factor



Figure 3. Balloon plot showing the results of the head-to-head comparison of standard T1-SPACE and Wave-T1-SPACE for visualization of enhancing parenchymal, dural, leptomeningeal, and ependymal lesions, including the evaluation of noise and motion artifacts, as well as the overall diagnostic quality. The percentage of cases receiving a given score is indicated below each circle, which is also represented by the circles' size and color. A zero-score indicates equivalency, negative scores (left) favor standard T1-SPACE, and positive scores (right) favor Wave-T1-SPACE. The P-value of the noninferiority test is provided for each evaluated category. The critical value ($P_{critical}$) is also provided, corresponding to the upper bound of the 95% confidence interval for the proportion of cases in which Standard T1-SPACE was preferred. N = population size.



Figure 4. (A) A 51-year-old male with a presumed meningioma underlying the right tentorial leaflet with **invasion** of the adjacent right transverse sinus (arrows) which remains patent without evidence of thrombosis. **(B)** A 22-year-old male with von Hippel-Lindau syndrome presenting with multiple hemangioblastomas in the posterior fossa, status post suboccipital craniectomy and decompression. The black-blood effect of the spin echo-based T1-SPACE improves the visualization of the serpiginous flow voids surrounding the solid mass (arrowheads). R Acceleration factor