Multi-centre, multi-vendor reproducibility of 7T QSM and R_2* in the human brain: results from the UK7T study

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Abstract

We present the reliability of ultra-high field T_2* MRI at 7T, as part of the UK7T Network's "Travelling Heads" study. T_2*-weighted MRI images can be processed to produce quantitative susceptibility maps (QSM) and R_2* maps. These reflect iron and myelin concentrations, which are altered in many pathophysiological processes. The relaxation parameters of human brain tissue are such that R_2* mapping and QSM show particularly strong gains in contrast-to-noise ratio at ultra-high field (7T) *vs* clinical field strengths (1.5 - 3T). We aimed to determine the inter-subject and inter-site reproducibility of QSM and R_2* mapping at 7T, in readiness for future multi-site clinical studies.

Methods: Ten healthy volunteers were scanned with harmonised single- and multi-echo T_2*-weighted gradient echo pulse sequences. Participants were scanned five times at each "home" site and once at each of four other sites. The five sites had 1x Philips, 2x Siemens Magnetom, and 2x Siemens Terra scanners. QSM and R_2* maps were computed with the Multi-Scale Dipole Inversion (MSDI) algorithm (https://github.com/fil-physics/Publication-Code). Results were assessed in relevant subcortical and cortical regions of interest (ROIs) defined manually or by the MNI152 standard space.

Results and Discussion: Mean susceptibility (χ) and R_2* values agreed broadly with literature values in all ROIs. The inter-site within-subject standard deviation was 0.001 – 0.005 ppm (χ) and 0.0005 – 0.001 ms^{-1} (R_2*). For χ this is 21-95% better than 3T reports, and 15-124% better for R_2*. The median ICC from within- and cross-site R_2* data was 0.98 and 0.91, respectively. Multi-echo QSM had greater variability *vs* single-echo QSM especially in areas with large B_0 inhomogeneity such as the inferior frontal cortex. Across sites, R_2* values were more consistent than QSM in subcortical structures due to differences in B_0-shimming. On a between-subject level, our measured χ and R_2* cross-site variance is comparable to within-site variance in the literature, suggesting that it is reasonable to pool data across sites using our harmonised protocol.

Conclusion: The harmonized UK7T protocol and pipeline delivers over a 2-fold improvement in the coefficient of reproducibility for QSM and R_2* at 7T compared to previous reports of multi-site reproducibility at 3T. These protocols are ready for use in multi-site clinical studies at 7T.

Keywords

7 tesla; MRI; Quantitative Susceptibility Mapping; R_2* mapping; Multi-centre; Reproducibility.

1. Introduction

Neurodegenerative diseases are a significant global health burden. In many instances, neurodegeneration is associated with the deposition of iron in the brain. Understanding the patterns of deposition and their association with other risk factors is a key area of clinical research, but progress has been limited by the need to scale over multi-centre trials.

A popular approach to estimating iron concentration in the human brain uses gradient-echo (GE) magnetic resonance imaging (MRI). In grey matter, iron is mainly found in the protein ferritin, where it exists in a paramagnetic state (Langkammer et al., 2012). This paramagnetic iron interacts with the MRI scanner's static magnetic field (B_0) causing local dipolar field perturbations. These accentuate the rate of transverse signal decay causing T_2* relaxation in surrounding tissue, which is visible as decreasing signal amplitude with increasing echo time in a series of GE images. This effect causes an increase in the *rate* of transverse relaxation, R_2*, which correlates well with non-heme iron concentrations in grey matter (Gelman et al., 1999; Langkammer et al., 2010), and has been used to investigate the distribution of iron in the healthy brain and in disease (Haacke et al., 2005; Yao et al., 2009; Li et al., 2019).

The local presence of iron (and to a lesser extent myelin and calcium) also affects the signal phase of GE images because of the effect of the field perturbation on the local Larmor frequency (House et al., 2007; He et al., 2009; Lee et al., 2012). Quantitative Susceptibility Mapping (QSM) methods attempt to deconvolve these dipole phase patterns to identify the sources of the magnetic field inhomogeneity. In other words, QSM estimates quantitative maps of tissue magnetic susceptibility χ from GE phase data (Li and Leigh, 2004; Reichenbach, 2012; Wang and Liu, 2015). This approach has shown sensitivity to several neurological conditions (Lotfipour et al., 2012; Acosta-Cabronero et al., 2013; Blazejewska et al., 2015; Acosta-Cabronero et al., 2016) and offers advantages over magnitude R_2* such as having reduced blooming artifacts or being able to distinguish between paramagnetic and diamagnetic substances (Eskreis-Winkler et al., 2017).

R_2* imaging and QSM have been shown to provide reproducible results in single-site and cross-site studies at 1.5T and 3T (Hinoda et al., 2015; Cobzas et al., 2015; Deh et al., 2015; Lin et al., 2015; Santin et al., 2017; Feng et al., 2018; Spincemaille et al., 2019).

The dipole-inversion problem at the heart of QSM methods benefits from the increased sensitivity to magnetic susceptibility variation and spatial resolution at ultra-high fields ($B_0 \geq 7$ T) (Yacoub et al., 2001; Reichenbach et al., 2001; Tie-Qiang et al., 2006; Duyn et al., 2007; Wharton and Bowtel, 2010). At 7T, close attention must be paid to B_0 shimming and gradient linearity to achieve accurate QSM and R_2* mapping (Yang et al., 2010). Head position is also an important factor that affects the susceptibility anisotropy (Lancione et al., 2017; Li et al., 2017).

In this study, we introduce single-echo and multi-echo GE imaging protocols for QSM and R_2* mapping at 7T which were standardised on three different 7T MRI scanner platforms, from two different vendors. We applied this standardised protocol in the UK7T Network's "Travelling Heads" study on 10 subjects scanned at 5 sites. We report reproducibility for derived R_2* and QSM maps and make recommendations for the design of future multi-centre studies.

#	Site	Vendor	Scanner Model	Gradient Performance	Installation Date (Month-Year)	Software Version
1	Wellcome Centre for Integrative Neuroimaging (FMRIB), University of Oxford	Siemens	Magnetom 7T	70 mT m^{-1} 200 mT m^{-1} ms^{-1}	Dec-2011	VB17A
2	Cardiff University Brain Research Imaging Centre, Cardiff University	Siemens	Magnetom 7T	70 mT m^{-1} 200 mT m^{-1} ms^{-1}	Dec-2015	VB17A
3	Sir Peter Mansfield Imaging Centre, University of Nottingham	Philips	Achieva 7T	40 mT m^{-1} 200 mT m^{-1} ms^{-1}	Sep-2005	R5.1.7.0
4	Wolfson Brain Imaging Centre, University of Cambridge	Siemens	Magnetom Terra	80 mT m^{-1} 200 mT m^{-1} ms^{-1}	Dec-2016	VE11U
5	Imaging Centre of Excellence, University of Glasgow	Siemens	Magnetom Terra	80 mT m^{-1} 200 mT m^{-1} ms^{-1}	Mar-2017	VE11U

Table 1: Details of the scanners and hardware used for the UK7T Network's Travelling Heads study.

