

# Iterative Denoising Applied to 3D SPACE CAIPIRINHA: A New Approach to Accelerate 3D Brain Examination in Clinical Routine

Alexis Vaussy<sup>1</sup>; Michael Eliezer<sup>2</sup>; Nicolas Menjot de Champfleur<sup>3</sup>; Emmanuelle Le Bars<sup>3</sup>; Thien Huong Nguyen<sup>4</sup>; Christophe Habas<sup>4</sup>; Alto Stemmer<sup>5</sup>; Thomas Trolen<sup>1</sup>

<sup>1</sup>Siemens Healthineers, Saint-Denis, France

<sup>2</sup>Department of Neuroradiology, Lariboisière University Hospital, Paris, France

<sup>3</sup>Department of Neuroradiology, Hôpital Gui de Chauliac, Montpellier University Medical Center, Montpellier, France

<sup>4</sup>Radiodiagnostic and Medical Imaging, Quinze-Vingts National Ophthalmology Hospital, Paris, France

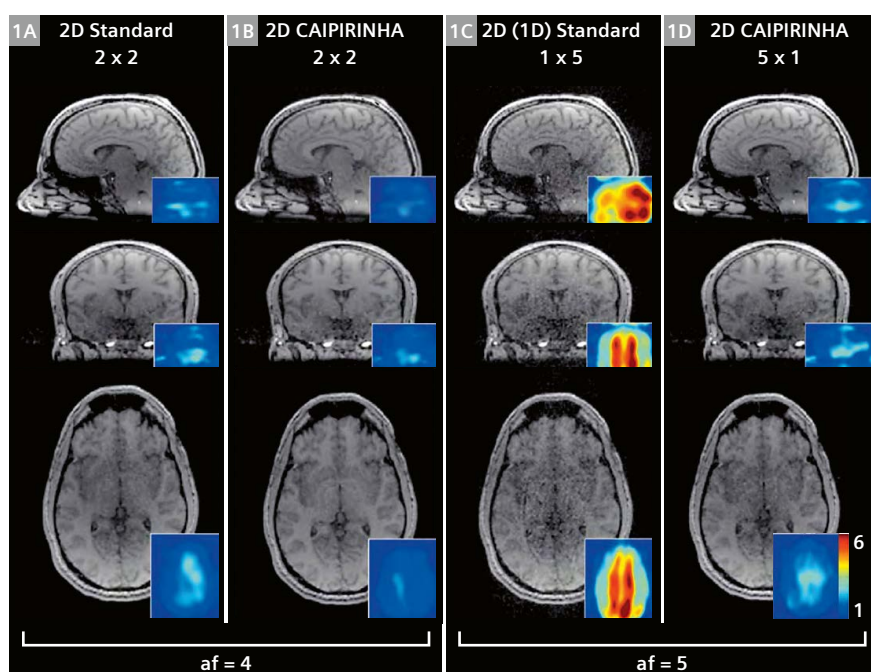
<sup>5</sup>Siemens Healthineers, Erlangen, Germany

## Introduction

Magnetic Resonance Imaging (MRI) is an inherently slow imaging modality, since it acquires multi-dimensional  $k$ -space data through 1-dimensional (1D) free induction decay or echo signals. This can limit the use of long acquisition time sequences in clinical practice, especially for high-resolution or dynamic imaging. For that reason, one of the main aims over the past three decades has been to focus research and development activities on various acceleration techniques. Parallel imaging (PI) is the most commonly used acceleration technique. PI allows to reduce the number of  $k$ -space lines needed and to reconstruct the final images without aliasing artifacts. Parallel imaging has

emerged in the late 90's with SENSE [1] and GRAPPA [2] techniques. These pioneering works demonstrated that spatial diversity information from coil sensitivity maps have additional information that can be exploited to speed-up signal acquisition. The data redundancy in Fourier encoding of 2D or 3D spaces can be used to reduce the required sampling rate, in other words, without the need to satisfy Nyquist sampling criteria to avoid aliasing artifacts.

The penalty for acquiring fewer signals is a loss of signal-to-noise ratio (SNR) in the final image by a factor of the square root of the acceleration factor ( $\sqrt{R}$ ) due to reduced signal averaging [3]. Additionally, PI reconstruc-



**1** In vivo 3D FLASH brain imaging using different acceleration schemes with a 20-channels Head&Neck coil: (1A) Standard 2D-GRAPPA 2 x 2. (1B) 2D-CAIPIRINHA 2 x 2. (1C) Standard 5 x 1. (1D) 2D-CAIPIRINHA 1 x 5. Displayed are central slices in the sagittal, coronal, and axial view. In addition, the corresponding GRAPPA  $g$ -factor maps are shown. Reproduced with permission from [6].

tions result in spatially varying noise amplification in the final images, characterized by the so-called *g*-factor, which depends on the specific geometry of the radiofrequency (RF) coil array used for signal reception.

