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Clinical Validation of Wave-CAIPI Susceptibility-Weighted Imaging for Routine Brain MRI at 1.5T

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HIGHLIGHTS

- Wave-SWI accelerated the acquisition of 3D high-resolution susceptibility images in 70% of the acquisition time of the conventional T2*GRE.
- Wave-SWI performed superior to T2*w-GRE for visualization of pathology, signal dropout artifacts, and overall diagnostic image quality.
- Wave-SWI was noninferior to standard SWI for visualization of normal anatomy and pathology, signal dropout artifacts, and overall diagnostic image quality.

ABSTRACT

Objectives: Wave-CAIPI (Controlled Aliasing in Parallel Imaging) enables dramatic reduction in acquisition time of 3D MRI sequences such as 3D susceptibility-weighted imaging (SWI) but has not been clinically evaluated at 1.5T. We sought to compare highly-accelerated Wave-CAIPI SWI (Wave-SWI) with two alternative standard sequences, conventional three-dimensional SWI and two-dimensional T2*-weighted Gradient-Echo (T2*w-GRE), in patients undergoing routine brain MRI at 1.5T.

METHODS: In this study, 172 patients undergoing 1.5T brain MRI were scanned with a more commonly used susceptibility sequence (standard SWI or T2*w-GRE) and a highly-accelerated Wave-SWI sequence. Two radiologists blinded to the acquisition technique scored each sequence for visualization of pathology, motion and signal dropout artifacts, image noise, visualization of normal anatomy (vessels and basal ganglia mineralization), and overall diagnostic quality. Superiority testing was performed to compare Wave-SWI to T2*w-GRE, and non-inferiority testing with 15% margin was performed to compare Wave-SWI to standard SWI.

RESULTS: Wave-SWI performed superior in terms of visualization of pathology, signal dropout artifacts, visualization of normal anatomy, and overall image quality when compared to T2*w-GRE (all $P < 0.001$). Wave-SWI was non-inferior to standard SWI for visualization of normal anatomy and pathology, signal dropout artifacts, and overall image quality (all $P < 0.001$). Wave-SWI was superior to standard SWI for motion artifact ($P < 0.001$), while both conventional susceptibility sequences were superior to Wave-SWI for image noise ($P < 0.001$).

CONCLUSIONS: Wave-SWI can be performed in a 1.5T clinical setting with robust performance and preservation of diagnostic quality.

ABBREVIATIONS:

CAIPI = Controlled Aliasing In Parallel Imaging;

SWI = Susceptibility-Weighted Imaging;

T2*w-GRE = T2*-Weighted Gradient-Echo

Keywords:

1. Susceptibility-Weighted Imaging
2. Controlled Aliasing In Parallel Imaging
3. Brain
4. Magnetic resonance imaging

Introduction

Susceptibility-weighted imaging (SWI) provides complimentary information to structural MRI sequences, and is particularly valuable in the evaluation of hemorrhagic, vascular or mineralized lesions.[1,2] SWI provides greater sensitivity for small hemorrhagic foci,[3–5] but suffers from longer acquisition times (typically 4-5 minutes or more)[1–5] comparing to T2*-weighted gradient-echo imaging (T2*w-GRE), which may limit widespread clinical application and increase sensitivity to motion.

To address this limitation, a highly accelerated SWI acquisition using Wave-Controlled Aliasing In Parallel Imaging (Wave-CAIPI)[6] was recently validated for clinical brain imaging at 3T.[7] However, despite the increasing prevalence of higher field imaging, 1.5T scanners predominate in clinical practice, comprising approximately 70-80% of clinical MRI scanners in the USA, Canada, and United Kingdom.[8–10] Further, scanning at 1.5T is sometimes required even when 3T systems are available (e.g., many cardiac devices are MR-conditional at 1.5T),[11] and is generally preferred over 3T for patients with metallic hardware (e.g., braces) that may produce severe susceptibility artifacts at higher field strengths.[12] Wave-CAIPI has not been previously evaluated at 1.5T, where the lower signal-to-noise ratio and susceptibility contrast pose additional challenges and the clinical performance previously demonstrated at 3T[7] cannot be assumed. Validation of Wave-CAIPI SWI (Wave-SWI) at 1.5T may facilitate broader use of SWI in routine brain MRI protocols, increasing diagnostic sensitivity for a wide range of pathology[2–5] while reducing scan time and motion artifacts.