2. Methods

2.1. Measurement setup

Ten healthy volunteers (3 female, 7 male; age 32.0±5.9 years) were recruited: comprising two subjects from each of the five 7T imaging sites in the UK7T Network (described in Table 1). Each subject was scanned five times at their "home" site, and once at the other sites, under local ethics approval for multi-site studies obtained at Site-4 (HBREC.2017.08). Scans for each subject were completed within a period of between 83 and 258 days.

In every scan session, B_0 shimming was performed using the vendors' default second-order (or third-order for Site-4 and Site-5) B_0-shimming routines. B_1^+-calibration was performed initially using the vendor's default adjustment scans. A 3D DREAM sequence (Nehrke et al., 2012; Ehses et al., 2019) was subsequently acquired and the transmit voltage (or power attenuation) was then adjusted for all subsequent imaging based on the mean flip-angle from the brain in an anatomically-specified axial slice of the 3D DREAM flip angle map as described in Clarke et al. (2019). Single-echo (SE) 0.7mm isotropic resolution T_2*-weighted GE data were then acquired with: TE/TR=20/31ms; FA=15°; bandwidth=70Hz/px; in-plane acceleration-factor=4 (Sites-1/2/4/5) or 2x2 (Site-3); FOV=224x224x157mm^3; scan-time=~9min. Multi-echo (ME) 1.4mm isotropic resolution T_2*-weighted GE data were acquired with: TE_1/TR=4/43ms; 8 echoes with monopolar gradient readouts; echo-spacing=5ms; FA=15°; bandwidth=260Hz/px; acceleration-factor=4 (Sites-1/2/4/5) or 2x1.5 (Site-3); FOV=269x218x157mm^3; scan-time ~6min (Sites-1/2/4/5) and ~4min (Site-3). For Siemens data, coil combination was performed using a custom implementation of Roemer's algorithm, as previously described (Clarke et al., 2019). Subject 6's SE scan failed to reconstruct using Roemer's method on data from the 1st visit at Site-5 so a sum-of-squares (SoS) algorithm was used for coil combination for that scan instead. A 0.7mm isotropic MP2RAGE scan was used for within- and cross-site registration as previously described (Mougin et al., 2019).

2.2. QSM and R_2* data processing

QSM maps were generated from both the SE and ME T_2*-weighted datasets using the Multi-Scale Dipole Inversion (MSDI) algorithm, as implemented in QSMbox v2.0 (Acosta-Cabronero et al., 2018). Briefly: first the local field was estimated by phase unwrapping (Abdul-Rahman et al., 2005) and weighted least squares phase echo fitting was performed on the ME data. Then, for both SE and ME data, background field was removed using the Laplacian Boundary Value (LBV) method followed by the variable Spherical Mean Value (vSMV) algorithm with an initial kernel radius of 40mm (Zhou et al., 2014; Acosta-Cabronero et al., 2018). MSDI inversion was estimated with two scales: the self-optimised lambda method was used on the first scale with filtering performed using a kernel with 1mm radius, and on the second scale the regularization term was set to $\lambda=10^{2.7}$ (the optimal value for *in-vivo* 7T datasets found in (Acosta-Cabronero et al., 2018)) and filtering was done with a kernel radius set to 5mm. Brain masks used in the analysis were obtained with FSL's Brain Extraction Tool (BET) with fractional intensity threshold=0.2 for SE data (Smith, 2002). These were then mapped to ME data space.

On the ME data, QSM was reconstructed seven more times: with the shortest echo (TE1=4 ms), with the two shortest echoes (i.e. TE_1/TE_2 = 4/9 ms), with the three shortest echoes (i.e. $TE_1/TE_2/TE_3$ = 4/9/14 ms), and so forth.

On the ME dataset, voxel-wise quantitative maps of R_2* were obtained using the Auto-Regression on Linear Operations (ARLO) algorithm for fast monoexponential fitting (Pei et al., 2015).

2.3. Data Registration

The neck was cropped from the magnitude data with FSL's "robustfov" command (https://fsl.fmrib.ox.ac.uk/fsl/), applied to the SE data and the 4th echo of the ME data. High-resolution SE and ME templates were made from this cropped data for each subject with antsMultivariateTemplateConstruction2.sh from the Advanced Normalization Tools (ANTs, http://stnava.github.io/ANTs/). Two approaches were compared: transformations using rigid registration with mutual information similarity metric (denoted as "Rigid" below) or using symmetric diffeomorphic image registration

with cross-correlation similarity metric (denoted "SyN" below). Other settings were kept the same for both approaches: 4 steps with 0.1 gradient step size, maximum iterations per step 1000, 500, 250 and 100, smoothing factors per step of 4, 3, 2, and 1 voxels, and shrink factors per step of 12x, 8x, 4x, and 2x. The resulting registrations were then applied to the QSM and R_2* maps which were averaged to create SE and ME QSM and R_2* templates for each subject.

2.4. Selection of Regions of Interest (ROIs)

Five regions of interest (Substantia Nigra, Red Nucleus, Caudate Nucleus, Putamen and Globus Pallidus) were manually segmented based on the subject-specific QSM templates of the SE data registered with the "SyN" approach. In order to minimize the amount of segmentation variability, these ROIs were then mapped to the SE "Rigid", and ME "SyN" and ME "Rigid" spaces with nearest neighbour interpolation and via non-linear registrations obtained with the default settings in the antsRegistrationSyN.sh command in ANTs.

Magnitude data were first registered to the T_1-weighted MP2RAGE scans (Rigid transformations; MI similarity metric) and later to the standard T_1 "MNI152 brain" (Montreal Neurological Institute 152) (using settings in antsRegistrationSyN.sh) applied to the SE data and to the 1st echo of the ME data. These registrations were then used to map the 48 probabilistic cortical ROIs, "cortical ROIs", from the Harvard-Oxford Cortical Atlas and the 21 probabilistic subcortical ROIs, "subcortical ROIs", from the Harvard Oxford Subcortical Atlas to the QSM and R_2* template spaces.

The T_1-weighted MP2RAGE data was bias-field corrected, brain extracted, and segmented into five tissues using SPM (https://www.fil.ion.ucl.ac.uk/spm/): the grey matter (GM), white matter (WM) and cerebral-spinal fluid (CSF) volumes were mapped into each subject-specific QSM template space. Then, using "fslmaths" from FSL (https://fsl.fmrib.ox.ac.uk/fsl/), the mapped cortical ROIs were thresholded at 10% of the "robust range" of non-zero voxels and multiplied by the GM tissue map in order to obtain GM-specific cortical ROIs. The mapped subcortical ROIs were thresholded at 50% of the "robust range" of non-zero voxels. From these, any CSF voxels were

excluded from the left and right Caudate Nucleus, Putamen and Globus Pallidus, and the voxel sets from the left and right counterparts were merged together.

