Ultra-high field MRI (≥7 T) has recently shown great sensitivity to depict patterns of tissue microarchitecture. Moreover, recent studies have demonstrated a dependency between $T_2^*$ and orientation of white matter fibers with respect to the main magnetic field $B_0$. In this study we probed the potential of $T_2^*$ mapping at 7 T to provide new markers of cortical architecture. We acquired multi-echo measurements at 7 T and mapped $T_2^*$ over the entire cortex of eight healthy individuals using surface-based analysis. $B_0$ dependence was tested by computing the angle $\theta_z$ between the normal of the surface and the direction of $B_0$, then fitting $T_2^*(\theta_z)$ using model from the literature. Average $T_2^*$ in the cortex was 32.20+/−1.35 ms. Patterns of lower $T_2^*$ were detected in the sensorimotor, visual and auditory cortices, likely reflecting higher myelin content. Significantly lower $T_2^*$ was detected in the left hemisphere of the auditory region ($p<0.005$), suggesting higher myelin content, in accordance with previous investigations. $B_0$ orientation dependence was detected in some areas of the cortex, the strongest being in the primary motor cortex ($\Delta R_2^*=4.10$ Hz). This study demonstrates that quantitative $T_2^*$ measures at 7 T MRI can reveal patterns of cytoarchitectural organization of the human cortex in vivo and that $B_0$ orientation dependence can probe the coherency and orientation of gray matter fibers in the cortex, shedding light into the potential use of this type of contrast to characterize cyto-/myeloarchitecture and to understand the pathophysiology of diseases associated with changes in iron and/or myelin concentration.
the study of patterns of cell morphology, size and density (Brodmann, 1909; Economo and Koskinas, 1925) while myeloarchitectonics refers to the study of patterns of myelinated fibers (including size, density orientation, and myelination) (Flechsig, 1920; Vogt, 1910).

Magnetic resonance imaging (MRI) has shown great potential for retrieving features of tissue microarchitecture in the living brain. Previous works demonstrated associations between myelin concentration and $T_1$-weighted (Barbier et al., 2002; Clark et al., 1992) and $T_1$-weighted/$T_2$-weighted (Glasser and Van Essen, 2011) signals. Quantitative relaxometry measures have been shown to reflect myelin and iron content (Duyn et al., 2007; Eickhoff et al., 2005; Haacke et al., 2005); for example, previous in vivo studies at 3 T reported shorter $T_1$ in the visual cortex (Fischl et al., 2004; Sigalovsky et al., 2006) and shorter $T_2$-weighted signal in the primary motor (Dinçer et al., 2010; Kamada et al., 2008; Kim et al., 2009) and auditory (Yoshiura et al., 2000) cortices. Identification of cortical lamination structure has also been demonstrated using ultra-high resolution MRI measures (Barazany and Assaf, 2011; Chen et al., 2011; Walters et al., 2003).

Ultra-high field MRI ($\geq 7$ T) enables higher spatial resolution and provides higher contrast on $T_2^*$-weighted imaging, resulting in greater sensitivity to depict patterns of tissue microarchitecture and myelin density (Bock et al., 2009, 2011; Duyn et al., 2007; Fukunaga et al., 2010; Sati et al., 2012). Recently, we mapped $T_2^*$-weighted signal from 7 T data using a surface-based analysis technique (Cohen-Adad et al., 2011). Cortical mapping of MRI signal has previously been proposed as a means to study anatomical features in the gray matter cortex (Fischl et al., 2004; Glasser and Van Essen, 2011; Rebmann and Butman, 2003; Sigalovsky et al., 2006; Weiss et al., 2011). Surface rendering allows the robust visualization of MRI measurements across the entire cortex and enables the calculation of spatial statistics at a population scale. Being able to co-register cortical maps of structural and functional MRI data with probabilistic cytoarchitectonic maps in a common template will be of tremendous help for pursuing the parcellation of the cortex into microstructural and functional units in the living human brain (Geyer et al., 2011; Roland and Zilles, 1994). While efforts have been made to characterize ex vivo anatomical features of the cortex from 7 T data (Augustinack et al., 2005; Duyn et al., 2007; Fukunaga et al., 2010) and to compute voxel-wise $T_2^*$ values over the cortex (Peters et al., 2007), no study has provided cortical mapping of $T_2^*$ over the entire human cortex at 7 T.

