Time-efficient, High Resolution 3T Whole Brain Quantitative Relaxometry using 3D-QALAS with Wave-CAIPI Readouts

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Short title: Fast whole-brain quantitative imaging using wave-CAIPI 3D QALAS
ABSTRACT

Purpose: Volumetric, high-resolution, quantitative mapping of brain tissue relaxation properties is hindered by long acquisition times and signal-to-noise (SNR) challenges. This study, for the first time, combines the time-efficient wave-CAIPI readouts into the 3D-quantification using an interleaved Look-Locker acquisition sequence with a $T_2$ preparation pulse (3D-QALAS) acquisition scheme, enabling full brain quantitative $T_1$, $T_2$ and proton density (PD) maps at 1.15 mm$^3$ isotropic voxels in only 3 minutes.

Methods: Wave-CAIPI readouts were embedded in the standard 3D-QALAS encoding scheme, enabling full brain quantitative parameter maps ($T_1$, $T_2$, and PD) at acceleration factors of $R=3x2$ with minimum SNR loss due to g-factor penalties. The quantitative parameter maps were estimated using a dictionary-based mapping algorithm incorporating inversion efficiency and $B_1$ field inhomogeneity. The quantitative maps using the accelerated protocol were quantitatively compared against those obtained from conventional 3D-QALAS sequence using GRAPPA acceleration of $R=2$ in the ISMRM NIST phantom, and ten healthy volunteers.

Results: When tested in both the ISMRM/NIST phantom and ten healthy volunteers, the quantitative maps using the accelerated protocol showed excellent agreement against those obtained from conventional 3D-QALAS at $R_{GRAPPA}=2$.

Conclusion: 3D-QALAS enhanced with wave-CAIPI readouts enables time-efficient, full brain quantitative $T_1$, $T_2$, and PD mapping at 1.15 mm$^3$ in 3 minutes at $R=3x2$ acceleration. When tested on the NIST phantom and ten healthy volunteers, the quantitative maps obtained from the accelerated wave-CAIPI 3D-QALAS protocol showed very similar values to those obtained from the standard 3D-QALAS ($R=2$) protocol, alluding to the robustness and reliability of the proposed methods.

Keywords: wave-CAIPI, 3D-QALAS, time-efficient quantitative mapping, $T_1$/$T_2$/PD mapping
1. INTRODUCTION

Magnetic resonance imaging (MRI) is a powerful tool capable of probing and visualizing the human body non-invasively. Its use in clinical settings is mainly dominated by MR acquisitions that provide a qualitative assessment of tissues’ properties, where contrast-weighted images are used to make decisions related to the presence or absence of particular abnormalities. Specifically, neuroimaging protocols routinely include structural acquisitions such as $T_1$-weighted ($T_1$w) MPRAGE (1), $T_2$-weighted ($T_2$w) turbo-spin echo, $T_2$-weighted fluid-attenuated inversion recovery ($T_2$w-FLAIR) (2), or a $T_2^*$-weighted ($T_2^*$w) 3D gradient recalled echo (GRE) from which susceptibility weighted imaging (SWI) (3) can be derived. Furthermore, typical runs of these standard sequences underutilize parallel imaging acceleration available on today’s modern hardware, leading to acquisition inefficiency and making structural imaging consume a substantial portion of the scan time budget. Although this mode of operation has been used in clinical settings for decades now, it often prohibits the detection of subtle tissue changes in various pathologies, as the limited set of different contrast-weighted volumes might not provide the contrast needed to differentiate between healthy and abnormal tissue.

To that end, during the past decade, there has been a significant push toward the development of quantitative MRI (qMRI) techniques that aim to provide quantitative estimates of tissue relaxation parameters. These methods (4–9) have developed different pulse sequences with specific, carefully chosen set/range of imaging parameters (e.g. inversion times, echo times, repetition times, etc), and use Bloch simulations of the acquired signals to calculate $T_1$, $T_2$, $T_2^*$ or proton density (PD) maps in quantitative units (percentage for the PD maps, and seconds for the others). In clinical settings, qMRI can help identify physiological changes undetected by qualitative imaging (10), provide specific information to characterize pathologies (11,12), help assess treatment response and repair processes (13), and detect disease before morphological changes (14). qMRI has been applied in epilepsy (15), with some studies showing the correlation between $T_1$ value changes across cortical layers and myelin histological staining in those same brain regions (16,17), while other studies demonstrating that a $T_2$ value increase is concordant with the putative seizure onset (18,19). Similarly, qMRI has been applied in patients with multiple sclerosis, linking disease activity with $T_2$ value changes in normal-appearing white matter (20). Similarly, other studies (21,22) have also shown that $T_1$ relaxation values change in both lesions and white matter in patients with multiple sclerosis and that these changes correlate with increased patients’ disabilities (22).
Moreover, qMRI is also beneficial in research settings, as standard qualitative sequences produce system-dependent pixel intensities that cannot be meaningfully compared across sites. Therefore, qMRI is well-suited for multi-center studies, not only because it obtains objective measures of tissue-specific parameters that do not (ideally) depend on the particular sequence or hardware used to obtain them, but also because it has demonstrated significantly higher inter-site reproducibility compared to contrast-weighted imaging (23). In addition, qMRI also provides an elegant solution whereby contrast-weighted images can be derived from calculated relaxation parameter maps (24,25).