From the SE and ME data, average χ and R_2* values were extracted from the manual and Atlas-based ROIs for all volunteers and sessions in template space (values given in Supplementary Material 1).

In order to estimate where the magnetic field is spatially more variable, field-maps were first estimated from the ME datasets. ΔB_0 was then calculated per-voxel as the average difference between the field in a voxel and its immediate nearest neighbors. The average ΔB_0 was extracted for each of the cortical ROIs and averaged across all subjects and sessions. Then the cortical ROIs were divided into two groups based on the ΔB_0 values: wherever $|\Delta B_0| > 0.005\ Hz$ the ROI was grouped into "high ΔB_0" regions, otherwise it was grouped into "low ΔB_0" regions.

We explored three possible susceptibility reference regions for QSM processing. The average QSM signal was extracted from:

1. A whole brain mask, "wb";
2. A whole-brain CSF mask eroded in two steps, "csf";
3. A manually placed cylindrical ROI in the right ventricle, "cyl" (across all subjects the ROI volume was 104±11 mm^3).

2.5. Statistical Analysis

Statistical analysis was performed with R 3.5.3 (R Core Team, 2013). Cross-site analysis used only the 1st scan at the "home" site along with the scans at the other four sites. To obtain the within subject average, AV_w, the χ and R_2* values were averaged within the same site and across the sites and then averaged across subjects:

$$\mathrm{AV}_w = \frac{\sum_{i=1}^{m} \left(\sum_{j=1}^{n} x_{ij}/n\right)}{m} \qquad [1]$$

where n is the number of sessions ($n = 5$ for within-site and cross-site) and m the number of subjects. Relative reliability was measured using the intra-class correlation coefficient (ICC) from within and cross-site data independently for each ROI (Weir, 2005):

$$\mathrm{ICC} = \frac{MS_b - MS_w}{MS_b + MS_w(n-1)} \qquad [2]$$

where MS_b and MS_w are the between-subjects and within-subjects mean square from a random-effects, one-way analysis of variance (ANOVA) model. Intra-subject absolute variability is assessed by measuring the within-subject standard-deviation (SD_w) calculated as (Santin et al., 2017):

$$SD_w = \sqrt{\frac{\sum_{i=1}^{m} \sigma_i^2}{m}} \text{ with } \sigma_i = \frac{\sqrt{\sum_{j=1}^{n} (x_{ij} - \bar{x}_i)^2}}{n-1} \qquad [3]$$

where $\bar{x}_i = \sum_{j=1}^{n} x_{ij}/n$ is the replicate average for each subject. SD_w was computed using within-site data and cross-site data independently. Similarly, cross-subject variability was calculated by measuring the between-subject standard-deviation (SD_b):

$$SD_b = \sqrt{\frac{\sum_{i=1}^{m} \sum_{j=1}^{n} (x_{ij} - x_{avg})^2}{n \times m - 1}} \qquad [4]$$

where $x_{avg} = \sum_{i=1}^{m} \sum_{j=1}^{n} x_{ij} \,/(n \times m)$ is the measurement average across subjects and sessions. Note that SD_b is computed using data from all sites.

Statistical testing on AV_w, SD_w and ICC values extracted from manual and template-based ROIs was done by first fitting the data with normal, log-normal, gamma and logistic distributions. The goodness-of-fit statistics for the parametric distributions were calculated and the distribution which showed the lowest Akaikes Information Criterion was then used on a general linear model fitting. All models included as fixed main effects ROI number and data type (within- and cross-site). When evaluating the data registration type, the model also included registration type ("Rigid" and "SyN") as a fixed main effect. When testing for QSM reference, the model also included reference region ("wb", "csf", and "cyl") as a fixed main effect. On ME QSM data, a model was fitted which also included the number of echoes processed as a fixed main effect. When comparing the manual and subcortical ROIs, the ROI type (manual vs. atlas-based) was also included as a fixed main effect. Finally, on the data from the cortical ROIs, ROI number was replaced with "high ΔB_0" and "low ΔB_0" ROI type as covariate. A p-value less than 0.05 was considered significant.

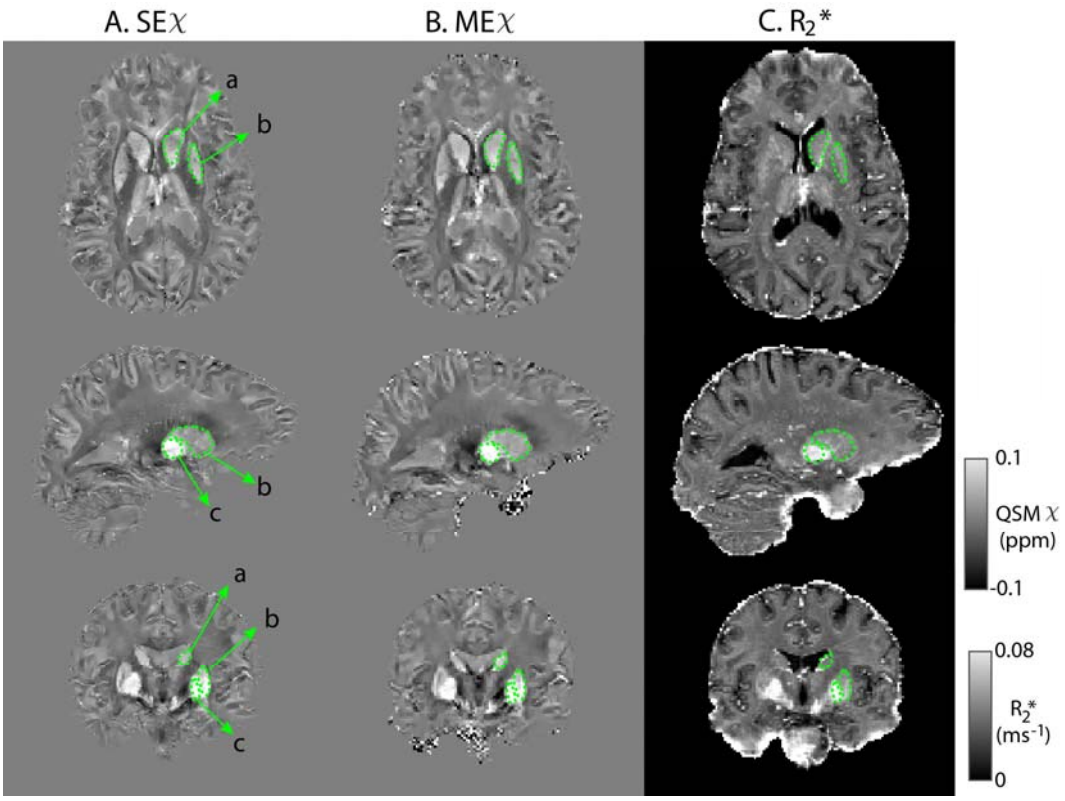

Figure 1: Representative slices of SE χ (A) ME χ (B) and R_2* maps (C) from an example subject. The right Caudate Nucleus (a), Putamen (b) and Globus Pallidus (c) are shown in green.