The development of ultra-high field MRI has also raised interests about the dependence of $T_2^*$ on the orientation of myelinated fibers with respect to the main magnetic field, $B_0$ (Bender and Klose, 2010; Cherubini et al., 2009; Denk et al., 2011; Lee et al., 2010b; Liu, 2010; Sati et al., 2012; Schäfer et al., 2009b; Wiggins et al., 2008). This dependence is thought to arise from highly coherent and anisotropic structure of the myelin sheath in the white matter (Lee et al., 2011; Liu, 2010; Sati et al., 2012). These observations led to the recent development of susceptibility tensor imaging (Liu, 2010), which provides information on the orientation of white matter fibers based on the anisotropic effect of fibers on local susceptibility. Given that some fibers in the gray matter are myelinated and that the cortical gray matter has been shown to exhibit detectible anisotropy in diffusion tensor imaging measurements (Miller et al., 2011), we can ask whether such $B_0$ orientation dependency also exists in the cortex.

The aims of this study were: (i) to acquire high-resolution multi-echo measurements at 7 T in order to map $T_2^*$ over the entire cortex of healthy individuals using a surface-based analysis; (ii) to test the presence of a dependency between $T_2^*$ and the orientation of the cortical surface relative to $B_0$, and to assess whether this dependency underlies patterns of cyto- and myeloarchitectural organization of the human cortex.
Material and methods

Acquisition

Healthy subjects (N=8, age=41+/−8 years) were recruited. General exclusion criteria were significant medical, psychiatric, or neurologic history. The Institutional Review Board of the Massachusetts General Hospital approved all experimental procedures of the study, and written informed consent was obtained from each subject.

Subjects were scanned with a 7 T whole-body scanner (Siemens Healthcare, Erlangen, Germany) using an AC84 head gradient set and a custom-built 32-channel array coil (Keil et al., 2010). At the beginning of the session, multiple $B_0$ shimming was performed to minimize susceptibility effects. A transmit voltage map was acquired (‘actual flip angle image’ method) to manually set the voltage that produced a desired flip angle at the center of the brain. A multiecho 2D FLASH $T_2^*$-weighted spoiled gradient-echo pulse sequence was run with the following parameter values: two axial slabs covering the supratentorial brain, TR=2020 ms, TE=6.34+3.2n [n=1,…,12], in-plane resolution = 0.33x0.33 mm$^2$, 1 mm slice thickness (25% gap), 40 slices, matrix = 576x504, BW = 335 Hz/pixel. For registration purposes a $T_1$-weighted MPRAGE was acquired with parameter values: TR/TI/TE = 2600/1100/3.26 ms, 0.60x0.60x1.5 mm$^3$.

Subjects were also scanned at 3 T (Tim Trio, Siemens Healthcare) using the vendor-supplied 32-channel coil. A multi-echo MPRAGE (van der Kouwe et al., 2008) was acquired for surface reconstruction and cortical thickness measurements. Parameter values were: TR/TI = 2530/1200 ms, TE = [1.7, 3.6, 5.4, 7.3] ms, flip angle=7°, FOV = 230x230 mm$^2$, resolution = 0.9x0.9x0.9 mm$^3$, bandwidth = 651 Hz/pixel.