Besides these benefits, routine deployment of qMRI in clinical and research studies is still quite limited, mainly because all the current qMRI methods are encoding intensive, suffering from long scan times and/or lower spatial resolution. One of the most time-efficient qMRI methods is the 3D quantification using an interleaved Look-Locker acquisition sequence with $T_2$ preparation pulse (QALAS) (9) - a 3D acquisition employing spoiled turbo-flash readouts with interleaved $T_2$-preparation and inversion recovery RF pulses. Specifically, a typical 3D QALAS acquisition includes five turbo-flash readouts separated 900ms apart, with a 100ms long $T_2$-preparation module preceding the first readout and the remaining four readouts following an inversion pulse that captures $T_1$ dynamics. The 3D-QALAS sequence has shown a strong correlation with reference $T_1$, $T_2$, and PD values in the NIST/ISMRM phantom and high reproducibility in brain imaging (25). The estimated parameter maps further lend themselves to the generation of contrast-weighted images (e.g. $T_1w$, $T_2w$, FLAIR, etc) via Bloch simulation. It has been shown that cortical thickness measurements from synthetically generated (simulated) $T_1w$ volumes, obtained from a 12 minutes long QALAS acquisition at 1mm³ isotropic voxels, have high reproducibility and are in agreement with those obtained from a standard MPRAGE (26). Even though the richness of the data obtained in a single 3D QALAS scan is indisputable - $T_1$, $T_2$, PD maps, as well as synthesized volumes that can be easily tuned to different contrast weightings - the overall scan times of over 10 minutes still remain the main hurdle that prevents the widespread use of this technique in both clinical and research studies.

Previous attempts to mitigate the long acquisition times of the 3D QALAS sequence have incorporated compressed sensing acceleration (27), enabling multi-parametric quantitative whole-brain imaging at 1mm³ isotropic voxels in a bit less than 6 minutes. The main aim of this work is to accelerate 3D QALAS even further (while keeping similar voxel sizes), by using an alternative acceleration scheme - the wave-controlled aliasing in parallel imaging (wave-CAIPI) algorithm - which has been shown to maximize the signal-to-noise ratios (SNR) by minimizing g-factor ratios (28,29). Specifically, by playing sinusoidal gradients along two spatial axes, the
wave-CAIPI encoding scheme spreads the aliasing evenly in all spatial directions, thereby taking full advantage of 3D coil sensitivity distribution, and thus achieving mean and maximum g-factor ratio values of 1.03 and 1.08 at 3T for R = 3×3 acceleration, respectively. Wave-CAIPI has been successfully employed in various different sequences (30–33), including the $T_1$w MPRAGE (34), and it has been successfully deployed in clinical settings, enabling dramatic decreases in the overall scan times compared to the standard, longer clinical protocol, without losing any of the image quality needed for clinical diagnosis (35–38).

This work embeds the time-efficient wave-CAIPI readouts in the 3D QALAS sequence, enabling one to obtain whole brain qMRI in a little over 3 minutes at 1.15mm$^3$ isotropic voxels. It demonstrates that the $T_1$, $T_2$ and PD maps calculated from this accelerated wave-CAIPI QALAS scans show high accuracy when compared with the reference $T_1$, $T_2$ and PD values in the NIST/ISMRM phantom, and are also in good agreement with the equivalent parametric maps obtained from the standard QALAS acquisition (R=2, TA = ~9 minutes) in normal adult volunteers.