3. Results

Figure 1 shows QSM and R_2* maps for one example subject. Basal ganglia structures, including Caudate Nucleus, Putamen and Globus Pallidus are clearly visible consistent with previous findings (Langkammer et al., 2010; Wang et al., 2015; Betts et al., 2016; Acosta-Cabronero et al., 2016). Supplementary Material 2 Figure 1 highlights the difference in QSM data quality when using our chosen Roemer coil combination method *vs* using sum-of-squares coil combination.

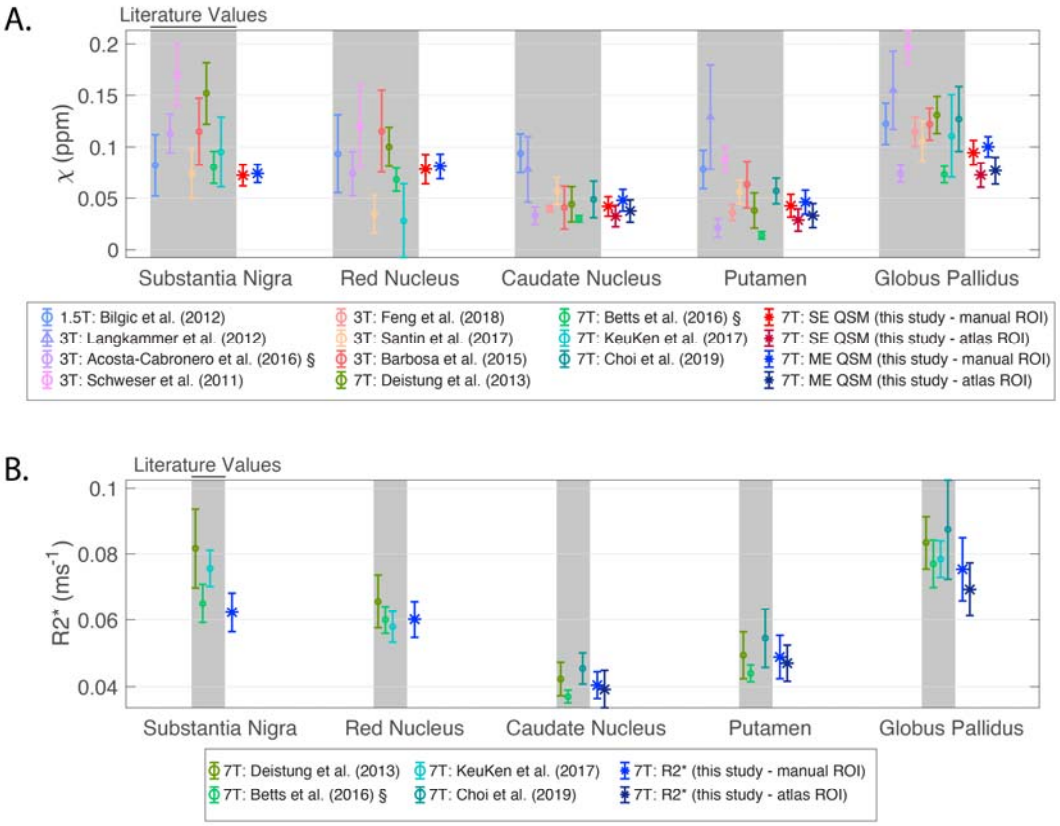

Figure 2: Mean and standard deviation literature values of QSM (A) and R_2* (B). The mean and standard deviation results from this study are also plotted. For data with the symbol '§' the standard error of the mean was originally reported and has been rescaled by reported N. Shaded regions correspond to literature data.

3.1. QSM and R_2* results and literature

Figure 2 compares average χ and R_2* values calculated in this study in the five manual ROIs and three corresponding atlas-based subcortical ROIs against literature ranges. The SE χ-values and ME χ-values from this study are consistent with literature values at 1.5T, 3T and 7T. R_2* values from this study also agree closely with 7T literature values.