In this study, we compared Wave-SWI to two conventional alternatives, standard 3D SWI and 2D T2*w-GRE, in patients undergoing routine brain MRI at 1.5T. We aimed at comparing an ultrafast Wave-SWI to standard T2*w-GRE with similar acquisition time, and to standard SWI despite a 70% reduction in scanning time.

Materials and Methods

Approvals and Disclosures

This prospective single-institutional study conformed with the Health Insurance Portability and Accountability Act (HIPAA) and was approved by our Institutional Review Board.

Patients

We prospectively enrolled adult patients who were scheduled for outpatient brain MRI for clinically indicated reasons on one of two 1.5T MRI systems (MAGNETOM Aera and Avanto, Siemens Healthcare), from January to March 2019. The exclusion criteria were similar to those for routine clinical MR imaging. All patients gave verbal consent prior to MRI scanning. Written consent was not required by the IRB since no significant time (less than 2 minutes) was added to each exam.

Wave-SWI Pulse Sequence and Processing

Wave-SWI images were obtained using a prototype dual-echo 3D gradient-echo pulse sequence and reconstruction pipeline (Siemens), with approximately 60 seconds online reconstruction time. Phase unwrapping of the multi-echo phase data was performed, and the images were combined using a weighted combination that accounted for the TE phase evolution. The formula for calculation of the weighting factors used to combine the two echoes is provided in the Online Supplemental Material. High-pass filtered phase images and susceptibility-weighted images were then produced using the Standard vendor processing.

MRI Protocol

Images were obtained using a 20-channel head and neck receiver coil array (Siemens). All exams included one of two conventional susceptibility sequences (either standard SWI or T2*w-GRE) based on standardized institutional brain MRI protocols. In addition, the Wave-SWI sequence was performed immediately before or after the conventional susceptibility sequence. In some cases, with possible patient

motion on the later sequence, the acquisition order was reversed at the mid-point of the study. Pulse sequence parameters for the Wave-SWI, standard SWI, and T2*w-GRE sequences are provided in Online Table 1.

Image Evaluation

Two neuroradiologists (G.F. and J.C. with 7 and 8 years of experience, respectively) blinded to clinical history and details of the acquisition protocol independently reviewed the processed SWI images for all subjects in a randomized order. Because we sought to compare the visualization of pathology between sequences, cases in which no abnormality was identified by either radiologist underwent a limited evaluation for image quality and visualization of normal anatomy. For all cases in which at least one focus of abnormal susceptibility signal was identified, a predefined semi-quantitative scoring system[13] was used to compare Wave-SWI with the conventional susceptibility sequence (standard SWI or T2*w-GRE). The images were randomly selected left and right screen positions side by side on a single monitor. The raters compared the two sequences in terms of: visualization of pathology; signal dropout artifact; motion artifact; image noise; overall diagnostic image quality; visibility of normal vessels; and visualization of basal ganglia mineralization. Images were graded using a 5-point scale, where negative numbers favored the sequence on the left and positive numbers favored the sequence on the right side of the screen (Online Table 2). A third neuroradiologist (S.H.) with 9 years of experience adjudicated the divergences between readers. For cases in which no abnormal susceptibility signal was identified, the same two radiologists evaluated signal dropout artifact, motion artifact, image noise, visibility of normal vessels and visualization of basal ganglia mineralization, with discrepancies resolved by consensus.

Statistical analysis

Based on our previous experience with Wave-SWI at 3T,[7] we hypothesized that Wave-SWI would be superior to T2*w-GRE and non-inferior to standard SWI. Wilcoxon signed-rank test was used to compare the ordinal radiologist scores for superiority testing, with the null hypothesis (H0) of no difference