2. METHODS

![Pulse sequence diagram of the proposed wave-CAIPI 3D-QALAS sequence. The top of the figure shows one repetition period, where one can see the $T_2$-prep and inversion RF modules, as well as clearly distinguish the five echo-train readouts, each sampling covering the wave-encoding gradients.](image)

**Figure 1:** Pulse sequence diagram of the proposed wave-CAIPI 3D-QALAS sequence. The top of the figure shows one repetition period, where one can see the $T_2$-prep and inversion RF modules, as well as clearly distinguish the five echo-train readouts, each sampling covering the wave-encoding gradients.
same portion of k-space in each TR. The bottom of the figure provides a more detailed view of the timing diagram, where one can easily identify the wave-encoded gradient being played along Gₓ and Gᵧ for a sagittal MRI acquisition.

2.1. Wave 3D-QALAS Sequence

The 3D-QALAS acquisition includes five turbo-flash readouts separated 900ms apart, with a 100ms long T₂-preparation module preceding the first readout and the remaining four readouts following an inversion pulse that captures T₁ dynamics. On the other hand, wave-CAIPI readouts play sinusoidal gradients along two spatial axes, thereby effectively spreading the aliasing evenly in all spatial directions, and thus taking full advantage of 3D coil sensitivity distribution (28,29). Figure 1 shows the sequence diagram of the proposed wave-CAIPI 3D-QALAS sequence. In sagittal imaging, sine and cosine wave gradients are being played in the Gₓ and Gᵧ directions, respectively.

2.2. Experiment

Both phantom and in-vivo experiments were conducted on a 3T MAGNETOM Prisma scanner (Siemens Healthcare, Erlangen, Germany) using a 32-ch head receive array. Wave 3D-QALAS has the following imaging parameters: FOV=240x240x202mm³, matrix size=208x208x176, BW=330 Hz/pixel, echo-spacing=5.9ms, turbo factor=125, TR=4.5s, TE=2.36ms, 10 wave cycles and Rᵧz=3x2 acceleration, yielding a scan time of 3:03 minutes. This accelerated protocol was compared against a standard (Cartesian) 3D-QALAS acquisition with equivalent imaging parameters, but with the conventional acceleration of Rᵧ=2, resulting in an 8.5 minutes scan. Both 3D-QALAS acquisitions were elliptically acquired. Both acquisitions were run on the ISMRM/NIST phantom, and the two sets of quantitative maps were compared using the Bland-Altman analysis. Similarly, the T₁ and T₂ maps agreement between the two acquisitions was also evaluated in vivo on 10 adult volunteers, by directly comparing the estimated values and performing a Bland-Altman analysis on cortical deep gray and white matter regions. These regions were segmented in FreeSurfer (39) using the synthetically generated T₁w volume generated as the following equation.
\[ I_{T_1w} = \frac{\rho \sin \alpha \left(1 - e^{\frac{T_{TE}}{T_1}}\right) e^{\frac{T_{TE}}{T_2}}} {1 - \left(\cos \alpha \cdot e^{\frac{T_{TR}}{T_1}}\right)} \]

where \( \rho \), \( T_1 \), \( T_2 \) are the estimated PD, \( T_1 \), and \( T_2 \) maps, and \( \alpha \) is the excitation pulse degree. We used \( T_{TE}=4\text{ms}, T_{TR}=50\text{ms}, \) and \( \alpha=60^\circ \) to synthesize \( T_{1w} \) images.

### 2.3. Reconstruction and Quantitative Map Estimation

The wave-CAIPI reconstruction used no regularization and was performed online with DICOM images being available on the scanner after the scan was done. For estimating quantitative maps, a dictionary-based matching algorithm was used. In a practical acquisition, RF pulses are not perfectly applied as those are designed. To take into account this, the dictionary was generated for the 50 bins of the inversion efficiency (IE) from 0.75 to 1 and for the 25 bins of the \( B_1 \) field that was directly acquired from the scanner.

### 3. RESULTS

![Figure 2](image-url)

**Figure 2.** Quantitative \( T_1 \) and \( T_2 \) maps calculated from standard R=2 and wave-CAIPI R=3x2 3D-QALAS and their Bland-Altman analysis against the reference values. In the Bland-Altman plots, the center black lines represent the mean differences, while the upper and lower red lines represent the 95% confidence interval. Both standard R=2 and wave-CAIPI R=3x2 3D-QALAS results were quantitatively well aligned with the reference values.
Figure 2 shows the $T_1$ and $T_2$ estimates of the ISMRM/NIST phantom from the conventional (R=2) and wave-CAIPI (R=3x2) 3D-QALAS acquisitions. Vials with $T_1$ and $T_2$ values within the brain’s physiological range were included in the fit, i.e. between 80 - 2500 ms and 5 - 600 ms for $T_1$ and $T_2$, respectively. Bland-Altman analysis of the estimated $T_1$ and $T_2$ values against the reference values of the phantom shows that the $T_1$ and $T_2$ values are well aligned with the reference values. Most of the difference values are within the 95% confidence interval.

