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**Manuscript title**

Improved susceptibility-weighted imaging for high contrast and resolution thalamic nuclei mapping at 7T

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# Abstract

(word count: 249)

**Purpose:** The thalamus is an important brain structure and neurosurgical target, but its constituting nuclei are challenging to image non-invasively. Recently, susceptibility-weighted imaging (SWI) at ultra-high field has shown promising capabilities for thalamic nuclei mapping. In this work, several methodological improvements were explored for the first time to enhance SWI quality and contrast, and specifically its ability for thalamic imaging.

**Methods:** High-resolution SWI was performed at 7T in healthy participants, and the following techniques were applied: (i) monitoring and retrospective correction of head motion and  $B_0$  perturbations using integrated MR navigators; (ii) segmentation and removal of venous vessels on the SWI data using vessel enhancement filtering; (iii) contrast enhancement by tuning the parameters of the SWI phase-magnitude combination. The resulting improvements were evaluated with quantitative metrics of image quality, and by comparison to anatomo-histological thalamic atlases.

**Results:** Even with sub-millimeter motion and natural breathing, motion and field correction produced clear improvements in both magnitude and phase data quality (76% and 41%, respectively). The improvements were stronger in cases of larger motion/field deviations, mitigating the dependence of image quality on subject performance. Optimizing the SWI phase-magnitude combination yielded substantial improvements in image contrast, particularly in the thalamus, well beyond previously-reported SWI results. The atlas comparisons provided compelling evidence of anatomical correspondence between SWI features and several thalamic nuclei, e.g. the ventral intermediate nucleus. Vein detection performed favorably inside the thalamus, and vein removal further improved visualization.

**Conclusion:** Altogether, the proposed developments substantially improve high-resolution SWI, particularly for thalamic nuclei imaging.

**Keywords:** susceptibility-weighted imaging, thalamic nuclei, motion correction, field tracking, vein segmentation

# 1. Introduction

Magnetic susceptibility is a tissue property that is sensitive to composition and microstructure, and can be probed non-invasively with certain magnetic resonance imaging (MRI) modalities (1,2). Crucially, the pursuit of increasingly higher magnetic field strengths ( $B_0$ ) has brought key enhancements in signal-to-noise ratio and contrast to these modalities (3,4), resulting in enhanced sensitivity, and offering the possibility of exploring higher spatial resolutions. Along this line, recent works at ultra-high field strengths of 7T, investigating sub-millimeter  $T_2^*$ -weighted magnitude and phase data, have shown exquisite mapping capabilities for various cortical and subcortical features (5,6). Also among these modalities is susceptibility-weighted imaging (SWI), which combines  $T_2^*$ -weighted magnitude and phase information at long echo time. While originally developed primarily for venography (7), taking advantage of the geometry and paramagnetic content of veins (8), SWI was soon found valuable for numerous other applications, including the detection of trauma, stroke, cortical dysplasia and tumors (9,10). At 7T, SWI has shown enhanced sensitivity in detecting multiple sclerosis lesions (11) and features of polymicrogyria in epilepsy (12), for example. These reports suggest a potentially substantial impact of SWI at ultra-high field for clinical neuroimaging in the near future, particularly as the number of clinically-certified 7T systems rapidly increases worldwide.

Notably, 7T SWI has also shown promising capabilities for imaging the thalamus (13). This subcortical brain structure is organized in smaller nuclei with specialized functions, that play key roles in neuronal signal transmission and modulation (14,15), and have been a strong focus of neuroscience research, as well as clinical interventions. For example, neuronal deficits in the anterior and mediodorsal nuclei, as well as the pulvinar, have been linked to psychotic disorders such as schizophrenia (16). The ventral intermediate nucleus (Vim) is commonly targeted to treat essential tremor (17); this intervention can be done non-invasively, by radiosurgery (18-21) or focused ultrasound (22), but requires accurate non-invasive targeting. Unfortunately, conventional modalities such as  $T_1$  and  $T_2$ -weighted imaging offer poor contrast in the thalamus, and diffusion tensor imaging cannot resolve some of its individual nuclei, such as the Vim (23). Indirect mapping approaches relying on standard atlases can provide further differentiation, but cannot fully account for individual anatomical variability. Promisingly, recent work with 7T SWI at high resolution has found unprecedented contrast features within the thalamus, which appear to be in good correspondence with the expected anatomy of its nuclei (13).

Despite the potential of high-resolution SWI at 7T, the technique currently presents important unsolved challenges that can compromise image quality and diagnostic value. First, the high spatial specificity afforded by sub-millimeter voxel resolutions can be easily compromised by head motion occurring throughout the periods of several minutes required for acquisition, even in compliant subjects (24).

Additionally, susceptibility-based contrasts (typically  $T_2^*$ -weighted) are particularly sensitive to perturbations in  $B_0$  over time, which can arise due to breathing (25). Altogether, motion and field-related artifacts can introduce substantial blurring, ghosting and ringing artifacts, signal loss and inhomogeneities (24,26,27). Numerous groups have proposed techniques to monitor and compensate for motion-related effects (28), and in some cases for field perturbations as well (25,29). Yet, most studies so far have only tested such corrections on relatively limited datasets, focusing primarily on image magnitude, not phase, and often in conditions of large intentional motion or deep breathing, for proof-of-concept purposes.

Second, SWI, as conventionally implemented in commercial MR systems, is optimized to image veins (7,8). The diverse applications for which it was subsequently found valuable constitute empirical findings, and most likely remain suboptimal with regard to contrast. It is currently unknown whether modifications of the SWI phase-magnitude combination, in particular, could enhance its ability to image non-venous tissues such as the thalamus. Previous reports have found promising results for thalamic mapping using the conventional, venography-oriented SWI contrast, but to our knowledge none have proposed or explored potential dedicated improvements (13,30). A main reason for this shortcoming could be the fact that, to our knowledge, the SWI combination parameters are typically fixed and cannot be modified by users directly on the console (“online”), requiring dedicated expertise in MRI data reconstruction to explore such modifications.

Third, the inherent high sensitivity to the presence of veins of conventional SWI can, by itself, pose a nuisance to visualization in non-vein-related applications, and to processing tasks like thalamic nuclei segmentation (31). The inclusion of effective vein detection and segmentation approaches could prove valuable to inform subsequent processing steps, or even to remove the presence of veins altogether.

The present work aims to address the above-described limitations, introducing novel improvements to conventional SWI for high-resolution imaging at 7T, with a particular focus on thalamic nuclei mapping. The work comprised three main modifications: (i) concurrent monitoring of head motion and  $B_0$  perturbations using integrated MR navigators (32-34), and retrospective correction of the acquired data; (ii) segmentation of venous vessels on the SWI data using vessel enhancement filtering (35), and suppression of the veins by interpolation (36); and (iii) enhancement of the SWI contrast by tuning the parameters of phase high-pass filtering and phase-magnitude combination (7). These modifications were implemented and tested on a group of healthy human participants, at 7T. Post-acquisition, the improvements obtained with motion and field correction were evaluated with quantitative metrics of image quality; the improvements produced by vein removal and contrast enhancement were evaluated by direct comparison with the more conventional (venography-oriented) version, and the anatomical correspondence of the enhanced features was studied by comparison to anatomo-histological atlas information, in the thalamus.

## 2. Methods

This study was approved by the local ethics committee (CER-VD), and involved the participation of 12 healthy volunteers ( $69 \pm 7$  years old, 4 male/8 female), who provided written informed consent. The dataset was acquired as part of a larger study on essential tremor, belonging to an age-matched control sub-group. All participants were clinically healthy, and did not exhibit any brain anomalies in previous 3T MRI scans.

Data processing was mainly performed in Matlab (Mathworks, Natick MA) using routines developed in-house, combined with tools from the Berkeley Advanced Reconstruction Toolbox (37) and the FMRIB Software Library (FSL) (38).