Processing

Correction for background field gradients—Despite careful $B_0$ shimming, some inhomogeneities remained, especially in lower brain regions and in regions of air/tissue interface (e.g., close to the sinuses). These inhomogeneities induced background field gradients within each voxel, resulting in shorter $T_2^*$ decay (Yablonskiy and Haacke, 1994) and therefore underestimation of $T_2^*$ (Fernández-Seara and Wehrli, 2000; Peters et al., 2007). When anisotropic voxel is used, the slice-select direction (Z) is particularly sensitive to these background gradients (Frahm et al., 1988). This effect can be compensated by correcting each $T_2^*$-weighted signal according to the formulation introduced in Yablonskiy and Haacke (1994), which expresses the signal $S(T_E)$ in the presence of background field gradient:

$$S(T_E) = S_0 \cdot \exp \left( -\frac{T_E}{T_2^*} \right) \cdot \frac{\gamma \cdot G \cdot \Delta z \cdot T_E}{2}$$

where $S_0$ is the signal strength at $T_E=0$, $\gamma$ is the Larmor frequency, $G$ is the strength of a constant field gradient in the slice direction and $\Delta z$ is the slice thickness. We corrected the signal $S(T_E)$ by first estimating the gradient frequency field along Z, $\Delta Bz = \gamma \cdot G \cdot \Delta z$ and then dividing the signal $S(T_E)$ by the sinc term in Eq. (1), as done in Fernández-Seara and Wehrli (2000) and Peters et al. (2007). Estimation of the gradient frequency field $\Delta Bz$ was performed as follows: after unwrapping the phase evolution at each voxel, the resonance frequency was calculated by fitting the slope of the phase versus echo time $T_E$ using a linear least-square approach. The frequency map was then downsampled by 2 and fitted using a 3D polynomial regression model (3rd order). The frequency gradient $\Delta Bz$ was calculated analytically by deriving the polynomial expression along Z.
$T_2^*$ fitting—$T_2^*$ was estimated voxel-wise by fitting the corrected $T_2^*$-weighted signal ($S_{corr}$) versus echo time ($T_E$) using a Levenberg–Marquardt nonlinear regression model (tolerance = 0.0001, max iterations = 20). The fitting equation was:

$$S_{corr}(T_E) = S_0 \cdot \exp\left(-\frac{T_E}{T_2^*}\right) \tag{2}$$

Parameters $T_2^*$ and $S_0$ were initialized from linear least square fitting of log($S_{corr}$) versus $T_E$. Voxels with poor goodness of fit from the nonlinear estimation were excluded from further analysis (adjusted $R^2 < 0.8$).

Correction for gradient non-linearities—$T_2^*$ data were corrected for gradient non-linearity using a 3D deformation field calculated from the specifications of the Siemens AC84 head gradient, and the image data was resampled using trilinear interpolation.

Surface-based analysis—Cortical surface models were reconstructed from 3 T image data using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). Each of the two 7 T FLASH slabs was registered to the 3 T surface using a boundary-based registration technique (Greve and Fischl, 2009) with 9 degrees of freedom. The registration to the surface was achieved using the average of the first 4 echoes (6.34–15.94 ms), empirically found to be an acceptable compromise between SNR, white/gray matter contrast, and through-plane susceptibility artifacts. Registered slabs were then concatenated using FreeSurfer tools. For more details on the registration, the reader is referred to Cohen-Adad et al. (2011). $T_2^*$ was sampled along the midline between the pial and the white matter surface (50% depth) across the entire cortical hemisphere. Each individual $T_2^*$ map was normalized to the ‘fsaverage’ template surface available in FreeSurfer, then averaged across subjects and smoothed along the surface using a 3 mm FWHM Gaussian kernel. To identify regions of lower/higher $T_2^*$, one-sample Student’s $t$-test was performed on a vertex-by-vertex basis between the $T_2^*$ distribution (across subjects) and the median $T_2^*$ (across the cortex). Maps of $-\log(p)$ were generated (threshold at $p = 0.0001$ with FDR correction). To assess inter-hemispheric differences in $T_2^*$, two-sample Student’s $t$-test was performed in each sub-region of the cortex defined by the PALS-B12 Brodmann atlas available in FreeSurfer (Van Essen, 2005).

Cortical thickness was estimated for each subject based on the 3 T multi-echo MPRAGE using FreeSurfer (Fischl and Dale, 2000). The resulting thickness map was spatially normalized to the fsaverage template and then averaged across subjects for comparison with the $T_2^*$ maps.