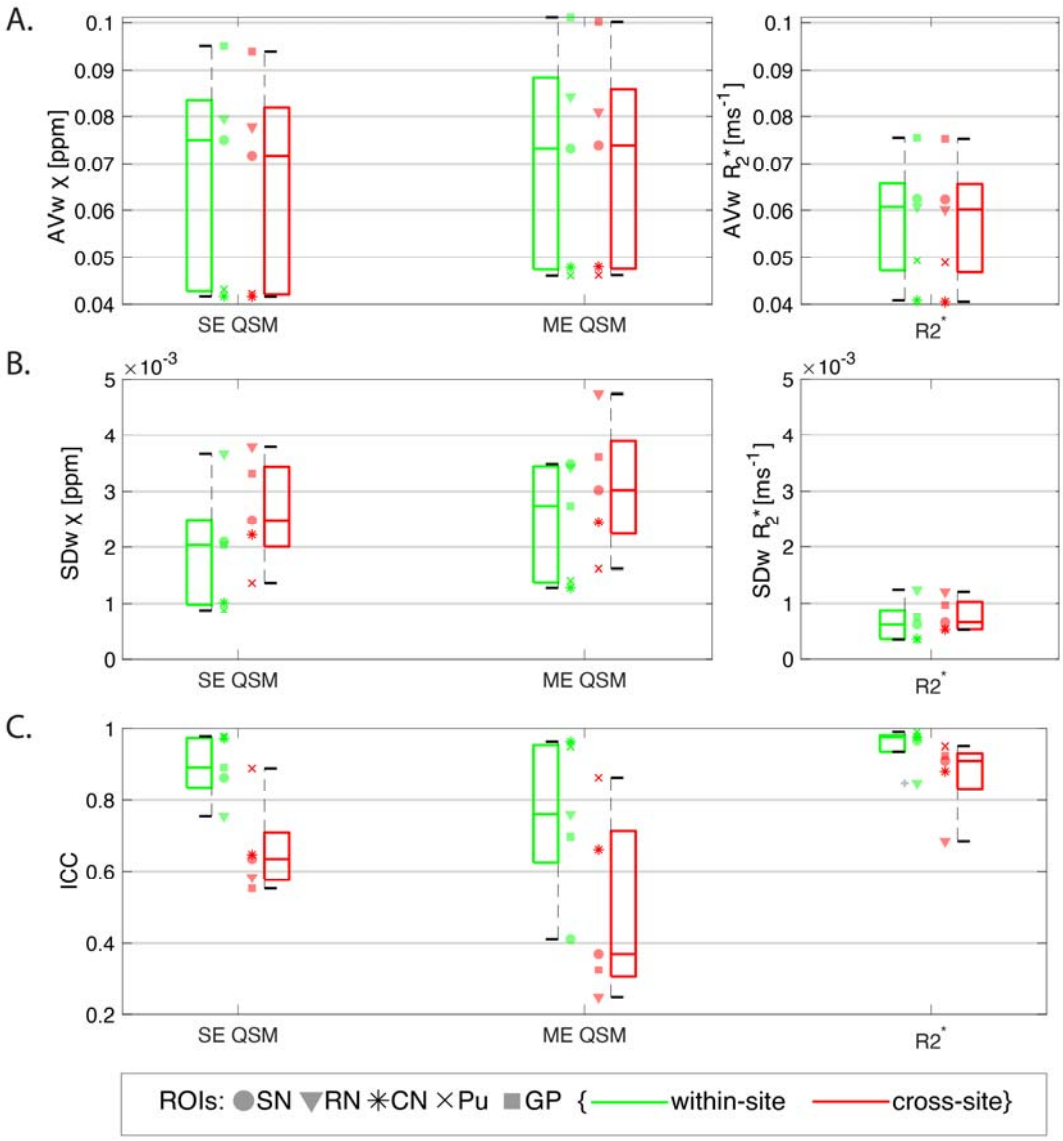

Figure 3. Boxplots from data obtained on the manual ROIs of within- and cross-site AV_w (A), SD_w (B) and ICC (C) of SE and ME QSM, and R_2*. Data from each ROI is shown with a different marker for each boxplot. Legend: SN=Substantia Nigra; RN: Red Nucleus; CN: Caudate Nucleus; Pu: Putamen; GP: Globus Pallidus.

3.2. Reproducibility of QSM and R_2*

Figure 3 shows boxplots over ROIs of the within- and cross-site AV_w (A), SD_w (B) and ICC (C) values for the manual ROIs on the χ and R_2* maps. The AV_w from R_2* maps measured on the same site is systematically higher compared to the AV_w measured across sites ($p < 0.0001$; e.g., on the Putamen ROI, $AV_{w_within\text{-}site} = 0.0493$ ms^{-1} vs $AV_{w_cross\text{-}site} = 0.0489$ ms^{-1}). On this comparison, QSM data did not show significant

differences between within-site and cross-site groups for either SE data ($p = 0.053$) or ME data ($p = 0.65$).

From all the data in the manual ROIs, the median SD_w of SE χ-values was approximately 29% lower than for ME χ-values ($p = 0.0010$). There was a significantly larger SD_w cross-site compared to within-site on SE χ data ($p < 0.0001$; e.g., on the PN ROI, $SD_{w_within\text{-}site} = 0.00088$ ppm vs $SD_{w_cross\text{-}site} = 0.0014$ ppm), ME χ ($p = 0.033$) and on R_2* data ($p < 0.0001$).

The ICC values for within- and cross-site R_2* data (median ICC was 0.98 and 0.91, respectively) were found to be significantly higher than values for SE χ (median ICC was 0.89 and 0.64, respectively) or for ME χ (median was ICC 0.76 and 0.38, respectively) ($p = 0.00011$). For all measurements, the ICC for cross-site data was significantly lower than for within-site data (SE QSM: $p < 0.0001$; ME QSM: $p = 0.017$; R_2*: $p < 0.0001$). Similar statistics were obtained for AV_w, SD_w and ICC measurements in the altas-based cortical ROIs (Table 2, Supplementary Material 2).

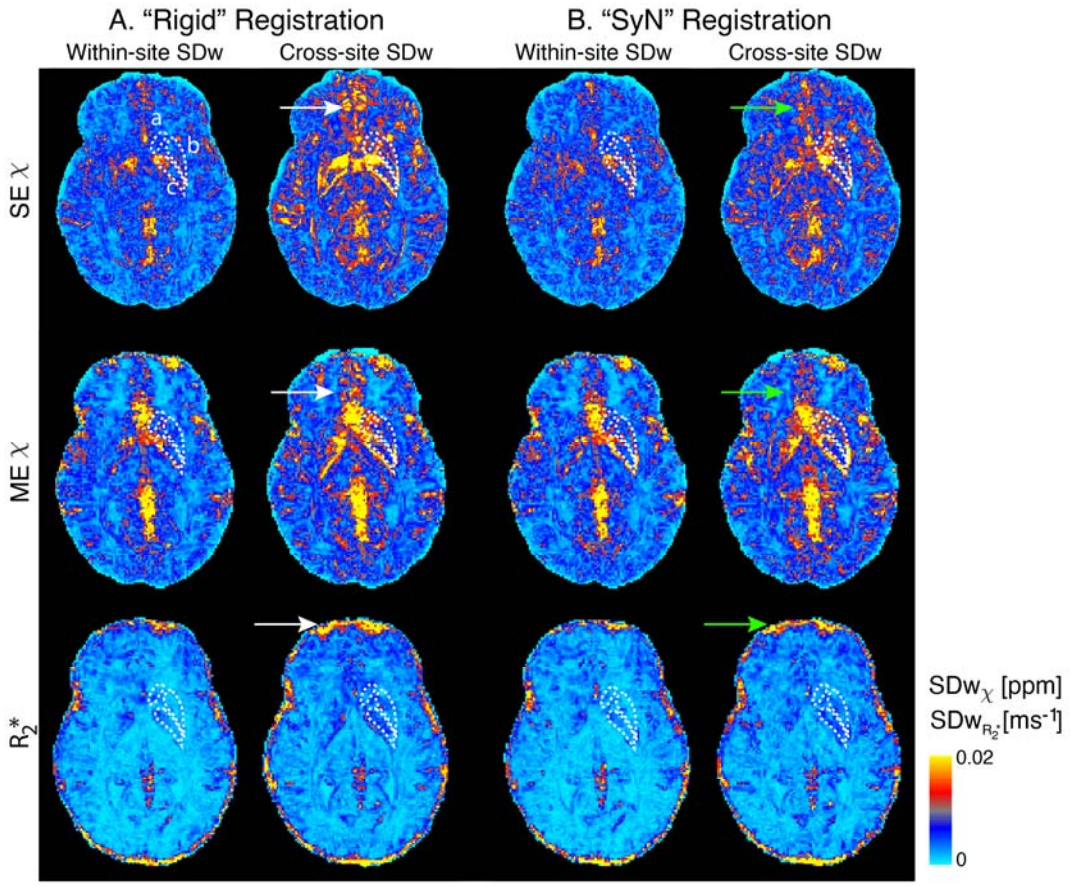

Figure 4. Voxel-wise within- and cross-site standard deviation of an example subject from SE and ME QSM and R_2* data with data registered with "Rigid" (A) and "SyN" (B) transformations. Arrows point to regions where the SD_w decreased with the "SyN" transformations (green) are compared to "Rigid" (white). The right Caudate Nucleus (a), Putamen (b) and Globus Pallidus (c) are outlined in white.