### 2.1. Data acquisition

The acquisitions were performed on a Magnetom 7T head scanner (Siemens Healthcare, Erlangen, Germany) equipped with a birdcage transmit/32-channel receive RF array (Nova Medical, Wilmington, MA, USA). The participants were asked to lie as still as possible during image acquisition, with their eyes closed; head padding was employed to minimize motion. Each participant underwent a high-resolution SWI acquisition, and a whole-brain  $T_1$ -weighted acquisition for registration and comparison purposes. The SWI scan consisted of a flow-compensated 3D-GRE sequence with  $0.375 \times 0.375 \times 1$ -mm resolution,  $192 \times 192 \times 72$ -mm field-of-view,  $TR/TE = 41/20$ ms,  $\alpha = 12^\circ$ , 120 Hz/Px bandwidth,  $2 \times$  undersampling and  $6/8$ -partial Fourier in the first phase-encoding direction, and a total acquisition time (TA) of approximately 11 min. The imaging slab was placed in an axial-oblique orientation centered at the thalamus. The  $T_1$ -weighted scan employed a 3D MP2RAGE sequence (39) with 0.6-mm isotropic spatial resolution,  $192 \times 192 \times 154$ -mm (whole-brain) field-of-view,  $TE/TI_1/TI_2/TR = 4.94/800/2700/6000$ ms,  $\alpha_1/\alpha_2 = 7^\circ/5^\circ$ , 240 Hz/Px bandwidth,  $3 \times$  GRAPPA acceleration in the first phase-encoding direction and  $6/8$  partial Fourier in both phase-encoding directions, and a TA of approximately 10 min. The raw GRE data of the SWI acquisition were exported for offline reconstruction, while the  $T_1$ -weighted image was reconstructed on-scanner.

### 2.2. Integrated MR-based navigators and artifact correction

The GRE (SWI) acquisition included integrated MR-based navigators to monitor head motion and  $B_0$  perturbations occurring throughout the acquisition. These navigators included two elements: highly-undersampled 3D GRE images of the head fat signal, termed FatNavs (32,33,40), and free induction decay-based navigators, or FIDNavs (see Supporting Fig. S1 for sequence diagram). The FatNavs were implemented in segmented fashion, with two k-space lines acquired after each k-space line acquisition of

the GRE host sequence, at a nominal spatial resolution of 4 mm isotropic, and yielding a temporal resolution of 2.2s. The FatNav readouts contained two echoes to enable field map estimation, as previously proposed (33), acquired with  $TE_1/TE_2 = 1.17/4.17$ ms. An FIDNav was acquired directly after each excitation pulse of the host sequence (34). The FIDNav was measured in 0.2ms, and the total duration for the FatNav module was 10.8ms, leading to an effective TR of 41ms for the host sequence, as mentioned above.

After acquisition, and before reconstruction of the complex images, the acquired k-space lines of the host GRE were corrected for motion and field-related artifacts. As proposed in previous work (34), 10 time-varying parameters (6 to describe rigid-body head motion, 4 to describe 1<sup>st</sup>-order linear field perturbations) were estimated from the FatNavs and used to train a 1<sup>st</sup>-order model linking a representative FIDNav signal to the correction parameters. In detail, the representative FIDNav signal was defined as the mean signal during the associated FatNav measurement. For the  $k^{\text{th}}$  FatNav correction parameter vector  $p_k$  (of length 10), the associated representative FIDNav signal  $f_k$  is then a vector of length  $2N_c + 1$  (with  $N_c$  the number of receiver channels), containing the real and imaginary parts of the signal, as well as a constant term of 1 which allows for slight time reference offsets between the FatNav and FIDNav signals. The coefficients of the matrix  $C$  describing the 1<sup>st</sup>-order model were then found by direct matrix inversion of the following equation:

$$Cf_k = p_k \quad [1]$$

using all the FatNav-derived parameters (i.e. the  $f_k$  for all the values of  $k$ ) for the estimation. Details of a similar method can be found elsewhere (41).

The estimated model  $C$  was then reapplied to the individual FIDNav signals, to obtain correction parameters at higher temporal resolution (approximately 24Hz). The parameter timecourses were then smoothed using a Tukey filter with 0.5-Hz constant window, 1-Hz passband (34). As shown in previous work (33), both motion and magnetic field perturbations up to the 1<sup>st</sup> spatial order can be efficiently corrected using a phase correction for translation and 0<sup>th</sup>-order field component, followed by a non-uniform FFT for rotation and 1<sup>st</sup>-order field component. This correction was applied to the host GRE sequence, individually for each receive channel.

### 2.3. GRE image reconstruction

In order to obtain high-quality reconstructions of both magnitude and phase data, well separated from coil sensitivity contributions (42), the ESPIRiT approach was employed to estimate the complex coil sensitivities (43), and combined with block coil compression to obtain a virtual “body coil-like” channel (42), as proposed in previous work (44). These steps were performed on the calibration data of the GRE

acquisition (512×64×72 matrix, 32 receive channels). A geometric coil compression step was applied beforehand (from 32 to 15 channels), to reduce computational costs (45). After ESPIRiT estimation, the actual coil sensitivities were joined with the virtual “body coil” channel, which provided a singularity-free phase reference, and the full GRE data were thereby reconstructed using SENSE (42,43). Subsequently, the phase data underwent Laplacian-based spatial unwrapping (46), and background field removal using the Laplacian boundary value approach (47). These pre-processing steps have previously been found to improve SWI quality (48), and the additional computation time was not problematic for this offline processing.

#### 2.4. Evaluation of motion and field artifact correction effects

Seeking to quantitatively evaluate the impact of motion and field artifact corrections on image quality, a number of quality metrics were tested based on previous reports (49,50). Among these, a modified version of the “normalized gradient squared” metric (49) exhibited the best trade-off between low variability across subjects and high sensitivity to artifact reductions, and was therefore selected for analysis. The metric was applied to the GRE data reconstructed with (i) no correction, (ii) motion correction, and (iii) motion and field correction. It was evaluated not only on the magnitude, but also, separately, on the phase images, given the importance of both for susceptibility-based contrasts in general, and SWI in particular (2). The adopted metric can be referred to as “excess normalized gradient squared”,  $S$ . Given a magnitude or phase image  $I$ , and a region of interest  $ROI$ ,  $S$  was defined as:

$$S_{ROI} = \frac{E\{G(\vec{r})^2\}_{ROI}}{E\{G(\vec{r})\}_{ROI}^2} - C \quad [2]$$

$G(\vec{r})$  denotes the norm of the image gradient of  $I(\vec{r})$ , computed based on finite differences, at position  $\vec{r}$ ;  $I$  was lightly smoothed beforehand (Gaussian smoothing, 1.1mm full-width-at-half-maximum (FWHM)), to reduce the impact of random noise on the gradient computation.  $E\{\cdot\}_{ROI}$  denotes the average over all voxels of  $ROI$ ; two regions were considered: the whole brain, segmented from the magnitude image (51), and the thalamus, given by an atlas mask co-registered from MNI space (see section 2.7).  $C$  is a correction factor that centers the metric at 0, such that an input image of pure noise would yield  $S=0$ , and a structured image will yield the “excess” relative to this pure noise case.  $C$  was estimated to be approximately 1.59 for magnitude images, and 1.33 for phase images.

To evaluate potential links between image quality and motion or field perturbations, each subject was also attributed a single measure reflecting the extent of head motion exhibited during acquisition, and another for the extent of field perturbations. First, head displacement at each timepoint was estimated as the norm of the displacement of each voxel in the brain relative to its position at the time of acquisition of

the k-space center, averaged across all brain voxels. A single measure was then extracted as the root-mean-square (RMS) of the displacement across time. The field deviation at each timepoint was calculated as the absolute field shift relative to  $B_0$  in each voxel, averaged across all brain voxels. A single measure was then extracted as the RMS of this field deviation across time.

## 2.5. Vein segmentation and exclusion

Vein segmentation was performed using multiscale vessel enhancement filtering (35), an image-based technique that uses second-order (curvature) information to highlight vessel-like structures. Several variants of this approach have been successfully applied to MRI modalities (52,53), including SWI (54). In the present work, the technique was applied to the reconstructed SWI data tuned to the conventional contrast (see section 2.6), which is optimal for vessel visualization (8). Based on preliminary tests, the technique was found most effective when applied in 2D fashion, slice by slice (see section 3.2 for details). The filter was set to cover a range of spatial scales of 0.4–1.2mm, which was chosen based on the image resolution and the size of vessels typically found inside the thalamus. Filter parameters  $\beta = 0.5$  and  $c = 5.0$  were determined empirically by direct visual inspection of the resulting vein maps, where we sought to optimize the compromise between false negatives and false positives in vein detection – an approach which was feasible since veins are visually well discernible in SWI data, and the subject group size was not prohibitively long. The resulting filter maps were thresholded at 0.4 (also determined by visual inspection) to create vein masks. The corresponding vein voxels were accordingly marked as “corrupted”, and replaced by interpolation using neighboring voxel information (also termed “in-painting”), using the discrete cosine transform (36).