More recently, Controlled Aliasing in Parallel Imaging Results in Higher Acceleration (CAIPIRINHA) was first introduced for 2D multi-slice imaging [4] and then for volumetric 3D imaging (known as 2D CAIPIRINHHA) [5]. This concept in PI modifies the appearance of aliasing artifacts during data acquisition in order to improve the subsequent PI reconstruction procedure by reducing the *g*-factor for a certain coil geometry and a certain imaging protocol. CAIPIRINHA applied to 3D imaging has been shown to be superior to more standard 2D SENSE/GRAPPA schemes in terms of signal loss and image quality [6], especially in the central part of the field of view (Fig. 1). This acceleration technique has been successfully implemented as a product solution unique to Siemens Healthineers, initially in the FLASH 3D Volumetric Interpolated Breath-hold Examination (f13d\_vibe) sequence for body applications, and later in the Sampling Perfection with Application-optimized Contrasts using a different flip angle Evolutions (SPACE) sequence for spin-echo based 3D acquisitions throughout the human body.

The common theme in these approaches is that the data redundancy can be exploited to reduce the required sampling rate. Since redundant data can be compactly represented in some transform domains, it is also closely related to the concept of ‘*sparsity*’. Ever since the introduction of the Compressed Sensing (CS) theory [7] and the first demonstration of CS MRI by Lustig et al. [8], CS has become the essential tool in modern MR imaging research by exploiting image sparsity to reduce scan time and/or improve image quality.

The three key components of CS are

- the incoherent subsampling of the Fourier space,
- the transformation of the image into a sparse representation, e.g., Wavelet transformation, and
- the non-linear iterative reconstruction to balance between enforcing sparsity and ensuring data consistency.

A comprehensive overview of the CS theory, applications, and limitations can be found in [9] and [10]. CS was first integrated into product sequences on MR systems from Siemens Healthineers for cardiac cine applications, exploiting the 2D+t data redundancy of the beating heart, and for post-gadolinium 3D+t liver dynamics by the aim of Golden-Angle Radial Sparse Parallel (GRASP) MRI acquisition. CS was then integrated into additional sparse applications such as Time-Of-Flight MR angiography

(CS TOF), MR cholangiopancreatography using 3D SPACE readout (CS SPACE), and Slice Encoding for Metal Artifact Correction (CS SEMAC) for musculoskeletal applications in the presence of medical implants.<sup>1</sup>

## Limitation of CS for non-sparse images

MRI is all about tradeoffs. The time available for acquiring the data for an MR image can be deployed in three quite different strategies: SNR, contrast, and spatial resolution. Due to their inherently low sparsity, some applications offer little acceleration potential with CS, these include 2D multi-slice imaging or static morphological 3D sequences where high spatial resolution is essential to analyze fine structures.

For 2D multi-slice imaging, the Simultaneous Multi-Slice (SMS) acceleration technique has been implemented and has already shown great potential to drastically reduce scan time without compromising image quality in MRI diffusion [11]. SMS consists of the simultaneous excitation of multiple slices by means of multiband RF pulses, combined with a slice-GRAPPA reconstruction algorithm to disentangle the simultaneously excited slices prior to standard 2D reconstruction. While this approach is best suited for 2D sequences, it can also be adapted to 3D multi-slab applications. However, it is not applicable for single-slab 3D static morphological scans.

Another potential pitfall of CS for 3D static morphological imaging is the presence of ‘not so common’ artifacts such as image blurring and a ‘global ringing’ similar in appearance to motion ghosting. These can have deleterious effects even at a two-fold acceleration [12] and have been described for MR neuroimaging [13]. While the presence of artifacts in any accelerated image is an expected phenomenon, the unfamiliar and unpredictable nature of these artifacts means that radiologists or technologists may not be able to troubleshoot or even recognize them which can limit the usage of modern CS applications in clinical routine. For this reason, recent studies performed on 3D static morphological neuroimaging usually do not exceed three to four acceleration rates [14, 15].

In this work, we propose to investigate the use of high acceleration factors using standard CAIPIRINHA acceleration for cartesian trajectories, in combination with a modern iterative denoising (ID) reconstruction algorithm. Applied to the 3D SPACE sequence for neurological imaging, we demonstrate that capturing the high frequencies of the Fourier space helps to maintain image sharpness, while the denoising reconstruction maintains a high SNR in the final 3D volumes.