3.3 Registration

The within- and cross-site standard deviations for one axial slice from one example subject using "Rigid" and "SyN" registration approaches are shown in Figure 4. Generally, with both registration methods, within-site and cross-site SD_w increases in veins, in the orbitofrontal regions and at the cortical surface (white and green arrows, Figure 4). These are areas associated with large B_0 inhomogeneities and gradient non-linearity. However, there is a decrease in the cross-site standard deviation in the orbitofrontal region and close to the edges of the cortex when using the "SyN" compared to the "Rigid" method (green arrows, Figure 4).

On the manual ROIs increased variability was observed for R_2* on "Rigid" registered data compared to "SyN" (SD_w: $p < 0.0001$; ICC: $p < 0.013$) but not for SE or ME χ: for example, the median cross-site R_2* SD_w from all ROIs was 0.00066 ms^{-1} using "SyN" method and 0.00086 ms^{-1} using the "Rigid" registration method. On the atlas-based cortical ROIs, the same significant trend was observed for R_2* and SE χ data (Table 2, Supplementary Material 2).

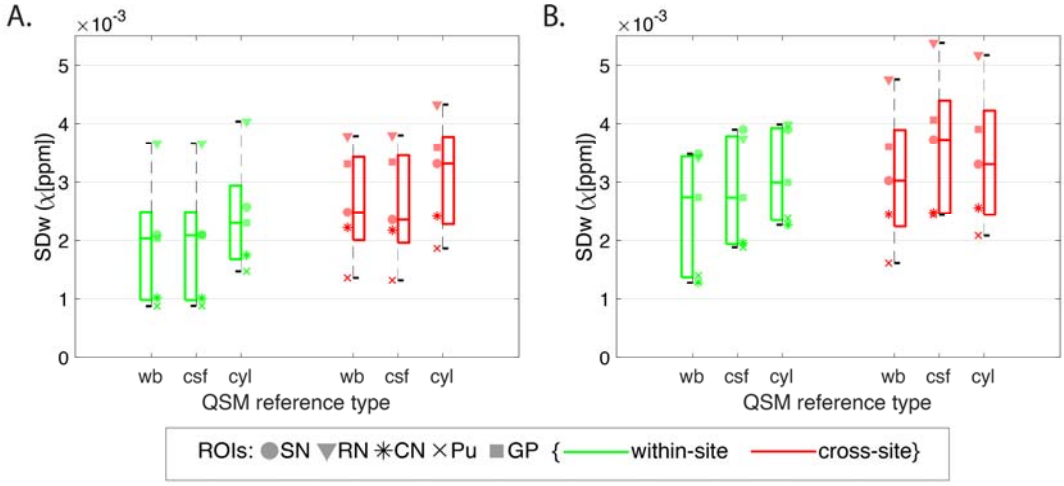

Figure 5: Boxplots from data obtained on the manual ROIs of within- and cross-site SD_w (red and green, respectively) of SE QSM (A) and ME QSM (B) with a whole-brain reference (wb), with a csf reference (csf), and with a cylinder reference (cyl). Data from

each ROI is shown with a different marker for each boxplot. Legend: SN=Substantia Nigra; RN: Red Nucleus; CN: Caudate Nucleus; Pu: Putamen; GP: Globus Pallidus.

3.4 QSM referencing

To assess the optimal QSM susceptibility referencing, Figure 5 shows boxplots of the SD_w for SE and ME χ using different referencing methods on the manual ROIs. On SE χ data, compared to "wb" correction (chosen correction for this study), the "csf" reference did not increase significantly the SD_w ($p = 0.93$) but with "cyl" the median SD_w increased by approximately 14% ($p < 0.0001$).

ME χ data showed an increase in the median SD_w of, respectively, 11% ($p = 0.00096$) and 8% ($p = 0.00064$) when using "csf" and "cyl" methods for correction. The effect of varying the referencing of QSM data was similar in within-site and cross-site data, for all methods tested.

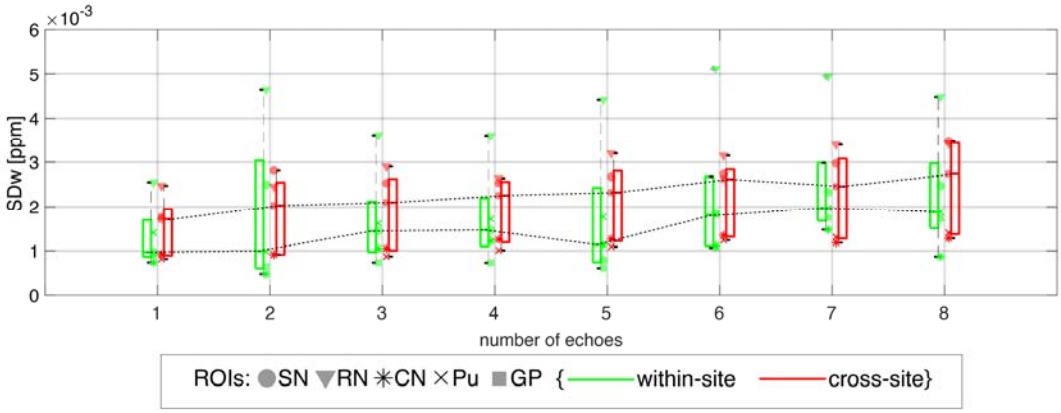

Figure 6. Boxplots from data obtained on the manual ROIs of within- and cross-site SD_w for ME QSM calculated with different number of echoes. Increasing trend on the median SD_w observed with increasing number of echoes (dotted lines). Legend: SN=Substantia Nigra; RN: Red Nucleus; CN: Caudate Nucleus; Pu: Putamen; GP: Globus Pallidus.

3.5 ME QSM

On average across all the manual ROIs and compared to single echo data, multi-echo data (using two or more echoes) showed a significant 14% increase of the SD_w (Figure 6) and 3% of the ICC (Table 1, Supplementary Material 2). This supports the SE and ME χ comparison in Section 3.2. Similar behaviour was observed on the atlas-based cortical ROIs (Table 2, Supplementary Material 2). In the atlas-based cortical ROIs, long

371 echo times (i.e. using 6 or more echoes) showed an average increase of 15.7% in SD_w (p
372 < 0.0001) compared to using 2 to 5 echoes and a decrease of 1.75% in ICC ($p < 0.0001$)
373 (Table 2, Supplementary Material 2).

374 ### 3.6 ROI selection

375 There is a small but significant higher average χ from manually drawn ROIs compared
376 to the atlas-based subcortical ROIs in SE QSM data ($p < 0.0001$; e.g. 0.042±0.009 ppm
377 vs 0.033±0.010 ppm in the caudate nucleus) and in ME QSM data ($p < 0.0001$; e.g.
378 0.048±0.010 ppm vs 0.038±0.011 ppm in the caudate nucleus) (Figure 2). Similarly, for
379 R_2* (e.g. 0.041±0.004 ms^{-1} vs 0.039±0.006 ms^{-1} in the caudate nucleus) this difference
380 was significant ($p < 0.0001$). In addition, the SD_w was, on average, approximately two
381 times higher and the ICC lower in the atlas-based subcortical ROIs compared to the
382 manual ROIs in all datasets (SD_w: SE QSM $p < 0.0001$, ME QSM $p < 0.0001$, R_2* $p <$
383 0.0001; ICC: SE QSM $p = 0.00021$, ME QSM $p = 0.0023$, R_2* $p = 0.012$). So, ROI selection
384 should be done consistently in a study.