## 2.6. SWI combination and contrast enhancement

After GRE reconstruction (magnitude and phase data), SWI images were obtained following the originally-proposed phase-magnitude combination (7): (i) the phase image is spatially highpass-filtered; (ii) a phase mask  $f(\vec{r})$  is created from the filtered phase map  $\varphi(\vec{r})$  following the expression:

$$f(\vec{r}) = \begin{cases} 1, & \varphi(\vec{r}) < 0 \\ (\pi - \varphi(\vec{r}))/\pi & \varphi(\vec{r}) \geq 0 \end{cases} \quad [3]$$

for each position  $\vec{r}$  in the image; (iii) the magnitude image is multiplied by the phase mask a number of times  $m$ , thereby progressively reducing the intensity of voxels with positive  $\varphi$ .

Unlike the Hanning filter employed in the original approach (55), the highpass filtering step was here based on Gaussian smoothing, i.e. the original phase image was subtracted of a lowpass-filtered version of the same image obtained with Gaussian smoothing, with FWHM  $\sigma$ . This allowed a more direct interpretation of the range of spatial scales that were preserved and passed on to the phase mask  $f$ .

Altogether, this framework allowed exploring multiple variations of the SWI contrast by varying both  $\sigma$  and  $m$ . Preliminary tests indicated that a combination of  $\sigma = 4\text{mm}$ ,  $m = 4$  yielded the closest match to a more conventional SWI contrast, as produced by the vendor-supplied online reconstruction in our system (see section 3.3).

### **2.7. Image co-registration and atlas comparisons**

In order to investigate the correspondence between SWI features and the expected thalamic anatomy, the processed images were compared with three histological atlases: (i) the Morel stereotactic atlas of the human thalamus (56); (ii) the Schaltenbrand atlas, based on detailed neuroanatomical information, including a delineation of the Vim (57); (iii) BigBrain, a high-resolution image of a histological brain preparation, stained for the presence of cell bodies (58). To allow direct comparisons, the individual subject data were registered to MNI space, using (i) the FLIRT tool of FSL (59) for linear registration between the SWI and  $T_1$ -weighted images of each subject, and (ii) the FNIRT tool (38) for non-linear registration between the individual  $T_1$ -weighted images and the MNI  $T_1$  template. The non-linear alignment between the  $T_1$  and MNI images yielded displacement fields that were then applied to the SWI data, in combination with the estimated linear registration matrices. This non-linear step was found valuable to account for individual anatomical variability; nonetheless, its estimation relied exclusively on the  $T_1$  (not SWI) data, thereby avoiding any potential comparison biases from “forced” local anatomical matching between the SWI and atlas features.

## **3. Results**

### **3.1. Motion and field artifact correction**

Based on the navigator estimates, the acquired subjects exhibited head displacement RMS values of 0.12–0.41 mm, and  $B_0$  field deviation RMS of 1.5–4.6 Hz, for the 11-min SWI acquisition. Across time, both measurements were dominated by slow drift contributions, but also faster oscillations around 0.18–0.32 Hz (Supporting Fig. S2). These oscillations were especially evident on the field perturbation timecourses.

The normalized gradient squared, serving as a metric of image quality, exhibited considerable variability across subjects, but showed nevertheless fairly consistent trends (Fig. 1). These trends were approximated with robust linear fits across subjects, to ease their evaluation – although without a priori expectations of a linear behavior. Averaged across the brain, image quality tended to decrease with increasing head motion (displacement RMS) in both magnitude and phase data, especially before corrections (Fig. 1a, upper). Correcting for motion, and further for motion and field artifacts, yielded consistently higher image quality

in each subject, and tended to mitigate the overall decrease in quality with displacement RMS, as shown by the weaker slopes of their linear fits. A tendency for decreasing image quality with increasing field deviation RMS could also be observed (Fig. 1a, lower), particularly in the phase data. Likewise, correcting for motion, and especially for motion and field artifacts, tended to mitigate this dependence. Overall, the trends observed for the whole brain were also reflected at the level of the thalamus (Fig. 1b), although the effects on the magnitude data were less clear, with stronger variability across subjects, whereas the effects on the phase were more pronounced.

[Please insert Fig. 1 approximately here, preferably 2 col-wide]

For further insights, the relative variation in gradient squared across the different correction steps (uncorrected, motion artifact-corrected, motion and field artifact-corrected) was also estimated. For the whole-brain ROI, the full correction resulted in substantial quality improvements of 4.4–75.9% for the magnitude data and 4.3–40.7% for the phase, across subjects. The previously observed concurrent dependences on head displacement and field deviation (Fig. 1) motivated plotting these improvements as a function of both parameters (Fig. 2). Overall, the quality improvements tended to be larger for the cases of larger head displacement and/or larger field deviation. Notably, the impact of motion correction was primarily dependent on the amount of head displacement (Fig. 2, left), while the impact of field correction showed a dependence on both displacement and field deviations (Fig. 2, center). These observations held for both magnitude and phase data, although the phase showed a more pronounced dependence on field perturbations than the magnitude.

[Please insert Fig. 2 approximately here, preferably 2 col-wide]

Alongside their ROI-averaged effects, motion and field perturbations each created particular local artifacts that were directly visible in the GRE images. For instance, in datasets more affected by motion than field perturbations (Fig. 3A; full slice in Supporting Fig. S3A), the most evident artifacts in the magnitude were typically blurring and ringing of fine high-contrast features such as veins (Fig. 3A, yellow circles; difference maps in Supporting Fig. S4A). In the phase, veins were also affected, albeit by more intricate artifacts due to the complex dipolar geometry of venous phase features (orange circles); blurring effects along the grey-white matter boundary could also be seen (red arrow). These artifacts were substantially reduced mainly by the motion correction step. In datasets relatively more affected by field perturbations than motion (Fig. 3B; full slice in Supporting Fig. S3B; difference maps in Supporting Fig. S4B), ringing and blurring effects could also be observed on the images (orange and yellow circles); additionally, both large-scale and focal regions of abnormal hypo- and hyper-intensity could be observed

(red arrows). In this case, the artifacts were not visibly reduced by the motion correction step, but only by field correction. The analysis of such “field-dominated” cases (i.e. with relatively more important field deviations than motion) evinces the improvements yielded by field correction alone, since the motion contribution to the motion+field correction is close to negligible. Also of note, some subjects in the group exhibited no discernible artifacts whatsoever – typically consistent with lower estimated displacements and field deviations (Supporting Fig. S5).

[Please insert Fig. 3 approximately here, preferably 2 col-wide]

### 3.2. Vein segmentation and exclusion

Based on visual inspection, the adopted vessel filtering approach was found considerably effective across the brain (Fig. 4a, Supporting Fig. S6). Preliminary tests showed that the 2D (slice by slice) implementation adopted for this work was more appropriate than a full 3D filter, most likely due to the strong anisotropy of the SWI voxel resolution (Supporting Fig. S7). The filter scale range allowed the correct detection of most vessel calibers, except for the large sinuses and veins larger than the vein of Galen (54), for example (Fig. 4b, red arrows). On the low-end of the range, only a few of the smallest visually-discernible veins were missed (Fig. 4a, red arrows). These filter parameters were also found effective for the particular range of vessels that traversed the thalamus (Fig. 4b). Based on the resulting vein masks, the interpolation procedure then yielded mostly vein-free thalamic images, while correctly preserving other hypo-intense regions of non-tubular geometry, and likely of anatomical relevance (Fig. 4b, yellow arrows).

[Please insert Fig. 4 approximately here, preferably 2 col-wide]

For a more comprehensive understanding of the presence of veins within the thalamus, the individual vein masks were brought to MNI space, and average vein densities were estimated for different thalamic sub-regions, based on the Morel atlas. On average, the thalamus as a whole exhibited a vein density of 4.7%, which then ranged between 0 and 21.6% across sub-regions. Higher densities were observed for more medial, relative to lateral nuclei (Fig. 5a). A direct inspection of individual SWI data confirmed this observation (Fig. 5b), showing that the medial thalamic regions were often perforated by superior thalamic (yellow arrows) and anterior thalamic veins (green), which drained to internal cerebral veins, in agreement with the expected anatomy (54,60). In a few cases, small perforating veins (red) could also be discerned in inferior-posterior areas, draining to basal veins; these possibly originated the slightly increased vein density observed for the pulvinar, although only seen on the right side (Fig. 5a).