$B_0$ orientation dependence—The effect of $B_0$ orientation on $T_2^*$ contrast was investigated on the basis of the radially and tangentially oriented fibers penetrating into the cortex and their potential effect on $T_2^*$. Instead of using diffusion tensor information to relate orientation of $B_0$ and orientation of fiber bundles (Bender and Klose, 2010; Cherubini et al., 2009; Denk et al., 2011; Lee et al., 2011), we related the orientation of $B_0$ to the vector normal to the cortical surface (Fig. 1). To probe the existence of any $B_0$ orientation dependence, it was necessary to sample the tissue at various orientations within the bore. Here, instead of rotating the head of participants as done previously (Bender and Klose, 2010; Wiggins et al., 2008), we took advantage of the convoluted nature of the human cortical folding pattern to obtain a wide range of angles between $B_0$ and any intracortical fibers that are consistently aligned with the direction of the cortical surface (i.e., radial or tangential). The angle $\theta_z$ between the main $B_0$ field and the vector normal to the mid surface was computed on a vertex-by-vertex basis. $R_2^*$ (inverse of $T_2^*$) was then plotted against $\theta_z \in [0, \pi/2)$ and a regression was conducted within each region of the PALS-B12 Brodmann...
The rationale for fitting the $R_2^* (\theta_z)$ data within Brodmann areas is that we can expect the local cyto/myeloarchitecture, which varies across the Brodmann areas, to drive the orientation dependence. The fitting equation is:

$$R_2^* = c_0 + c_1 \cdot \sin(2\theta_z + \phi_0) \quad (3)$$

where $c_0$ represents the background portion of $R_2^*$ that is not affected by $B_0$ orientation, $c_1$ represents the portion of $R_2^*$ that does depend on $B_0$ orientation, and $\phi_0$ is a phase offset term. This equation is derived from the model used by Lee et al. (2011) without the suggested $\sin(4\theta_z)$ term (i.e., Eq. (3) corresponds to the isotropic susceptibility model). The reason for not including the $4\theta_z$ dependence was that susceptibility anisotropy (Lee et al., 2010b; Liu, 2010) has not been assessed in the gray matter. Another argument for choosing the Lee model is that, here, no assumption could be made on the orientation of the fibers with respect to $B_0$, therefore a phase parameter was required in the sinusoidal term (e.g., to account for tangential versus radial fibers). Fitting was achieved in Matlab (The MathWorks, Inc., USA) using robust non-linear least squares fitting (bisquare weights method). Confidence bounds at 95% were calculated. The dependency of $T_2^*$ toward $B_0$ orientation was assessed by the $\gamma c_1 \gamma$ parameter, which scales the sinusoidal term in Eq. (3). Variation of $R_2^*$ was computed as $\Delta R_2^* = 2 |c_1|$.

Results

$T_2^*$-weighted data were successfully acquired and $T_2^*$ estimated in all subjects ($N = 8$). Fig. 2 shows $T_2^*$-weighted data with the fitted values and the adjusted $R^2$ statistics (capturing the goodness-of-fit of the $T_2^*$ model) in a representative subject.

The mean $T_2^*$ over the cortex of all individuals was 32.20+/−1.35 ms (this average does not include the medial wall). Fig. 3A shows the average $T_2^*$ mapped on the inflated surface. Regions with lower $T_2^*$ are noticeable in the primary sensorimotor, occipital and temporal cortices. The ‘strip’ pattern of lower $T_2^*$ in the sensorimotor region is centered along the central sulcus and extends across the pre- and post-central gyri. Missing or low $T_2^*$ values located in the lower brain are due to poor coverage or through-slice susceptibility artifacts caused by large $B_0$-inhomogeneities. Fig. 3B shows results of the one-sample Student’s t-test that assessed regional $T_2^*$ differences compared to the $T_2^*$ median across the cortex (threshold at $p<0.0001$ with correction for false discovery rate, FDR). As observed on the $T_2^*$ map, lower $T_2^*$ was detected in the primary sensorimotor (“1”), visual (“2”) and auditory areas (“3”). Conversely, higher $T_2^*$ was detected in the superior and middle frontal sulci (“4”) and in the anterior and posterior cingulate (“5”).