between sequences. For non-inferiority testing,[14] a non-inferiority margin (Δ) of 15% was selected, with the null hypothesis (H0) that the proportion of cases where standard SWI was preferred over Wave-SWI was > 15%. We used the Z statistic to calculate the probability of standard SWI being preferred over Wave-SWI in more than 15% of cases (H0>Δ) with a type 1 error rate (α) of 0.05. We also reported the critical value, $P_{critical}$,[15] corresponding to the upper bound on the 95% confidence interval for the proportion of cases where standard SWI was preferred over Wave-SWI. If non-inferiority could not be demonstrated for a given variable, post-hoc superiority testing was performed using the Wilcoxon signed-rank test. Superiority testing was also performed for motion artifact, to test whether the shorter acquisition time of Wave-SWI resulted in reduced sensitivity to motion. The primary outcome was defined as the 'visualization of pathology' score for the comparison of Wave-SWI and standard SWI. The sample size was estimated for a single proportion (proportion of cases where visualization of pathology was preferred on standard SWI over Wave-SWI), for an effect size of 0.15, a type 1 error rate (α) of 0.05, and a power (1–β) of 0.90. According to this calculation, a minimum of 63 cases was required. Weighted Cohen κ coefficient was used to evaluate inter-rater agreement, according to the standard interpretation of Landis and Koch.[16] A Bonferroni correction for multiple comparisons was applied, and the corrected threshold of 0.05 / (7 comparisons) = 0.007 was used to determine statistical significance. Statistical calculations were performed using R version 3.4.3.

Results

Consecutive 172 patients were enrolled in the study (49.5% male; mean age 57.9 years, age range 20–89 years). An abnormality was identified on at least one of the magnetic susceptibility sequences in 112 of these cases, including 67 cases with comparison of Wave-SWI to standard SWI and 45 cases with comparison of Wave-SWI to T2*w-GRE. Demographics and clinical indications for MRI scanning are provided in Online Table 3. Inter-rater agreement for the radiologist scores ranged from *moderate* to *substantial* (κ = 0.76 for visualization of pathology; 0.76 for signal dropout artifact; 0.52 for motion artifact; 0.73 for image noise; 0.74 for overall diagnostic quality; 0.70 for visualization of normal vessels; and 0.47 for visualization of basal ganglia mineralization). For the cases in which no abnormality was identified by either radiologist, the comparison of Wave-SWI to T2*w-GRE is provided in Online Figure 1, and the comparison of Wave-SWI to standard SWI is provided in Online Figure 2.

Representative images comparing Wave-SWI and T2*w-GRE are provided in Figure 1. Radiologist scores for the side by side comparison of Wave-SWI and T2*w-GRE are provided in Figure 2. Wave-SWI was superior for visualization of pathology, signal dropout artifacts, visualization of normal vessels, visualization of basal ganglia mineralization, and overall diagnostic quality when compared to T2*w-GRE (all $P < 0.001$). This included 21 cases where the differences in image quality would alter the clinical diagnosis provided by the radiologist (i.e., scores of +2 favoring Wave-SWI). T2*w-GRE was superior to Wave-SWI for image noise ($P < 0.001$), although there were no cases where this difference would alter the clinical diagnosis. There was a trend toward increased motion artifact on Wave-SWI compared to T2*w-GRE ($P = 0.008$, not significant after correction for multiple comparisons).

Representative images comparing Wave-SWI and standard SWI are provided in Figure 3. Radiologist scores for the head-to-head comparison of Wave-SWI and standard SWI are provided in Figure 4. Wave-SWI was non-inferior to standard SWI for visualization of pathology, signal dropout artifact, visualization of normal vessels, visualization of basal ganglia mineralization, and overall diagnostic quality (all $P < 0.001$). Wave-SWI was superior to standard SWI with respect to motion artifact ($P < 0.001$), while standard SWI was superior to Wave-SWI with respect to image noise ($P <$

0.001). However, there were no cases where these differences in motion artifact or image noise would alter the clinical diagnosis provided by the radiologist (i.e., no scores of +2 or -2; Figure 4).

Representative images in the presence of a variety of metallic implants are provided in Online Figure 3. Standard SWI and Wave-SWI provided a similar pattern of signal dropout in the presence of metallic implants, including craniotomy and cranioplasty hardware, aneurysm clips, embolic coil material, ventricular catheters, and scalp fiducials used for radiotherapy planning.

Discussion

We compared a highly accelerated Wave-SWI sequence to two universally used alternatives, standard SWI and T2*w-GRE, for outpatient brain MR imaging at 1.5T. We included consecutive patients without screening by indication to provide a representative sample of the pathology seen in routine clinical practice.