[Please insert Fig. 5 approximately here, preferably 2 col-wide]

### 3.3. SWI contrast enhancement

Variations in the phase highpass filtering FWHM  $\sigma$ , and the number of phase mask multiplications  $m$ , were both found to induce substantial changes in the resulting SWI contrast, namely in the thalamus (Fig. 6). In particular, applying less restrictive filtering (larger  $\sigma$ ) resulted in more extended, darker features; increasing the multiplication factor also enhanced their contrast relative to surrounding areas, eventually leading to signal saturation in regions like the pulvinar. As indicated in section 2.6, a combination of  $\sigma = 4\text{mm}$ ,  $m = 4$  (Fig. 6, blue) yielded the closest match to a conventional SWI contrast (Supporting Fig. S8). A higher-contrast combination of  $\sigma = 7\text{mm}$ ,  $m = 10$  (Fig. 6, green) displayed a favorable trade-off between enhancing contrast and avoiding saturation, and was thereby considered for further analyses.

[Please insert Fig. 6 approximately here, preferably 2 col-wide]

To investigate the anatomical correspondence of SWI features to sub-regions of the thalamus, these data were compared to the  $T_1$ -weighted acquisitions and to reference information from the Morel atlas and BigBrain, warped to the native SWI space, to preserve its sharpness (Fig. 7). Consistent with previous reports, the  $T_1$ -weighted modality exhibited poor contrast inside the thalamus. Conventional SWI exhibited more differentiated, though subtle, features. These features were then strengthened on the enhanced SWI contrast, clearly improving their visualization. It was also found that such improvements could not be achieved in conventional SWI by simply scaling the image contrast in visualization.

Regarding the anatomy, a comparison with the Morel atlas permitted several observations: at the posterior-inferior end, a relatively large hypo-intense region was well matched with the expected location of the pulvinar (Pu, Fig. 7,  $s=17/25$ ); in superior axial cuts ( $s=30$ ), the observed features mainly showed a lateral vs. medial differentiation, which followed the organization of the atlas, distinguishing more lateral nuclei, including lateral posterior (LP), ventral posterolateral (VPL), ventral lateral (VL) and ventral anterior (VA), from the mediodorsal group (MD); in more intermediate cuts ( $s=25$ ), this lateral vs. medial organization was further differentiated by light-dark alternations, which appeared in agreement with the organization of the parafascicular (Pf) and central lateral (CL) nuclei more medially, then the centromedian (Ce), and more laterally the VPL (anterior and posterior), VL and ventromedial (VM) nuclei. Regarding cell body density (BigBrain), an identifiable correspondence to SWI could be observed for regions like the Pu and MD, while several other features detected by SWI were not differentiated by the cell body contrast. Overall, these observations were fairly robust across the subject group (e.g. Supporting Fig. S9); some other interesting observations included a visibly heterogeneous structure within the MD, showing a hypointense “arc shape” in medial-anterior (and possibly posterior) sub-regions, around a lighter lateral sub-region, which could be observed in both SWI and BigBrain for several subjects (e.g. Supporting Fig. S9a,b, top

slice), but less clearly in others (e.g. Fig. 7). Of note, in the SWI data, a certain degree of spatial continuity across slices could be observed between regions like the MD and the red nucleus (RN) below, and similarly for the VM and the sub-thalamic nucleus (STN), for example (Supporting Fig. S10). While these pairs of regions showed clear differentiations in shape, excluding the possibility of some regions being simply an extension of the susceptibility effects produced by others, the geometries shown by the Morel atlas and BigBrain did suggest clearer spatial separations between these structures than those shown on SWI.

[Please insert Fig. 7 approximately here, preferably 2 col-wide]

Further anatomical insights were pursued by bringing the enhanced SWI data to MNI space, for direct comparison to the Schaltenbrand atlas. At  $z = 3.5\text{mm}$ , and consistent with the observations made in native space, SWI exhibited a rich distribution of hypo- and hyper-intense features (Fig. 8). The most posterior hypo-intense area matched the atlas indication for the Pu, particularly for its lateral sub-regions (Fig. 8, green); a medial region was well-matched to Pf (blue); laterally, two regions matched the ventro-caudalus (Vc, purple) and the ventro-odalis (Vo, red) / latero-polaris (Lpo, orange) group. Based on the distribution of these dark regions, a series of neighboring nuclei could then be indirectly located, such as Ce (pink) and the Vim nucleus (yellow). As in native space, the SWI features appeared to be anatomically richer than BigBrain's, and were overall fairly consistent across subjects (Fig. 8).

[Please insert Fig. 8 approximately here, preferably 2 col-wide]

## 4. Discussion

The present work builds on the promising brain imaging capabilities demonstrated by magnetic susceptibility-based contrasts at ultra-high field in recent years (2,5), and explored a series of novel technical improvements for high-resolution SWI, with a particular focus on thalamic imaging (13). These improvements included: (i) monitoring and compensation of head motion and  $B_0$  field perturbations during SWI acquisition, to increase image quality; (ii) segmentation and removal of venous vessels from the SWI data, to mitigate their confounding effects; (iii) modifications of the SWI contrast by tuning its phase-magnitude combination, for increased image contrast. To our knowledge, this is the first work employing these techniques for high-resolution SWI of the thalamic nuclei, and evaluating their benefits. The reported findings also extend to a wider scope of applications, namely regarding susceptibility-based contrasts in general.

### 4.1. Motion and field artifact correction

Despite continued efforts to accelerate MRI acquisitions (61,62), high-resolution 3D scans still typically require several minutes for completion, during which time even very compliant subjects can move by at least some hundreds of micrometers (63). The data collected in this work appear in line with this description, showing head displacements of 0.12–0.41 mm during the SWI scans (Supporting Fig. S2). While this indicates a relatively good subject performance, the extent of motion is nevertheless comparable to the in-plane voxel width (0.375 mm). Accordingly, the resulting images were generally of acceptable quality, and would likely be considered of diagnostic value in numerous applications; nonetheless, some of the finer features did exhibit visible blurring and ringing effects in several cases (e.g. Fig. 3A), effectively compromising the level of specificity originally sought. In parallel with motion, perturbations of the  $B_0$  field were found averaging at 1.6–4.6 Hz in amplitude, a range which is consistent with previous reports (26,27,64,65). The field perturbations contained both slow-drift and faster oscillatory patterns, which have been previously observed as well (64,65). The oscillatory contributions can be clearly attributed to the breathing cycle (64); the slower contributions could have diverse origins, including other physiological and metabolic sources (64), but may have been strongly driven by drifts in head position/orientation, as these have been found to generate important perturbations in the measured field at a similar order of magnitude (66). From these perturbations resulted diverse image artifacts (e.g. Fig. 3B), also consistent with previous reports (26,65). The contributions from motion and field perturbations did vary in their relative importance across subjects, likely related to both performance and individual anatomy. Altogether, these observations demonstrate the importance of both motion and field perturbations in high-resolution susceptibility imaging, even in realistic conditions of restricted head motion and natural breathing, thereby supporting, and complementing, previous methodological works (24-29,40,64,65,67).

The use of integrated navigators allowed substantially mitigating both motion and field artifacts, retrospectively. Despite a relatively good subject performance, this approach still yielded improvements of up to 76% in image quality across the brain. The motion and field correction steps each produced visible, specific improvements in local image features (Fig. 3). Across the group, the corrections were found to mitigate the originally observed decreases in image quality with increasing displacement/field deviations (Fig. 1), thereby making the resulting images less dependent on the subject performance. Nonetheless, the most affected cases still tended to rank lower than the least affected ones after correction, suggesting room for further improvements. Previous dedicated studies can also provide additional insight on how the FatNav and FatNav + FIDNav approach could potentially perform in regimes of larger motion and field perturbations, which could be relevant for other clinical applications (33,34,40,68).