Fig. 4 shows the left lateral view of the mean $T_2^*$ map with an overlay of the Brodmann areas predicted from the PALS-B12 atlas, the cortical thickness map computed from all subjects and the curvature map representing distribution of sulci and gyri. ‘Strips’ of lower $T_2^*$ are noticeable on both sides of the central sulcus (indicated by the arrow) and correspond to a relatively large cortical thickness (2.5–3 mm). Conversely, the posterior bank of the central sulcus (area 3b/1), which has thinner cortex (1.5–2 mm), is associated with slightly higher $T_2^*$, which could result from partial volume effects with the cerebrospinal fluid (CSF). A measure of spatial correlation was computed between the $T_2^*$ map and the cortical thickness map using the Spearman’s coefficient, yielding $\rho = 0.0046$ (degrees of freedom = 275,929). Distribution of $T_2^*$ resembles subdivisions of the Brodmann areas, with homogeneous regions of lower $T_2^*$ in areas such as BA1 (primary somatosensory cortex), BA4 (primary motor cortex), BA19 (visual cortex) and BA42 (auditory association cortex). The bar graph shows $T_2^*$ values averaged across subjects for each hemisphere. Most areas show fairly good reproducibility across hemispheres, however
significant differences were detected in areas BA22, BA37 ($p<0.05$) and BA42 ($p<0.005$). Significantly lower $T_2^*$ in the left hemisphere of the latter area (BA42) is of particular interest as it is in accordance with previous observations based on quantitative $T_1$ mapping (Sigalovsky et al., 2006) and will be further discussed.

Fig. 5A shows plots of $R_2^* (θ_z)$ in two regions of the cortex defined by the PALS-B12 atlas (BA2 and BA4). These plots result from a concatenation of data from both hemispheres and all subjects ($N=8$). Variation of $R_2^*$, expressed as $\Delta R_2^* = 2 \ln(1)$, was 0.48 Hz in BA2 and 4.10 Hz in BA4. This result suggests greater orientation dependence in BA4 compared to BA2 (by a factor 8.5). Fig. 5B shows a map of $\Delta R_2^*$ across 29 regions of the PALS-B12. Quantitative values for all regions are also displayed as a bar graph (error bars represent the 95% confidence bounds of the fit). $\Delta R_2^*$ ranges between 0 and 4.1 Hz. Highest $\Delta R_2^*$ values were detected in BA4, BA3 (primary somatosensory cortex), BA17 (V1, primary visual cortex), BA42 (auditory association cortex), BA44/45 (Broca’s area) and particularly low $\Delta R_2^*$ was observed in BA2. Fig. 5C shows independent estimates of $\Delta R_2^*$ in each hemisphere of the cortex. Important inter-hemispheric differences were observed in BA2-3, BA7, BA9-11, BA18-19, BA23, BA42 and BA45-47 (ratio >2).

Discussion

$T_2^*$ was estimated in the cerebral cortex in vivo in healthy individuals from multi-echo measurements at 7 T and mapped into a common surface space. Lower $T_2^*$ was detected in some regions of the cortex, such as in the sensorimotor, visual and auditory cortices. $B_0$ orientation dependence of $T_2^*$ was detected in the cortex, shedding light into the potential use of this contrast for studying myeloarchitecture.

Origin of $T_2^*$ contrast

$T_2^*$ contrast in the cortex has been associated with non-heme iron stored in ferritin (Fukunaga et al., 2010; Haacke et al., 2005). Given the co-localization of iron and myelinated fibers, the presence of myelin also correlates with $T_2^*$ contrast (Connor et al., 1990). Water trapped in myelin has low $T_2$ relaxation time ($\sim 20$ ms at 3 T) as opposed to the water within intra/extracellular compartments ($\sim 80$ ms at 3 T), which is another cause for shorter $T_2^*$ in the presence of myelin (Du et al., 2007). $T_2^*$ can also be modulated by the local concentration of deoxyhemoglobin in venous blood (Duyn et al., 2007; Haacke et al., 2005) and by calcium concentration—a diamagnetic ion present at synaptic sites (Marques et al., 2009). For more information on the origin of the $T_2^*$ contrast, the reader is referred to references (Fukunaga et al., 2010; Haacke et al., 2005).