385

386 ### 3.7 Spatial distribution of the magnetic field

387 On the altas-based cortical ROIs the SD_w increased by approximately 28% and 88% on
388 "high ΔB_0" regions compared to "low ΔB_0" regions on ME χ and R_2* data, respectively
389 ($p = 0.0011$ and $p < 0.0001$) (Table 2, Supplementary Material 2). Similarly, ICC values
390 decreased significantly for SE and ME χ and R_2* values.

391

392 ## 4. Discussion

393 In this paper, the reproducibility of QSM χ and R_2* measurements in cortical and
394 subcortical regions of the brain was assessed for the first time in a multi-site study at
395 7T for two different protocols (a single-echo 0.7mm isotropic T_2*-weighted scan and a
396 1.5mm isotropic multi-echo T_2*-weighted scan), using three different scanner
397 platforms provided by two different vendors.

398 Previous studies at 1.5T and 3T have shown good reproducibility for χ and R_2* data
399 acquired on the same scanner or across sites (1.5T and 3T) (Hinoda et al., 2015; Cobzas
400 et al., 2015; Deh et al., 2015; Lin et al., 2015; Santin et al., 2017; Feng et al., 2018;

Spincemaille et al., 2019). In terms of QSM and depending on the subcortical region, intra-scanner 3T repeatability studies report an SD_w of 0.002-0.005 ppm (Feng et al., 2018) and 0.004-0.006 ppm (Santin et al., 2017), and the cross-site 3T study by Lin et al. (2015) reported an average SD_W of 0.006-0.010 ppm. We observed a within-site SD_w range of 0.0009-0.004 ppm and cross-site SD_w range of 0.001-0.005 ppm at 7T. The latter is therefore 21-95% better than within sites studies at 3T.

The range of within-site SD_w values for R_2* was averaged 0.0003-0.001 ms^{-1} in our study and the cross-site SD_w range was 0.0005-0.001 ms^{-1}. The cross-site values are comparable to the *same site* reported at 3T: 0.0005-0.0009 ms^{-1} (Feng et al., 2018), 0.0006-0.002 ms^{-1} (Santin et al., 2017). Compared to the latter, our cross-site results show a reduction of 15-124% in R_2* variability.

The higher values of cross-site SD_w compared to the within-site values in our study may be attributed to the different gradient systems and automatic distortion corrections used in the different scanner platforms and to the different approaches to shimming, which lead to different geometrical distortions and dropout regions (Yang et al., 2010). We showed that the use of a non-linear registration method (here, "SyN" in ANTs) significantly reduced the inter-scanner variability of cortical QSM compared to rigid-body registration, indicating that differences in geometric distortion across scanners were present. The R_2* results for both cortical and subcortical structures also show significantly lower inter-scanner variability when a non-linear registration was used.

In this study, the reproducibility of QSM using single-echo (SE), high-resolution (0.7 mm isotropic resolution; TE=20ms) and multi-echo standard-resolution (ME) standard-resolution (1.4 mm isotropic resolution; TE=4, 9, 14, 19, 24, 29, 34 and 39 ms) protocols were compared, and the results show that the ME QSM data has a significantly higher variability than SE QSM. Although ME QSM data has been combined with a magnitude-weighted least squares regression of phase to echo time, it may carry incorrect phase from late echoes of the echo train that suffered multiple phase wraps. This has also been verified with an analysis on multi-echo QSM data reconstructed with different numbers of echoes: long echo times increase significantly the test-retest variability.

R_2* values show significantly lower variability, reflected in the higher ICC within and across-sites compared to corresponding values for χ in subcortical areas. This may be because the χ estimation is globally more sensitive to background field inhomogeneity compared to magnitude data. However, in orbitofrontal and lower temporal regions large through-plane field variations from tissue-air interfaces dominate the field changes and produce dropouts in the signal magnitude and increase the background phase, affecting both QSM and R_2* maps by increasing variability and decreasing ICC.

QSM can only determine relative susceptibility differences (Cheng et al., 2009) and most approaches to calculation of susceptibility from measured phase yield maps in which the average value of susceptibility is zero over the masked imaging volume. Issues related to referencing of QSM data have been investigated (Feng et al., 2018; Straub et al., 2017), with aim of finding a reference region or tissue to which all susceptibility values are referred that produces well-defined and reproducible values of susceptibility. Here we investigated how the choice of reference affects the within-site and cross-site variability of measured susceptibility at ultra-high-field. We tested three accepted reference regions: total whole brain signal, “wb”, whole brain CSF eroded in order to exclude any pial or skull surfaces, “csf”, and a manually selected cylindrical ROI in the right ventricle, “cyl”. We found that the “cyl” referencing generally increased the variability of the cross-site and within-site susceptibility measurements in cortical and subcortical ROIs compared to “wb” referencing. In the case of ME acquisition the “csf” referencing also increased the variability relative to “wb” data. This may be because of imprecision in systematically obtaining average QSM signal from CSF regions. Referencing using a small ROI in the ventricles might be prone to subjectivity given the natural variation in ventricle size in healthy subjects and in disease. Furthermore, the ventricles do not contain pure CSF: they are traversed by blood vessels with a different χ (Sullivan et al., 2002). This makes whole-brain referencing attractive in many situations. Yet, in patient cohorts where there is substantial iron load in subcortical structures (Snyder and Connor, 2009), whole brain referencing might not be an appropriate approach. In this case, the more appropriate approach will be to choose a small reference region which shows no changes in the particular disease to be “zero” susceptibility at a cost of a slight increase in SD.

To eliminate operator-dependent bias in segmentation when determining brain structures, we have analysed data using both manual and atlas-based segmentation. From our results, manual ROIs showed significantly lower variability compared to atlas-based methods. This happens because of imprecision in registration between MNI and subject space as well as the empirical thresholding that was chosen to obtain the subcortical ROIs. However, traditional manual drawing of ROIs for cohort studies is difficult, time consuming and potentially unsuitable as it biases results towards particular cohorts (Collins et al., 2003) so it may not always be the most appropriate approach.