In this report, the impact of motion and field perturbations was analyzed not only on the magnitude but also on the phase data, which is of crucial importance to susceptibility-based modalities like SWI, phase

imaging, quantitative susceptibility mapping (QSM) and susceptibility tensor imaging (STI) (2,64). Like the magnitude, phase images showed decreased quality with increasing displacement/field deviations, across the brain and more particularly at the thalamus (Fig. 1). The latter observation is possibly linked to the presence of valuable contrast features in the thalamus for the phase data, which SWI favorably exploits. Compared to the magnitude, the improvements in phase image quality with artifact correction were more moderate, but nevertheless well visible in the data (Fig. 3). Interestingly, some of the artifacts that strongly affected the magnitude were not particularly noticeable on the phase (e.g. Fig. 3B, putamen/globus pallidus), and vice-versa, supporting their distinct profiles of anatomical information, and artifact sensitivity. Beyond SWI, these findings also stress the importance of both motion and field correction for high-resolution susceptibility modalities, including QSM and STI, as previously pointed out by others as well (64).

#### **4.2. Vein segmentation and exclusion**

The vein detection approach was generally found considerably effective, demonstrating high specificity for features of tubular geometry, while sparing non-venous structures that also appeared hypo-intense, and likely of anatomical relevance (Fig. 4b). This is in agreement with previous studies reporting a good performance of this technique on SWI and other MRI modalities (52-54). Across the range of vessel scales probed by the filter, only a few of the smallest-caliber veins were missed (e.g. Fig. 4a, red arrows). These occurrences could be in part due to partial volume effects, especially across the slice direction, given the high anisotropy of SWI voxel dimensions. On the other hand, this anisotropy is important for venous contrast (8,69), and overall, such false negatives were fairly rare, particularly inside the thalamus. Concordantly, the distribution of vein densities in the thalamus estimated from this segmentation was fairly robust across subjects, and consistent with the expected anatomy (54,60). The group results could be linked to specific, well-defined veins on several of the individual images (e.g. Fig. 5b), demonstrating the excellent capabilities of high-resolution SWI at 7T for venography, including applications targeting the thalamic veins.

In principle, if necessary for certain targets other than the thalamus, the range of spatial scales covered by the filter could be expanded beyond the limit of 1.2mm used in this work, and in principle would allow the detection of the larger-caliber vessels that were missed here (Fig. 4b) (54). From a technical standpoint, the adopted interpolation approach does not impose any specific requirements on the shape and size of the masked regions, and would remain fully applicable, simply relying on its intrinsic assumptions to fill-in the masked region (36). However, it is important to keep in mind that, apart from partial volume effects, there is no actual brain tissue in the regions marked as veins. For smaller-caliber vessels, these partial volume effects will have a relatively larger contribution, and the intensities given by interpolation can still provide

useful estimates of the local non-venous compartments present in those vein-dominated voxels. When covering larger-caliber vessels, on the other hand, the information filled-in will be, in this sense, increasingly more “artificial” – and should be considered simply as a means to ease visualization and/or subsequent image processing steps. For certain applications, such as intensity-based segmentation/classification, the vein masks could alternatively be used to just exclude those voxels from the analyses, without attributing actual estimates. Nevertheless, overall, at the level of the thalamus, the caliber of vessels actually penetrating the thalamic regions was fairly moderate (Fig. 4b, 5b), and the non-venous anatomical features observed with SWI tended to be more spatially extended, and less sharply defined than the veins (Fig. 7, 8); this suggests that the intensities given by interpolation still provide fairly accurate estimates of the non-venous tissue present in the vein-dominated voxels.

### **4.3. SWI-based thalamic imaging**

As initially hypothesized, variations in the SWI combination parameters created substantial changes on the resulting contrast (Fig. 6), and improvements inside the thalamus were observed for parameters considerably beyond those of conventional SWI. This is not wholly unexpected given that the latter was optimized for vein imaging (7), whereas thalamic nuclei differentiation should depend on considerably different features of tissue composition, microstructure and spatial extent (2,5). Importantly, because phase effects extend beyond their originating regions, the high-pass filtering parameter  $\sigma$  required particular attention, to avoid introducing misleading non-local features when exploring more permissive filters. This behavior was not found problematic for the range of parameters tested, with the observed features remaining fairly well localized (Fig. 6). Nonetheless, it is expected that the observed features will invariably appear larger than the underlying anatomical features, as is already the case for veins in conventional SWI. Likely evidence of this effect can be seen on the observed extent of the RN and STN across slices, when compared to atlas information (Supporting Fig. S10) – this, however, is unrelated to the phase filtering process, as that was applied in 2D, slice by slice.

In line with insights from previous studies (13), the diverse anatomical comparisons performed in this work provide compelling evidence for the ability to differentiate several nuclei and nuclei groups within the thalamus with SWI (Fig. 7), especially rich in lower intermediate cuts at the level of the Vim nucleus, for instance (Fig. 8). The underlying mechanisms by which these tissues may generate the observed contrast remain, however, unclear. Previous works with diffusion-based modalities suggest complex variations in microstructure across the thalamic nuclei (14,23), and studies on the phase of the MR signal in white matter have shown that it is strongly affected by axonal orientation with respect to the main magnetic field (70). Cell body density may also play a relevant role, considering the similarities and differences found here between the SWI and BigBrain data (Fig. 7,8). This issue further relates to the rather empirical nature of

SWI, especially for vein-unrelated applications, and may be overcome in the future with more comprehensive studies exploring quantitative modalities such as QSM and STI, at high resolution. While technically more demanding and less practical to carry out routinely (2), these techniques could prove valuable to clarify the underlying contrast mechanisms, and provide clues to the development of further improved, and more practical new modalities. In the meantime, the results obtained in this work indicate that optimizing the SWI phase-magnitude combination provides an effective way to substantially enhance contrast in the thalamus, which can be fairly easily implemented. Future work could also include attempting this enhancement strategy at lower field strengths, which are currently more widely available in the clinics, but where, to our knowledge, little intra-thalamic contrast can typically be observed (71).

## **5. Conclusion**

High-resolution susceptibility-weighted modalities at 7T can strongly benefit from motion and breathing artifact corrections. In parallel, optimizing the SWI phase-magnitude combination provides an effective and straightforward way to improve contrast in the thalamus beyond the capabilities of conventional SWI, enhancing features with solid anatomical correspondence to known thalamic nuclei. Vein detection and suppression further improves thalamic visualization. Altogether, these developments substantially improve the capabilities of SWI for non-invasive thalamic nuclei imaging, a challenging task of importance to numerous scientific and clinical applications, including functional neurosurgery.

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## **Disclosure/Conflicts of Interest**

The authors declare no conflicts of interest.