Figure 3: Quantitative $T_1$, $T_2$, and PD maps from a representative adult volunteer estimated from the standard Cartesian R=2, and the accelerated R=3x2 wave-CAIPI 3D-QALAS acquisition. Despite the R=3x2 wave-CAIPI scan being almost three times faster, the obtained results show qualitatively similar maps.
Figure 4: Bland-Altman plots comparing estimated $T_1$ and $T_2$ values in the cortical white and deep gray matter in 10 adult volunteers, calculated from standard R=2 and wave-CAIPI R=3x2 3D-QALAS. The center black lines represent the mean differences, while the upper and lower red lines represent the 95% confidence interval. While most points are within the limits of agreement, some minor biases ($T_1$: -1.4ms, $T_2$: -0.15ms) are observed.

Figure 3 shows the $T_1$, $T_2$, and PD maps from both the conventional and wave-CAIPI 3D-QALAS acquisition from a representative subject, demonstrating how similar the two sets of maps are qualitative. Furthermore, Figure 4 shows Bland-Altman analysis of the estimated $T_1$ and $T_2$ values calculated from the two acquisitions in the cortical, white and deep gray matter from all 10 subjects. As seen, the most of $T_1$ and $T_2$ differences between the two acquisitions are within 95% confidence, demonstrating quantitatively that the two acquisitions yield very similar $T_1$ and $T_2$ estimates. Supporting Information Figure S1 shows plot charts of the mean and standard deviations of the $T_1$ and $T_2$ values in these two brain regions in all 10 subjects for both acquisitions.

4. DISCUSSION
In this study, we propose to incorporate the wave-CAIPI strategy into the 3D-QALAS acquisition that typically requires a long scan time. Phantom and in-vivo experiments show that wave
3D-QALAS successfully accelerated the scan from 8.5 minutes to 3 minutes at 1.15 mm³ while preserving the accuracy of the quantitative parameter maps.

We used the online DICOM images reconstructed right after the scan without using any regularization. Enabling a quantitative MR exam in less than 5 minutes at 1mm voxels or lower is possible by incorporating advanced reconstruction techniques (40,41), which are part of our future work. Our recent work using neural network denoisers allows a 2-minute exam, but it requires a network training procedure and offline reconstruction.

**Figure 5.** Bland-Altman analysis of the estimated $T_1$ and $T_2$ values, calculated from standard R=2 3D-QALAS with/without inversion efficiency (IE) and $B_1$ corrections, against the reference values in the ISMRM-NIST phantom.

To bridge the gap between the theoretical signal model and the practically acquired data, we incorporate IE and the $B_1$ field into the dictionary-based matching algorithm. Figure 5 shows the Bland-Altman analysis of the estimated $T_1$ and $T_2$ values using the standard 3D QALAS (R=2) and the reference values in the ISMRM/NIST phantom with and without IE and the $B_1$ field corrections. IE and $B_1$ field corrections significantly reduced the standard deviation of the difference as well as the mean difference values.
5. CONCLUSION

3D-QALAS with wave-CAIPI readouts allows for time-efficient quantitative $T_1$, $T_2$, and PD mapping of the entire brain at 1.15mm$^3$ in 3 minutes, using R=3x2 acceleration. In the quantitative maps in the ISMRM/NIST phantom and 10 adult volunteers, the maps from accelerated wave-CAIPI 3D-QALAS showed very similar values to those obtained from the standard (R=2) 3D-QALAS, alluding to the accuracy and robustness of the proposed methods. The inclusion of IE and $B_1$ field corrections in the dictionary-based matching algorithm further improves the accuracy of $T_1$ and $T_2$ values.

Acknowledgements: This work was supported by research grants NIH R01 EB028797, R03 EB031175, U01 EB025162, P41 EB030006, U01 EB026996, R01 EB017337, U01 HD087211, R01 HD100009 and the NVidia Corporation for computing support.
Supporting Information Figure S1. Plot charts of the mean and standard deviations of the $T_1$ and $T_2$ values in the cortical white and gray matter regions in all 10 subjects for the standard (R=2) and wave-CAIPI (R=3x2) 3D-QALAS acquisitions.
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