<sup>1</sup>The MRI restrictions (if any) of the metal implant must be considered prior to patient undergoing MRI exam. MR imaging of patients with metallic implants brings specific risks. However, certain implants are approved by the governing regulatory bodies to be MR conditionally safe. For such implants, the previously mentioned warning may not be applicable. Please contact the implant manufacturer for the specific conditional information. The conditions for MR safety are the responsibility of the implant manufacturer, not of Siemens Healthineers.

## Optimized SPACE CAIPIRINHA and Iterative Denoising

Turbo Spin Echo (TSE) based sequences are the workhorse of modern neuro imaging. While 2D TSE is commonly used in clinical routine for its acquisition speed and robustness, 3D TSE using variable refocusing pulses [16], known as SPACE, tends to replace 2D TSE imaging in clinical practice. Some imperfections have however been reported that limit its widespread use as a clinical standard in neuroimaging. These include the following:

- The increased scan time and its inherent sensitivity to patient motion.
- The resulting contrast that can be less marked than for 2D TSE due to the hybrid T1/T2 weighting in the readout train.
- The natural black-blood effect of TSE that can be limited for slow or turbulent flow using a thick excitation slab or non-selective RF-pulses.
- The presence of 'FID' artifacts caused by the variable refocusing pulses that create stimulated echoes along the readout.

## Contrast optimization

### T2 preparation applied to T2w SPACE FLAIR and DIR contrasts

3D Fluid-Attenuated Inversion Recovery (FLAIR) and Double Inversion Recovery (DIR) are well-established sequences in neuro examinations to improve brain lesion conspicuity. FLAIR uses an inversion preparation pulse combined with a long inversion time (TI) to suppress Cerebro-Spinal Fluid (CSF) magnetization. DIR uses two inversion pulses for suppressing white matter (WM) and CSF. However, it remains challenging to acquire whole-brain high-resolution 3D FLAIR/DIR in a clinically compatible scan time without compromising image quality, contrast, or SNR.

It is well established that 3T field strength is highly desirable over conventional 1.5T to improve lesion conspicuity in clinical neuroimaging. However, the consequence of a higher field strength is the lengthening of the T1 relaxation time of gray and white matter (GM and WM), while the T1 of CSF remains unchanged. As a result, the longitudinal magnetization recovery of GM and WM for a fixed repetition time is progressively reduced at higher field strengths, decreasing the lesion detectability due to increased T1 weighting. Furthermore, this incomplete magnetization recovery also compromises the theoretical SNR gain of a higher field strength.

An elegant way of addressing this issue is to use a T2 preparation module prior to the inversion pulse to mitigate the unwanted T1 weighting [17]. This preparation includes a 90° excitation RF pulse followed by a variable number

of 180° refocusing pulses and finally a -90° flip-back RF pulse [18]. Specific timing is required so that the transversal magnetization of GM and WM (with comparatively short T2 relaxation times) significantly decays while CSF transversal magnetization is nearly unaffected before the flip-back pulse. After inversion, CSF experiences an inversion recovery (as without T2 preparation module), while GM and WM experience a saturation recovery. This results in more complete recovery of GM and WM during the T1 period and hence less unwanted T1-weighting than without a T2 preparation module.

### DANTE preparation applied to T1w SPACE

The 3D T1w SPACE sequence has been increasingly used in clinical routine since the development of the variable flip angle technique with non-selective refocusing pulses and short echo spacing [19]. 3D T1w SPACE is now proposed as an alternative to the 3D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence due to its inherent reduction of artifacts from static field inhomogeneity and its better sensitivity for the detection of brain lesions or metastases. The advantages of 3D T1w SPACE over 3D T1w MPRAGE have been demonstrated for several applications, such as brain metastases [20] and multiple sclerosis [21] indications. The use of long echo train length (ETL) is mandatory to achieve a scan time compatible with clinical routine and allows for more effective flow suppression without compromising image quality and sensitivity. Long ETL also have the advantage to provide inherent black-blood effect.

However, residual slow blood signal may persist and mimic atherosclerotic plaque or vessel wall disease. This issue is especially present after gadolinium contrast agent injection, as the blood suppression efficiency is reduced by the shortened T1. Several techniques have been proposed to reduce residual blood flow effects, such as DIR preparations for cardiac imaging and a flow sensitive gradient technique called Motion Sensitized Driven Equilibrium (MSDE) for neuro imaging.

The use of DIR preparation provides an effective blood signal suppression but is limited to 2D imaging and is not easily adaptable to 3D imaging due to a larger outflow volume. MSDE provides several advantages, such as cancelling blood flow signals in any direction without impacting the scan time. This technique has been demonstrated to reduce plaque-mimicking flow artifacts in the carotid bifurcation, an area where the blood signal suppression is frequently imperfect [22]. However, the MSDE technique tends to introduce T2 decay and diffusion attenuation, leading to an overall SNR and contrast drop across the image. This signal attenuation can restrict the use of MSDE for high-resolution vascular imaging where SNR is already low, even at 3T.