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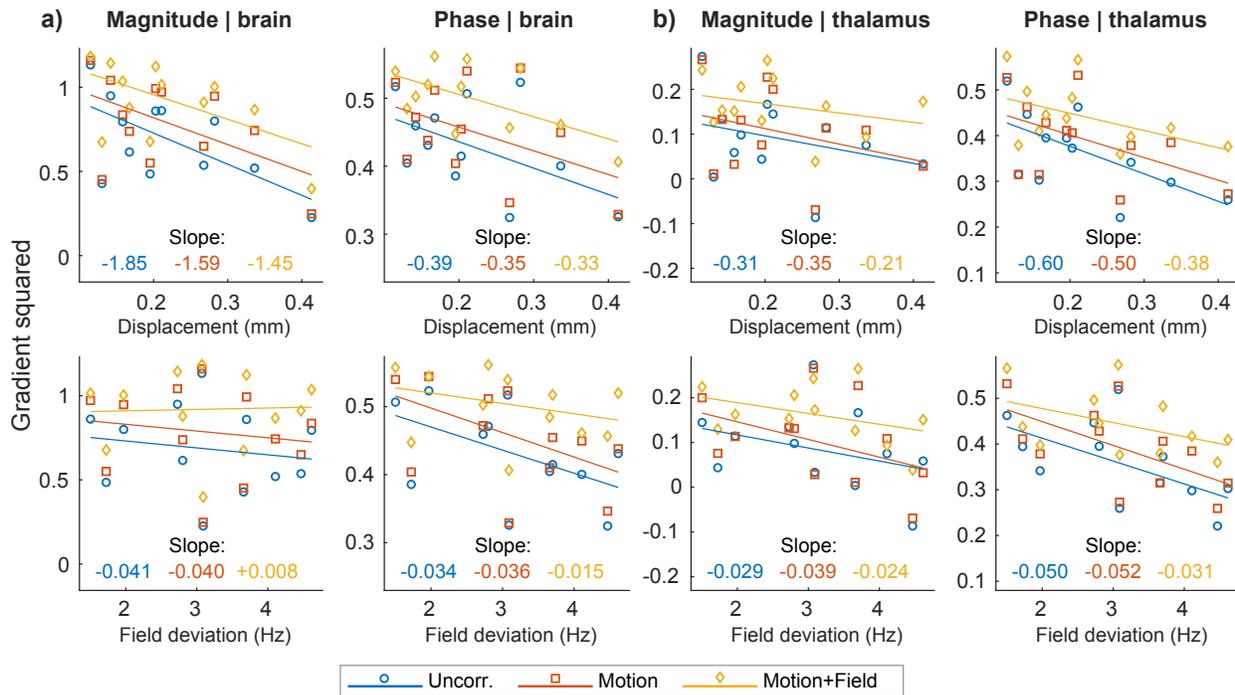
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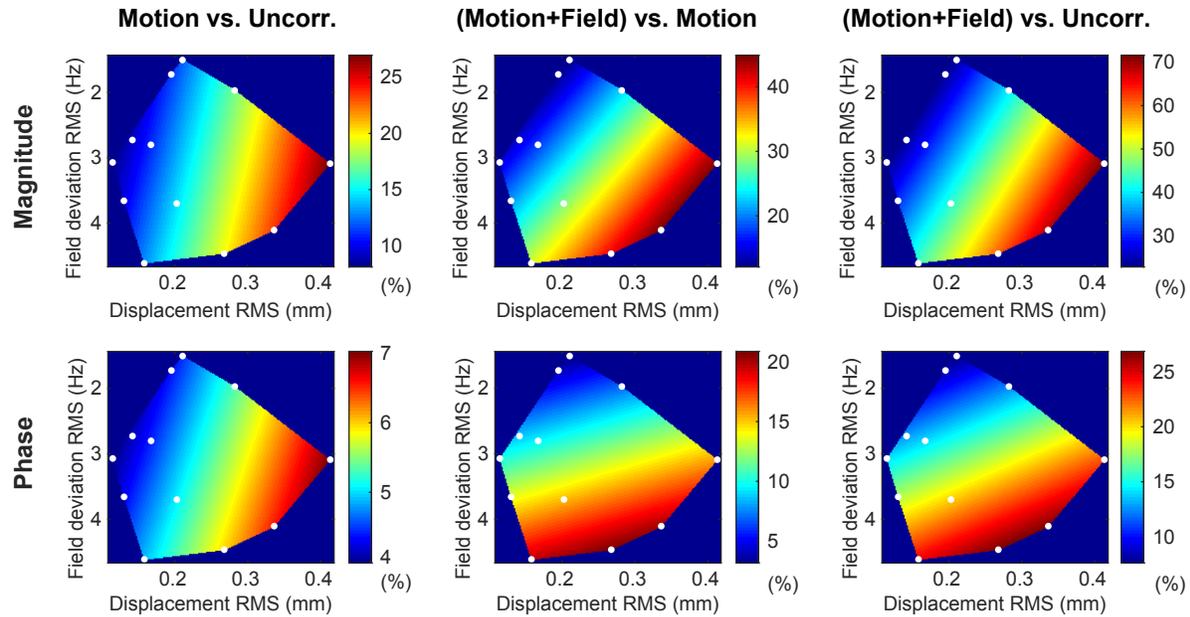
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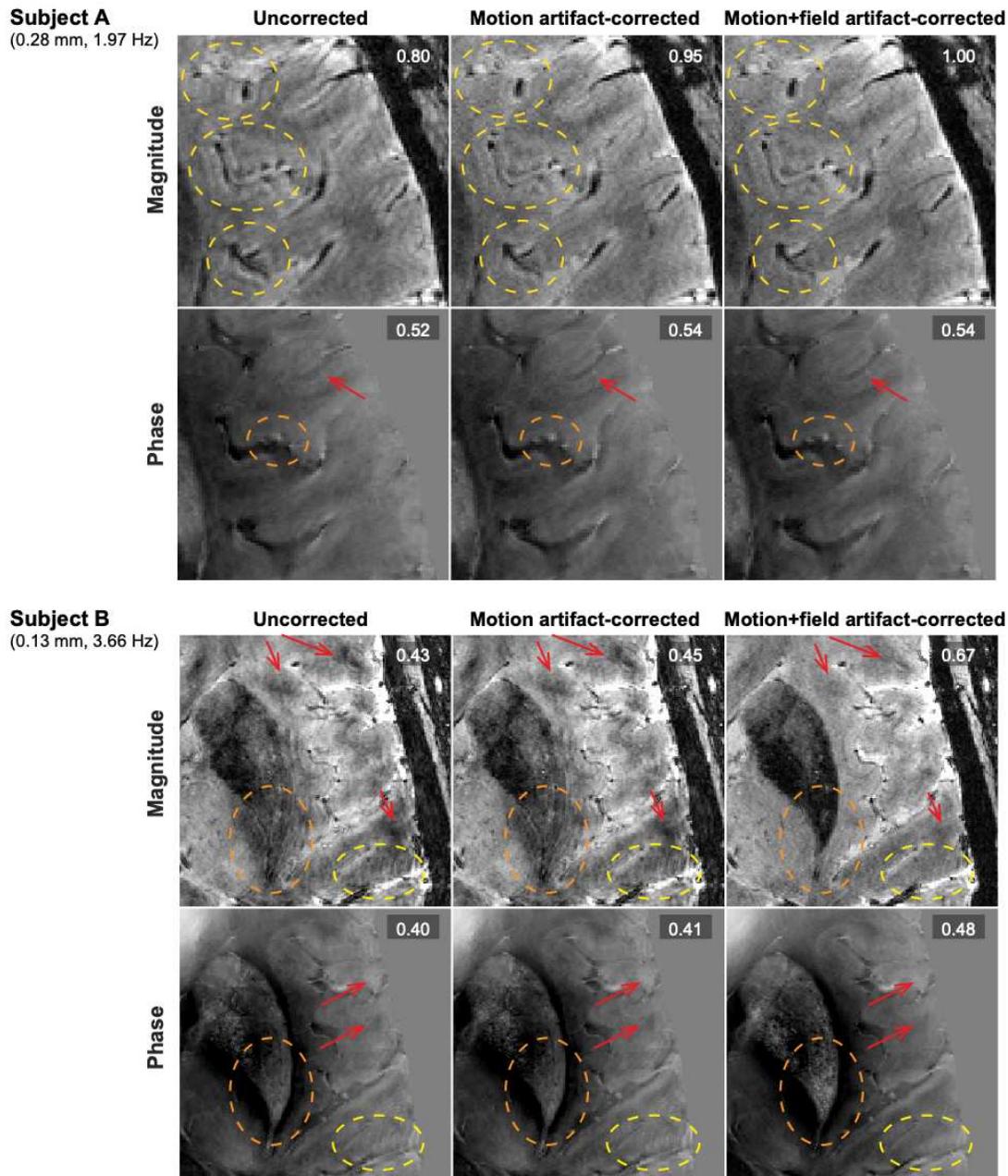
# Figures