Wave-SWI was better than T2*w-GRE for visualization of pathology, signal dropout artifact, and overall diagnostic image quality. The superiority of conventional SWI over T2*w-GRE has been demonstrated in prior studies,[3–5] however T2*w-GRE is still commonly used in routine practice, in part due to its shorter acquisition time. These results suggest that Wave-SWI could substitute T2*w-GRE for most indications, increasing diagnostic sensitivity without prolonging the overall acquisition time (Wave-SWI was slightly faster than T2*w-GRE, 1:37 min versus 2:28 min).

Wave-SWI was non-inferior to standard SWI for visibility of pathology, signal dropout artifacts and overall diagnostic quality, despite a 3-fold decrease in the acquisition time (1:37 min versus 4:56 min). Wave-SWI resulted in reduced motion artifacts compared to standard SWI, as a result of the shorter scan time. Wave-SWI showed subjectively greater image noise, an expected finding given that SNR scales with the square root of the acceleration factor *R* even in the absence of g-factor related noise amplification.[6] However, there were no cases where the difference in motion artifact or noise level between sequences would alter the radiologists' diagnosis. These results suggest that Wave-SWI could replace standard SWI for most indications, providing similar diagnostic capability with a 70% decrease in scan time.

Our results parallel those of a recent study evaluating Wave-SWI for brain imaging at 3T.[7] While fast imaging methods are often initially evaluated at 3T, where improved SNR partially mitigates against the noise amplification that occurs with high acceleration factors, 1.5T scanners continue to predominate in clinical practice. For example, recent estimates suggest that 1.5T scanners comprise approximately 69%, 83%, and 79% of the clinical install base in the USA,[8] Canada,[9] and United Kingdom,[10] respectively. Furthermore, scanning at 1.5T may be preferred over 3T in some settings, for example in patients with implantable devices that are MR-conditional at 1.5T but not at 3T,[11] or in the presence of metallic hardware that can cause severe susceptibility artifacts at higher field strengths.[12] To our knowledge, the present study represents the first clinical validation study of Wave-CAIPI at 1.5T, where the lower field strength results in both lower SNR and lower susceptibility contrast. This work may serve as a benchmark for future studies to build upon in translating rapid imaging techniques such as Wave-CAIPI into broader clinical practice. With respect to the imaging of specific implants, it is notable that the max slew rate for the wave gradient is editable in the vendor console software. In this study, a maximum slew rate of 160 T/m/s was used, but a lower max slew rate could be adopted to meet the requirements of a specific implant, if needed.

In addition to high sensitivity for blood products, SWI can be useful for the differentiation of blood products and mineralization, specifically through the evaluation of filtered phase maps. In our experience, reliable differentiation is often limited due to aliasing artifacts, but in some cases the distinction can be made. Although this differentiation was not the purpose of the present study, we found that the filtered phase maps were qualitatively similar between the Wave-SWI and standard SWI sequences (see Online Figure 4 for representative examples).

Our study has several limitations. First, a reference standard is required to report standard measures of diagnostic accuracy. For example, visualization of hemorrhage on Wave-SWI but not on standard SWI might not represent a false positive finding, and could alternatively mirror greater motion artifact on the standard SWI sequence obscuring the relevant finding. To address this limitation, we compared the images in blinded head-to-head comparison using pre-defined and previously validated

scale that assessed the factors contributed to the radiologist in providing a clinical diagnosis (Online Table 2). Second, a non-inferiority margin selection for imaging studies is difficult and inherently somewhat subjective. We selected a non-inferiority margin of 15% based on previous similar studies,[17,18] and our group of neuroradiologists are in agreement that if the standard sequence was preferred in fewer than 15% of cases, Wave-SWI could be non-inferior to standard SWI with respect to a given variable. Third, although the raters were blinded to the details of the imaging protocols, features of the images may allow the rater to identify the sequence being evaluated, particularly for the comparison of Wave-SWI and T2*w-GRE.

In summary, highly accelerated Wave-CAIPI SWI provides superior visibility of pathology and overall image quality compared to T2*w-GRE for routine brain imaging at 1.5T, and is non-inferior to standard SWI despite a 70% reduction in scan time. Clinical application of Wave-SWI at 1.5T could result in more efficient utilization of valuable MRI resources, with fewer motion artifacts and non-diagnostic exams.