An improved black-blood technique called Delay Alternating with Nutation for Tailored Excitation (DANTE)<sup>2</sup> has recently been proposed [23] as an alternative to MSDE, providing less SNR and T2 weighting loss without any impact on the acquisition time. This technique has the advantage of being independent of the 3D volume size, without being sensitive to inflow or outflow effects. It uses a train of low-flip-angle pulses interleaved with dephasing gradients to suppress flowing spins. The DANTE blood flow suppression efficiency has been demonstrated for several applications, such as carotid arteries and vessel wall imaging [24, 25] evaluations.

### Removal of FID artifacts by simple averaging

The SPACE sequence uses variable-flip-angle refocusing RF pulses for extending the echo-train duration and reducing power deposition. However, like many things in MRI, the advantages of variable-flip-angle refocusing RF pulses also come with a potential problem – free-induction-decay (FID) artifacts [16]. An RF pulse with an intermediate flip-angle value plays three roles: excitation (to generate transverse magnetization), refocusing (to generate a spin-echo), and store/recall (to generate a stimulated echo). Therefore, if the flip angles of the refocusing RF pulses are not equal to 180°, longitudinal magnetization that regrows due to T1 relaxation during the time period between the excitation and first refocusing RF pulses, or between successive refocusing RF pulses, will be converted to transverse magnetization by the next refocusing RF pulse that is applied, and will thereby create an FID signal. While FID artifacts can be minimized by using fat saturation, or by increasing the readout crusher gradients at the expense of the echo-spacing, they can only be completely eliminated by simple signal averaging, alternating the phase of the refocusing RF pulses by 180° between averages. Scantime increase can be remedied by using higher acceleration factors, but at the expense of SNR due to the *g*-factor.

## Iterative Denoising

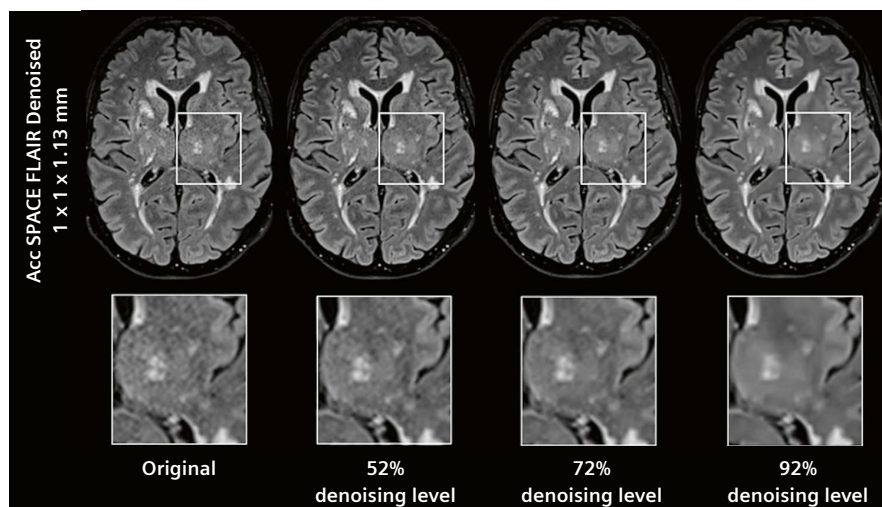
A prototype iterative denoising algorithm<sup>2</sup>, which consists of an inner core of multiwavelet thresholding as a regularizer, was integrated into the scanner reconstruction pipeline [26]. During the iterations, the current regularized image was optimally combined with the original image and the previous image estimate, according to Stein's unbiased risk estimator [27]. The algorithm works on complex-valued 3D volumes after channel combination, considering the spatially varying noise level in the image, the *g*-factor from parallel imaging, and *k*-space filter functions. Patient-specific noise distribution was measured via a pre-scan by the system and was used as a quantitative input during reconstruction. Where appropriate, some edge enhancement was applied after the denoising stage to compensate for perceived loss in sharpness.

The denoising strength can be adapted by the user according to the physician's needs, as shown in Figure 2. It is important to mention, though, that the iterative denoising algorithm automatically adapts to changes in the acquisition and reconstruction settings, including RF coil properties, via the noise measurements. Therefore, the denoising strength should not require application-specific manual tuning.

To our knowledge, the ID algorithm has not been evaluated in combination with SPACE readout for neurological diseases. In this work we propose

- to optimize signal and contrast for different image weightings by means of the above mentioned preparation schemes (T2 preparation and DANTE) and
- to propose a well-designed use of moderate-to-high CAIPIRINHA acceleration factors in combination with the iterative denoising reconstruction algorithm.