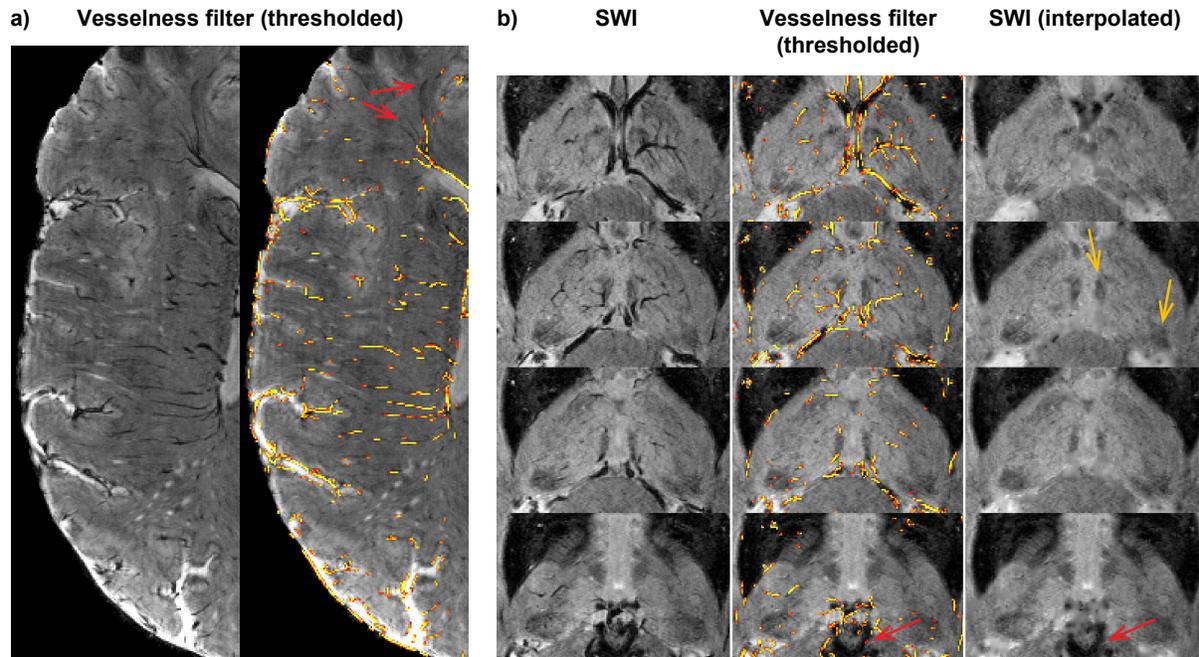
**Fig. 1.** Variations in GRE image quality across subjects as a function of head motion (displacement RMS) or field fluctuations (field deviation RMS), before and after correcting for motion and field artifact contributions. Image quality is described based on the (excess) gradient squared metric, applied separately to the magnitude and phase data, voxel by voxel, and averaged across the whole brain (**a**) or the thalamus (**b**). Each dot corresponds to a specific subject, with a given correction approach; the straight lines correspond to robust linear fits to the subject data points for each of the correction approaches (obtained with Matlab function *robustfit*), and their slopes are provided below in the same respective color.



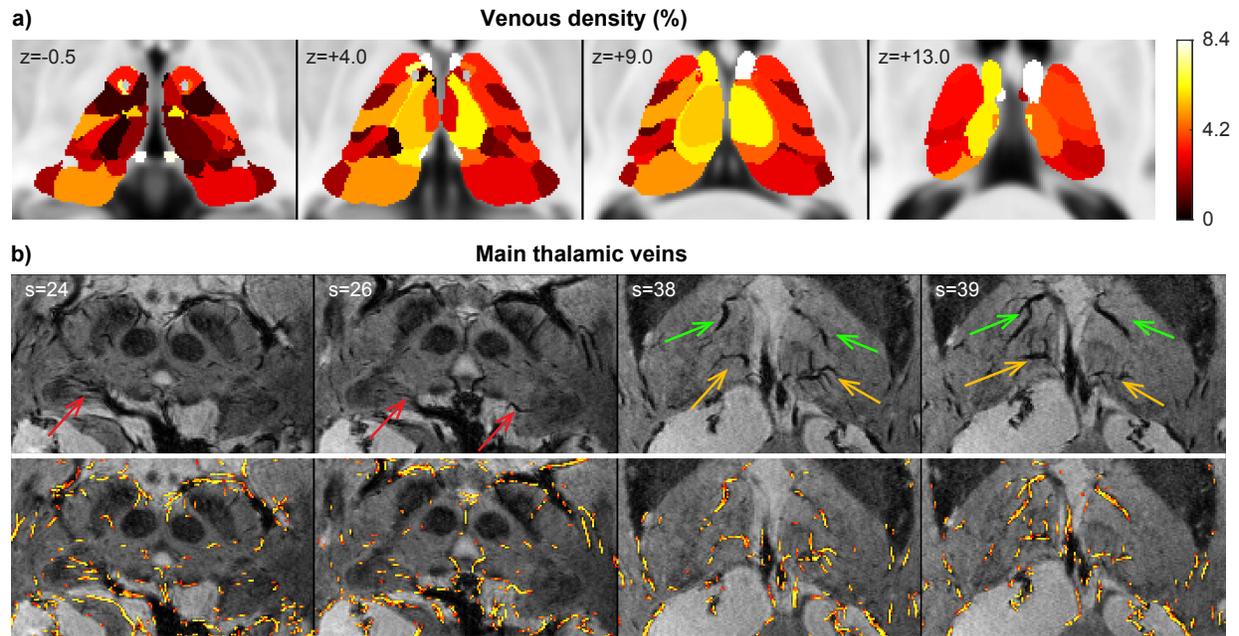
**Fig. 2.** Variations in individual GRE image quality between the different artifact correction steps, as a function of head motion (displacement RMS) and field fluctuations (field deviation RMS), combined. The variations in image quality are described in terms of relative changes in the excess normalized gradient squared, applied separately to the magnitude and phase data, voxel by voxel, and then averaged across the whole brain. Each white dot corresponds to a specific subject; the 2D distributions were obtained as robust linear fits to those individual data points.



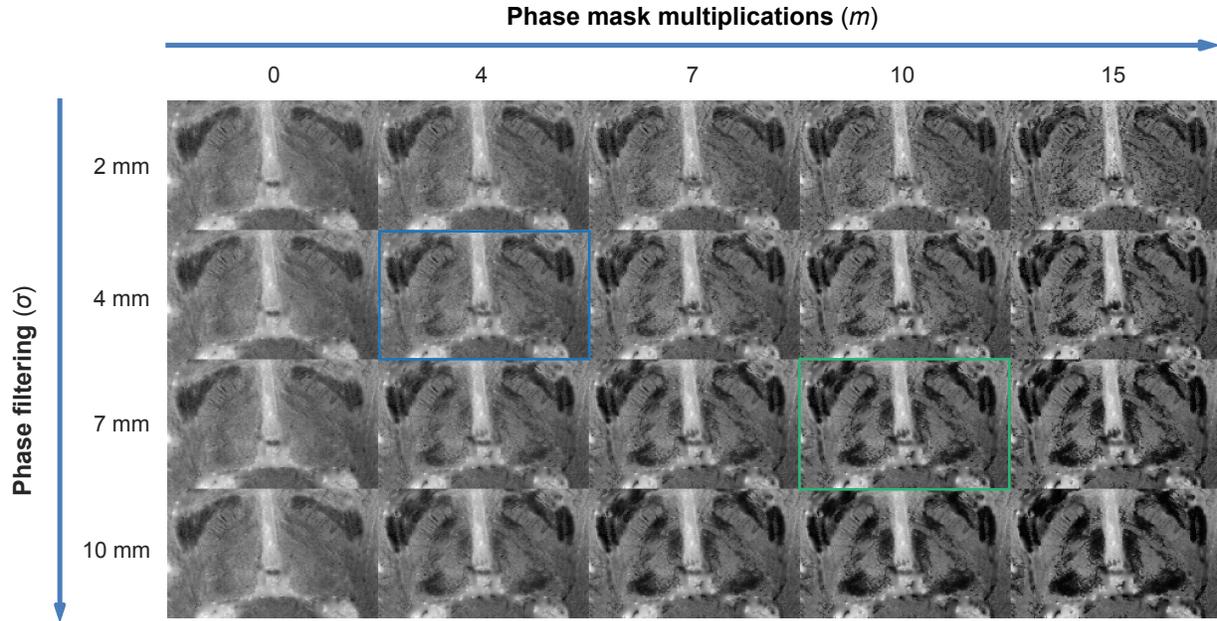
**Fig. 3.** Local improvements in GRE magnitude and phase data achieved with motion and field artifact correction, in two example subjects. Subject A exhibited a relatively larger incidence of motion (0.28 mm displacement RMS) than field perturbations (1.97 Hz deviation RMS); subject B exhibited the opposite (0.13 mm displacement, 3.66 Hz deviation). The gradient squared estimates for each magnitude and phase image are indicated on the respective top right corner. The arrows and traced circles highlight regions that were particularly affected, and improved with correction; these artifacts included blurring, ringing, ghosting, and local hypo- and hyper-intensities.