In this study, harmonized protocols were produced for all five scanners without any significant sequence alterations, as a product 3D gradient echo (GE) sequence was readily available on all systems (the product 'gre' sequence from Siemens and the product 'ffe' from Philips). The protocols and an example dataset are provided in (Clarke, 2018). Generally, we also relied on the vendors' reconstruction. However, at the end of the reconstruction pipeline of the Siemens systems we adopted a different coil combination approach based on Roemer et al. (1990) and Walsh et al. (2000), to match the SENSE approach implemented on Philips scanners (Pruessmann et al., 1999; Robinson et al., 2017). This was required due to artifacts appearing on phase images in Siemens data reconstructed with the vendor's pipeline, such as open-ended fringe lines or singularities (Chavez et al., 2002) (Figure 1, Supplementary Material 2). These reduce the consistency of the QSM results (Santin et al., 2017). However, other coil combination methods such as a selective channel combination approach (Vegh et al., 2016) or the COMPOSER (COMbining Phase data using a Short Echo-time Reference scan) method (Bollmann et al., 2018) have also been shown to reduce open-ended fringe lines and noise in the signal phase. For future investigations, the raw k-space data collected from all sites in this study has been stored and is available from the authors upon request.

On the QSM reconstruction, an imperfect background field filtering can influence the reproducibility of QSM data. For this reason, we performed background removal in

two steps as implemented in QSMbox v2.0 and as described in (Acosta-Cabronero et al., 2018): first with the LBV approach and then followed by the vSMV method. Regularized field-to-susceptibility inversion strategies have been proposed to overcome the ill-posed problem in QSM with data acquired at a single head orientation (de Rochefort et al., 2010). We opted to use the MSDI implementation in QSMbox v2.0 (Acosta-Cabronero et al., 2018), as it ranked top-10 in all metrics of the 2016 QSM Reconstruction Challenge (Langkammer et al., 2018), and also now includes a new self-optimized local scale, which results in a better preservation of phase noise texture and low susceptibility contrast features. On the second step, the regularization factor, λ, used for this study was set to $10^{2.7}$, as recommended by Acosta-Cabronero et al. (2018) based on an L-curve analysis (Hansen et al., 1993) with high-resolution 7T data.

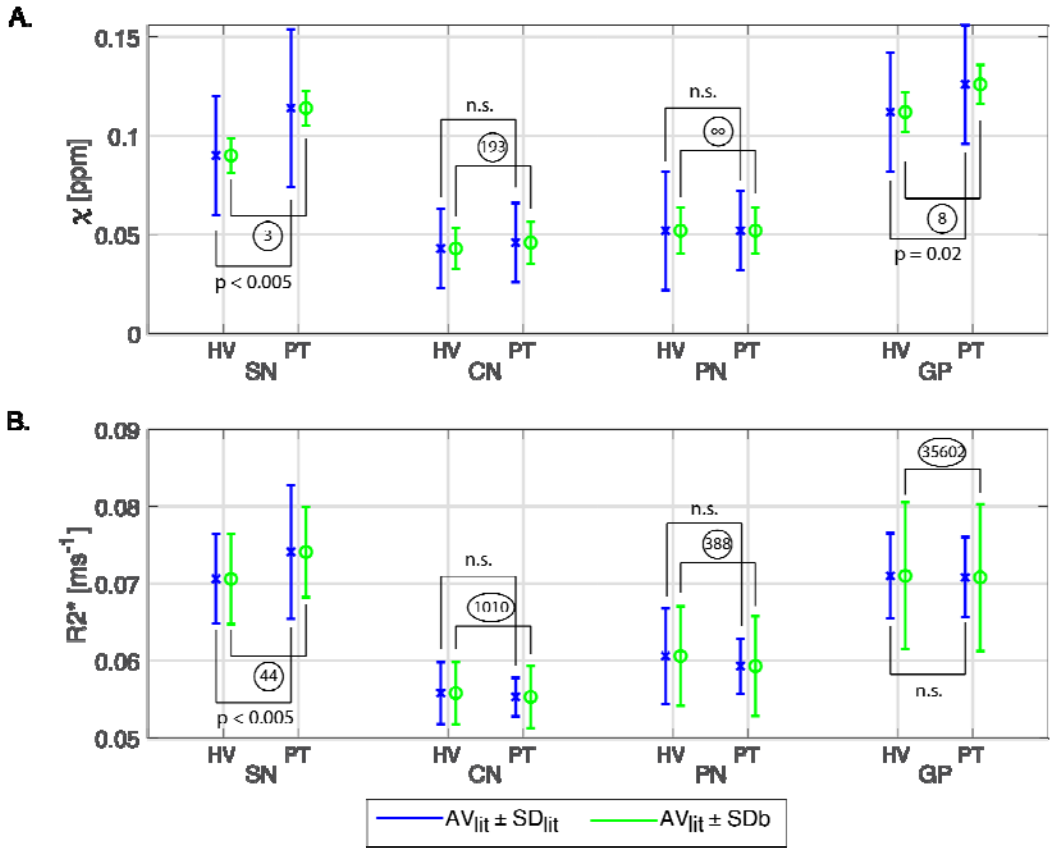

Figure 7. Illustration of the feasibility of a 7T QSM clinical study. χ (A) and R_2* (B) for four ROIs (Substantia Nigra, SN; Caudate Nucleus, CN; Putamen, Pu; Globus Pallidus, GP) from healthy volunteer (HV) and synthetic "patient" (PT) data for which AV_{lit} and SD_{lit} were obtained from Langkammer et al. (2016) and SD_b were calculated from data of the current study. AV_{lit} values for R_2* were linearly scaled to 7T according to Yao et al. (2007). Blue bars show the $AV_{lit} \pm SD_{lit}$ and green bars the $AV_{lit} \pm SD_b$. Statistical

differences between HV and PT obtained from Langkammer et al. (2016) are also shown. For each ROI, the sample size that would have been needed to give a significant effect was calculated from the group means, AV_{lit}, and the SD_b per ROI and is shown in circles.

To minimise confounding effects of age or pathology, we assessed test-retest reliability and cross-site variability with ten healthy young subjects. The cross-site, between-subject standard-deviation, SD_b, measured in this study was evaluated together with healthy and Parkinson's disease data from (Langkammer et al., 2016). A power analysis revealed a sample size that would have been required for a multi-site clinical study in each ROI as shown in Figure 7. For all the significant ROIs the number of subjects that would have been required per group was less or equal to 44. Since this is lower than the sample size we have used in this study (90 healthy volunteer scans) and the numbers in the Langkammer study (66 patients and 58 control subjects), it gives strong confidence of feasibility for future 7T QSM clinical studies.

5. Conclusion

We investigated test-retest reliability and reproducibility of T_2*-weighted imaging protocols at ultra-high field MRI. Considering the increase in susceptibility effects at 7T, we found that variability of measurements of QSM χ and R_2* in the basal ganglia are reduced compared to reports from lower field strengths, 1.5T and 3T. Scanner hardware differences give more modest improvements for cortical measurements of QSM χ and R_2*. Multi-echo protocols do not benefit from long echo times as these increase the imprecision in the estimation of QSM. We suggest that 7T MRI is suitable for multicentre quantitative analyses of brain iron, in health and disease.

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