<sup>2</sup>Work in progress: the application is currently under development and is not for sale in the U.S. and in other countries. Its future availability cannot be ensured.



**2** Impact of the denoising strength effect on image quality and appearance. For clinical examination, a value of 72% has been chosen at Lariboisiere Hospital for the Accelerated SPACE FLAIR protocol.

## Clinical experience with Iterative Denoising applied to the SPACE CAIPIRINHA sequence in Neurology

All patient images were obtained using a 3T MR scanner (MAGNETOM Skyra or Prisma, Siemens Healthcare, Erlangen, Germany) with a 64-channel Head&Neck coil. The prototype sequence consisted of a 3D SPACE CAIPIRINHA product implementation, combined with investigational magnetization preparation schemes and an inline iterative denoising reconstruction giving access to native image reconstruction and iteratively denoised image series.

As the presented results were obtained at different clinical sites, only spatial resolution and scan time are reported in Table 1 for the different applications and contrasts. For more information about the sequence parameters, please contact the corresponding authors. All FLAIR and DIR images were acquired using a short T2 preparation duration of 125 ms, followed by standard non-selective inversion pulses with specific inversion times to null the CSF, or two non-selective inversion pulses to suppress CSF and WM.

### Accelerated SPACE FLAIR in brain tumor

FLAIR is considered the most important sequence in brain examinations as it provides an excellent lesion visualization. Blood flow artifacts and partial volume effects of 2D imaging can be addressed with a 3D volume dataset acquisition. The use of a non-selective inversion pulse in 3D imaging avoids flow related CSF artifacts (e.g., in the subarachnoid space and ventricles) that commonly occur in 2D-based methods. However, the use of 3D in clinical routine is limited by its longer acquisition time over 2D imaging.

Figure 3 shows an example of a 68-year-old woman who was referred for follow-up exam of a cavernoma. A standard transversal 3D SPACE FLAIR of about 5 minutes scan time was acquired for comparison. Here, the use of a

highly accelerated 3D SPACE FLAIR reconstructed with ID maintains a high image quality and a voxel size close to 1 mm<sup>3</sup> with a scan time reduction of 37%. At Lariboisière neuroradiology department, approximately 110 patients undergo brain screening MRI sequences per week. This means that an additional scan time of 3 hours per week is provided only by integrating ID on 3D FLAIR sequences.

### Improved spatial resolution and contrast in multiple sclerosis

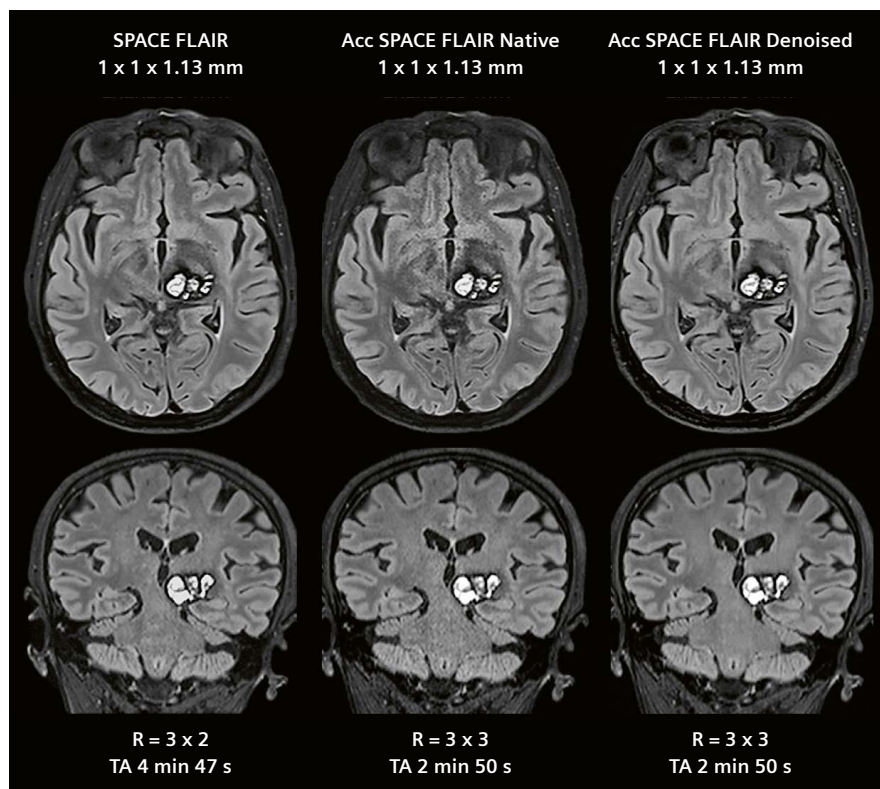
In multiple sclerosis (MS) and other inflammatory neurological disorders, FLAIR is also considered the most important contrast for lesion assessment and follow-up. 3D imaging with isotropic voxel size is essential to limit partial volume effect, especially as there is an increasing interest in cortical and juxta-cortical abnormalities in MS. Detection of WM and GM lesions requires high spatial resolution and excellent contrast and SNR. By combining T2 magnetization preparation to improve the lesion's contrast with the ID reconstruction technique, it is possible to achieve a 0.8 mm isotropic 3D SPACE FLAIR in a clinically acceptable imaging time of about 5 minutes (Fig. 4). Until now, this spatial resolution for FLAIR imaging has only been reported at higher field strengths such as 7 Tesla.