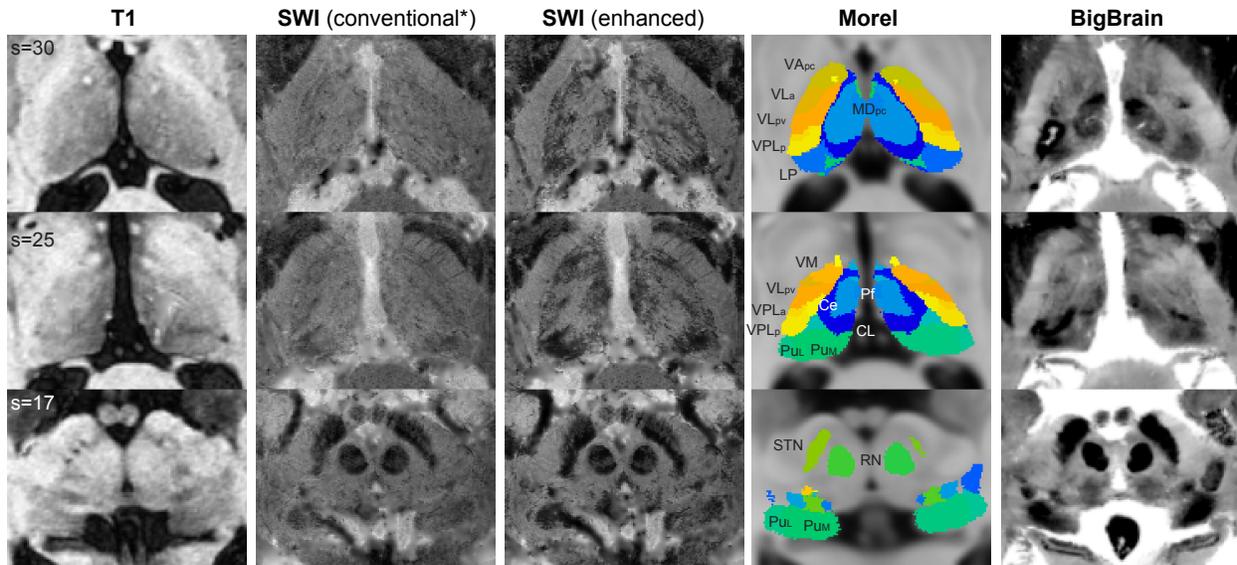
**Fig. 4.** Vein detection and interpolation in the SWI data (conventional contrast) of an example subject. **a)** Vesselness filter output overlaid on the SWI data, thresholded with the same cutoff applied to create the vein masks. The red arrows indicate an example of very small-caliber veins that were missed by the filter. **b)** Example of the performance of vein interpolation in four slices of the thalamus, which exhibited both subtle as well as larger veins, crossing various thalamic nuclei. The red arrows indicate an example of large-caliber veins that were not detected by the filter; the yellow arrows indicate examples of hypo-intense regions of non-tubular geometry, and likely of anatomical relevance, which were correctly ignored by the filter.



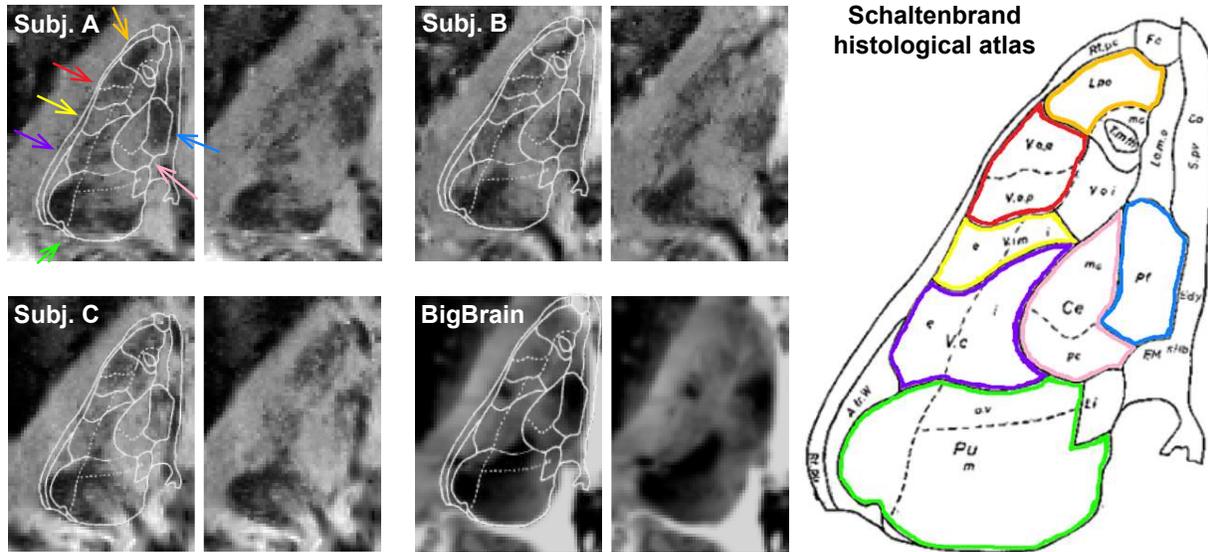
**Fig. 5.** Distribution of veins in the thalamus based on the estimated vein masks. **a)** Venous density averaged within each thalamic region of the Morel atlas (56) and across subjects, in MNI space; the high-end of the color scale is adjusted to the 90<sup>th</sup>-percentile of densities, for clearer visualization. **b)** Examples of the main thalamic veins observed in individual SWI data, including the basal veins, with perforating vessels (red arrows), superior thalamic veins (yellow arrows), and anterior thalamic veins (green arrows). The lower row shows an overlay of the vesselness filter output over the same thalamic slices, thresholded with the same cutoff used to create the vein masks. The numbers in black (a) indicate the  $z$ -planes selected from MNI space, in mm; the numbers in white (b) indicate the slices selected from the native SWI slab.



**Fig. 6.** Variations of the SWI contrast obtained when increasing the FWHM  $\sigma$  of the Gaussian-based high-pass filtering of the phase data (top to bottom) and the number  $m$  of multiplications of the phase mask into the magnitude data (left to right). The case that most closely matches a conventional SWI contrast, as produced by the online reconstruction of our system, is indicated in blue ( $\sigma = 4$ mm,  $m = 4$ ). An enhanced case, which was empirically selected for further analysis, is indicated in green ( $\sigma = 7$ mm,  $m = 10$ ).



**Fig. 7.** Image contrast in the thalamus of an example subject obtained with different imaging modalities, co-registered to the SWI native space: T<sub>1</sub>-weighted contrast from the MP2RAGE acquisition (1<sup>st</sup> column); SWI with close-to-conventional contrast, i.e. the closest output of our approach ( $\sigma = 4\text{mm}$ ,  $m = 4$ ) to the scanner online reconstruction (2<sup>nd</sup> column; marked with a \* to highlight its difference from the originally proposed approach (7)); and SWI with enhanced contrast ( $\sigma = 7\text{mm}$ ,  $m = 10$ ; 3<sup>rd</sup> column). Reference information from the Morel atlas (4<sup>th</sup> column) and BigBrain (5<sup>th</sup> column) are shown for anatomical comparison; the colors of the Morel atlas are attributed randomly, simply to differentiate its sub-regions; the contrast in BigBrain is hypo-intense for regions of higher cell body density (58). The Morel atlas labels indicate the ventral anterior (VA), ventral lateral (VL) ventral posterolateral (VPL), lateral posterior (LP), mediodorsal (MD), ventromedial (VM), pulvinar (Pu), centromedian (Ce), parafascicular (Pf), central lateral (CL), sub-thalamic (STN), and red (RN) nuclei. Three slices are shown, ascending through the thalamus from the bottom to the top row; the numbers on the top-left indicate the slices selected from the native SWI space.



**Fig. 8.** Image contrast in the right thalamus of 3 example subjects, in MNI space, for an axial slice positioned at  $z = 3.5$  mm, expected to contain multiple thalamic nuclei groups. A reference slice adapted from the Schaltenbrand histological atlas (57) is also shown for the same position ( $z = 3.5$  mm). The SWI data are shown with and without an overlay of the atlas contours, delineating the different nuclei groups, for anatomical comparison. The colored arrows indicate the nuclei identified with the same colors on the atlas (right side), comprising the latero-polaris (Lpo), ventro-odalis (Vo), ventral intermediate nucleus (Vim), ventro-caudalus (Vc), pulvinar (Pu), centromedian (Ce) and parafascicular (Pf). The BigBrain reference is also shown in the same position; its contrast is hypo-intense for regions of higher cell body density (58).