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Compliance with Ethical Standards.

3. Guarantor

The scientific guarantor of this publication is John Conklin and Susie Huang. The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

4. Conflict of Interest

The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

5. Statistics and Biometry

M. Gabriela Figueiro Longo, one of our authors, has significant statistical expertise and provided statistical advice for this manuscript.

6. Informed Consent

Written consent was not required by the IRB since no significant time (less than 2 minutes) was added to each exam.

7. Ethical Approval

Institutional Review Board approval was obtained.

8. **Methodology**

•Prospective

•Comparative

•Performed at one institution

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Figure Legends:

Figure 1: MR images of T2*-weighted GRE (T2*w-GRE) and Wave-CAIPI SWI (Wave-SWI). **A** and **B:** Small hemorrhagic foci in the right parietal lobe (arrows) and cerebellar hemisphere (arrowheads) reflecting posttreatment related changes in a 41-year-old woman with history of right parietal temporal craniotomy for tumor resection. The visibility of the scattered foci of susceptibility signal are better on Wave-SWI than T2*w-GRE. **C:** Hemorrhagic foci along the periphery of a right temporal lobe surgical cavity are better visualized on Wave-SWI than T2*w-GRE. **D:** Left anterior temporal lobe surgical cavity is better visualized on Wave-SWI and partially obscured on T2*w-GRE due to signal dropout artifact. **E:** Hemosiderin staining and scattered microhemorrhages (arrowheads) in the right frontal lobe due to a combination of post-surgical and post-treatment changes. The microhemorrhages are not visualized on the T2*w-GRE sequence, and the hemosiderin staining is less conspicuous. **F:** Status post-tumor resection demonstrating multiple areas of susceptibility, well delineated in both sequences.

Figure 2: Balloon plot showing the results of the head-to-head comparison of T2*-weighted gradient-echo (T2*w-GRE) and Wave-CAIPI susceptibility-weighted imaging (Wave-SWI). Each circle represents the percentage of cases associated with a given score based on the size and color, from a total of 45 abnormal cases. Negative scores (left) favor T2*w-GRE, and positive scores (right) favor Wave-SWI. Wilcoxon signed-rank test was used to compare the ordinal radiologist scores between sequences. *P*-values below the Bonferroni adjusted threshold of 0.007 indicate superiority of Wave-SWI compared to T2*w-GRE.

Figure 3: Axial MR images comparing standard SWI and Wave-CAIPI SWI (Wave-SWI). **A:** 70-year-old woman presenting with multiple cortical and juxtacortical punctate susceptibility foci due to amyloid angiopathy. **B:** Numerous small hemangioblastomas within the temporal and occipital lobes in a 57-year-old man with history of Von Hippel Lindau disease. The slightly decreased SNR in the Wave-SWI image does not limit the visualization of these small lesions. **C:** Serpiginous foci of susceptibility effect in the

parafalcine region consistent with an arteriovenous malformation. In this example, motion artifact is seen on the standard SWI sequence but not the Wave-SWI sequence. **D:** 57-year-old man with a hemorrhagic metastasis in the posterior fossa abutting the 4th ventricle, equally well seen on both sequences. Signal dropout artifacts are similar between the two sequences. **E:** Cavernous malformation in the left temporal lobe well demonstrated in both sequences. **F:** 63-year-old woman with an isolated microhemorrhage in the left pre-central gyrus, well seen on both sequences.

Figure 4: Balloon plot demonstrates the results of the side-by-side comparison of standard susceptibility-weighted imaging (SWI) and Wave-CAIPI SWI (Wave-SWI). The cases (correlated with the size and color of each circle) were assigned a given score, from a total of 67 abnormal cases. The *P*-values for non-inferiority of Wave-SWI compared to standard SWI are reported with a non-inferiority margin of 15%. *P*-values below than the Bonferroni adjusted threshold of 0.007 indicate non-inferiority of Wave-SWI compared to standard SWI. $P_{critical}$ corresponds to the upper bound on a 95% confidence interval for the proportion of cases where standard SWI was preferred over Wave-SWI.