Double-Inversion Recovery sequences have been shown to be more sensitive for the assessment of MS lesion or optic neuritis. However, the DIR preparation strongly reduces the remaining MR signal for the readout module, which makes this technique highly challenging and unstable for use in clinical practice. Indeed, standard reported 3D SPACE DIR sequences usually necessitate a scan time of more than 6 minutes for decent image quality. A strongly accelerated high-resolution SPACE DIR acquired in 3 minutes and 40 seconds on an MS patient is presented in Figure 5. This figure also presents the high-resolution coronal and transversal FLAIR reformats, with a scan time reduction of around 40% for both sequences.

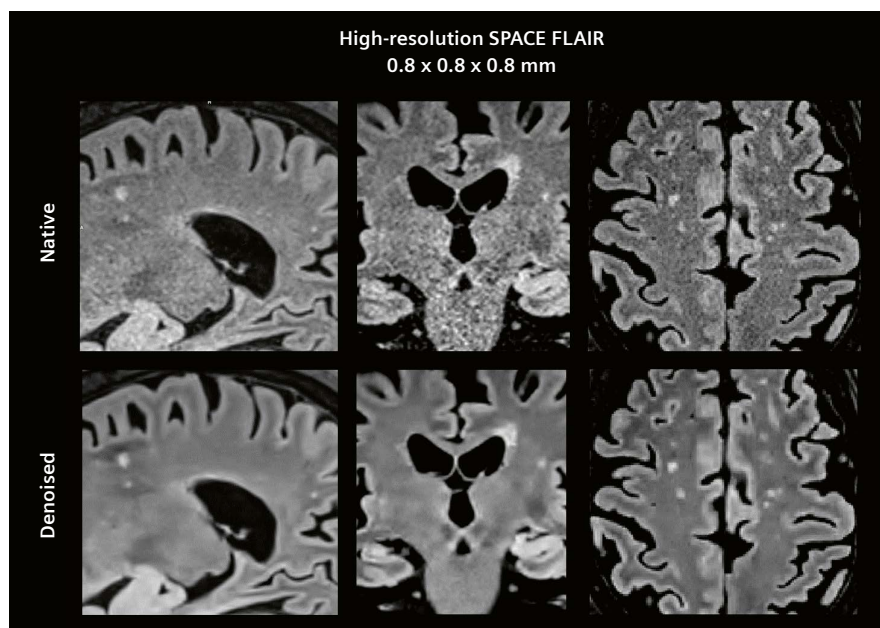
| Sequence & Site                         | Spatial Resolution (mm) | CAIPIRINHA Acceleration Factor | Scan Time  |
|---|-------------------------|--------------------------------|------------|
| Standard Space_FLAIR_Lariboisiere       | 1 x 1 x 1.13            | 3 x 2 (2 avg)                  | 4 min 47 s |
| Accelerated Space_FLAIR_Lariboisiere    | 1 x 1 x 1.13            | 3 x 3 (2 avg)                  | 2 min 50 s |
| High-resolution Space_FLAIR_Montpellier | 0.8 x 0.8 x 0.8         | 4 x 3 (2 avg)                  | 5 min 20 s |
| High-resolution Space_DIR_Montpellier   | 0.9 x 0.9 x 1.2         | 3 x 2                          | 3 min 40 s |
| High-resolution_Space_T1/T1 DANTE_CHNO  | 0.8 x 0.8 x 0.8         | 3 x 2 (2 avg)                  | 4 min 34 s |

**Table 1:** Principal sequence parameters for the different sites and applications.

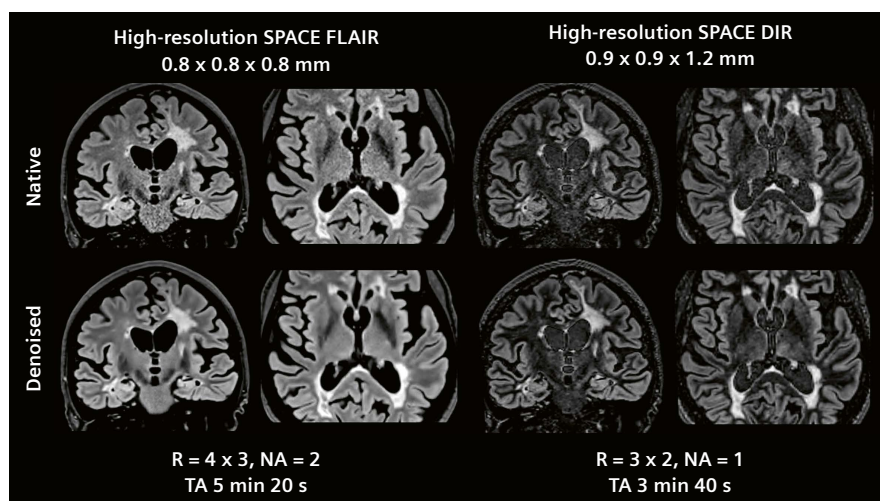




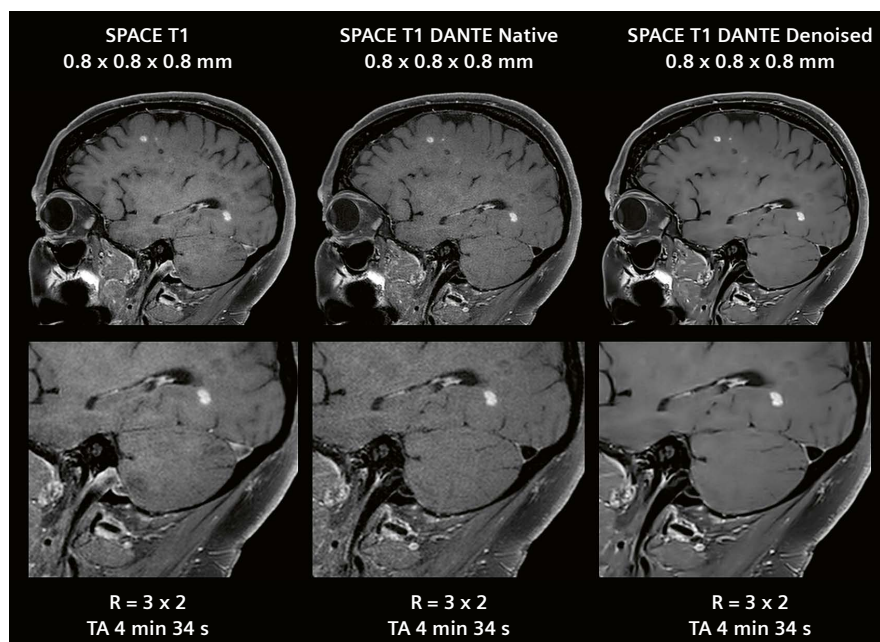
- 3** A 68-year-old woman was referred for follow-up of a cavernoma to Lariboisiere University Hospital Center (Paris, France). A standard Axial 3D SPACE FLAIR was acquired with an in-plane resolution of 1 mm in 4 min 47 s (left). The use of a higher acceleration factor dramatically decreases the SNR level especially in the image center (middle). After reconstruction with ID, the accelerated 3D SPACE FLAIR highlights a similar image quality as the conventional sequence with a decreased scan time of 37%.



- 4** A 68-year-old male with suspected autoimmune encephalitis was referred to Montpellier University Hospital. High resolution T2-prepared SPACE FLAIR images were acquired with an isotropic voxel of 0.8 mm. Conventional reconstructions are shown on the upper row with a SNR reduction that impedes clinical diagnosis. Iterative denoising (lower row) allows the same high spatial resolution with an enhanced SNR.



- 5** A 58-year-old female with multiple sclerosis was referred to Montpellier University Hospital. High resolution T2-prepared SPACE FLAIR and DIR images were acquired. Coronal and transversal reformat are shown with and without ID. Thanks to ID, FLAIR, and DIR are both acquired with a high spatial resolution, a high SNR and an acquisition time remaining compatible with clinical routine.



- 6** A 37-year-old woman was referred for follow-up of multiple brain metastases to the Centre Hospitalier National d'Ophthalmologie des Quinze-Vingts (Paris, France). A conventional post contrast SPACE T1 sequence acquired with a spatial resolution of 0.8 mm<sup>3</sup> (left) exhibits flow related artifacts enhancement in the carotid aera and the right sinus as well as a high SNR drop. With DANTE preparation (middle), both flow related artifacts are corrected. The additional ID reconstruction (right) highlights a much sharper image quality and compensate the low SNR level of the native sequence.

## Improved spatial resolution and contrast in brain metastasis

In vascular neuro MR, wall-thickening and mural-enhancement evaluations are challenging because of the tortuous course and small dimensions of the intracranial arterial vessels. The use of a high resolution and isotropic 3D SPACE T1 black-blood imaging is mandatory to reformat and analyze their whole courses; this therefore provides a larger and better imaging coverage than conventional

2D sequences. Moreover, the combination of an additional DANTE preparation can suppress residual blood flow and improves brain metastasis conspicuity [28]. The combination of a DANTE preparation with an ID reconstruction is proposed as an efficient method to provide a 0.8 mm isotropic sequence while maintaining scan time below 5 minutes, as shown in Figure 6.

## Acquisition speed ... what for?

Despite the development of new acceleration techniques over the past decades, fast brain MR examinations remain an ongoing topic to improve patient comfort, exam reproducibility, and the cost effectiveness of the MRI unit. Indeed, motion-related artifacts and image blurring hamper diagnostic quality, especially with uncooperative patients or in pediatric<sup>3</sup> populations. Several developments have already been proposed, such as the GOBrain protocol [29] that include fast and individual 2D sequence optimizations to provide an accurate diagnosis in less than 5 minutes. However, the advantage of 3D over 2D imaging has already been largely described for neurological diseases: providing thinner and contiguous slices, overcoming partial volume effect, and allowing for multiplanar image reconstruction with a high sensitivity in lesion detection. The longer acquisition time of 3D compared to 2D remains the major drawback that limits its general usage.

The use of CS to address this issue remains limited by the relatively low acceleration rates achievable, which does not exceed 3 to 4-fold for 3D static neuro imaging. CS is also limited by its extended reconstruction time, which increases with the number of coil elements, especially during whole-brain acquisition with a 64-channel head coil. The reconstruction time can be reduced with the use of Graphic Process Unit but not all clinical MR scanners are currently equipped with one, and the widespread use of CS sequences remains limited. While CS iterates on multi-channel under-sampled *k*-space data, the ID algorithm iterates on images after coil combination, i.e., a reduced amount of data. For that reason, it can be performed on conventional computers without noticeable reconstruction time increase. Finally, the use of a quantitative noise map acquired during the framework adjustment is particularly suited to limit the *g*-factor penalty associated with high acceleration rates. As a result, the final images after ID do not suffer from central SNR drop and ensure a near perfect receive-B<sub>1</sub> image homogeneity.

In this work, a novel iterative denoising technique was successfully evaluated for 3D brain imaging in different clinical questions. Combined with the SPACE sequence, the ID algorithm ensures excellent image quality regardless of the image contrast. Furthermore, its application on conventional Cartesian datasets allows the use of 6- to 12-fold acceleration rates without compromising image quality. Several optimizations were proposed for different pathologies and clinical needs. For instance, tumor follow-up exams can be performed with a fast millimetric 3D scan, improving the overall patient throughput. On the other hand, small MS lesions can only be depicted with

sub-millimetric 3D scans, that are usually not possible on 3T systems. Similarly, as intra-cranial blood vessels range from a few millimeters to capillaries, the higher the spatial resolution is, the more sensitive the scan will be. Improving spatial resolution while keeping the scan time under 5 minutes will not only maintain a constant total exam time, but will also help to move toward precision medicine and dedicated high-resolution scans when needed for the patient. The gain in acquisition speed can also be invested in acquiring additional scans that are beneficial for the patient, such as an additional DIR contrast as presented here, or quantitative T1 and T2 maps that can then be compared to a normative database.

In order to validate the use of ID in clinical routine, future work will focus on the quantitative evaluation of these contrast-optimized and highly accelerated sequences in patient cohorts. The acceleration capabilities could be further expanded by combining the iterative denoising reconstruction algorithm with more advanced Cartesian 3D acceleration such as the recently proposed Wave-CAIPI [30, 31]. The combination of both techniques would push the acceleration capabilities of the SPACE sequence even further, without SNR penalty.

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<sup>3</sup>MR scanning has not been established as safe for imaging fetuses and infants less than two years of age. The responsible physician must evaluate the benefits of the MR examination compared to those of other imaging procedures.



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## Contact

Alexis Vaussy  
Siemens Healthcare SAS  
40 Avenue des Fritiers  
93210, Saint Denis  
France  
alexis.vaussy@siemens-healthineers.com



Thomas Troalen  
Siemens Healthcare SAS  
40 Avenue des Fritiers  
93210, Saint Denis  
France  
thomas.troalen@siemens-healthineers.com