$T_2^*$ variations in the cortex

The averaged $T_2^*$ in the cortex was 32.20+/-1.35 ms (mean+/−SD). In comparison, Peters et al. (2007) found 33.2+/-1.3 ms. Although relatively small, this discrepancy might come from the possibly different regions of interest.

Lower $T_2^*$ was notably detected in BA1 (primary somatosensory cortex), BA4 (primary motor cortex), BA19 (visual cortex) and BA42 (auditory association cortex), relative to the rest of the cortex. Similar spatial patterns were also observed in the marmoset (Bock et al., 2011) and in humans using quantitative $T_1$ (Fischl et al., 2004; Geyer et al., 2011; Weiss et al., 2011) and measurements of the ratio between $T_1$- and $T_2$-weighted images (Glasser and Van Essen, 2011) and are likely due to an increase of myelin density in these regions.

The ‘strip’ pattern in the motor-somatosensory area has previously been reported in humans from $T_2$-weighted measurements at 3 T (Dinçer et al., 2010; Duyn et al., 2007; Kamada et al., 2008; Kim et al., 2009), from quantitative $T_1$ measurements (Fischl et al., 2004; Geyer et
al., 2011; Weiss et al., 2011) and from T₁w/T₂w signal (Glasser and Van Essen, 2011). In the
latter study, areas 4 and 3b were found to be the most myelinated in comparison with
areas 1 and 2. This is in agreement with our results that show shorter T₂* in areas 3 and 4
versus area 2. T₂* shortening is likely due to the higher myelin and iron content in cortical
layers III to VI (Duyn et al., 2007; Ogg et al., 1999).

Lower T₂* in the primary visual cortex (V1) has previously been reported at 3 T
(Wansapura et al., 1999) and 7 T (Duyun et al., 2007). Plausible causes for lower T₂* in V1
include the presence of high myelin content at cell layer IV (at the line of Gennari), also
observed ex vivo (Fukunaga et al., 2010; Hinds et al., 2008; Walters et al., 2003) and in vivo
using T₁-weighted (Barbier et al., 2002; Bridge et al., 2005; Clare et al., 2001; Clark et al.,
1992; Eickhoff et al., 2005), T₂-weighted (Carmichael et al., 2006; Trampel et al., 2011),
T₂*-weighted (Duyun et al., 2007) and quantitative T₁ (Fischl et al., 2004; Sigalovsky et al.,
2006; Turner et al., 2008) measurements. Given that V1 has relatively thin cortex, it is
possible that partial voluming with the CSF was higher in this region.

Lower T₂* in the auditory associative cortex (BA42) could also be explained by greater
myelin density, in accordance with a previous study reporting lower T₁ (Sigalovsky et al.,
2006) and lower T₂-weighted signal (Yoshiura et al., 2000) in the Heschl’s gyrus. In
addition, T₂* in BA42 of the left hemisphere was significantly lower than that in the right
hemisphere (p<0.005). In the same article by Sigalovsky et al., inter-hemispheric difference
in the auditory cortex was also detected, with lower T₁ in the left hemisphere. Lower T₁ and
lower T₂* are both consistent with greater gray matter myelination in left auditory cortex.
These observations are also supported by previous ex vivo data (Anderson et al., 1999;
Buxhoeveden et al., 2001; Galuske et al., 2000; Hutslers and Gazzaniga, 1996; Seldon,
1981a, b, 1982) and suggest that higher myelination may be a substrate for the left
hemisphere’s specialized processing of speech, language, and rapid acoustic changes. The
two other areas showing significant inter-hemispheric differences (BA22, BA37, p<0.05) are
located in lower regions of the brain that show high susceptibility artifacts, therefore no
conclusion could be drawn on the genuineness of this difference.

It is possible that the cellular organization (orientation, density) also contributed to the T₂*
singularities observed in some areas of the cortex, given the remarkable spatial
clustering of the T₂* maps with the Brodmann atlas (Van Essen, 2005), although at this
point it is still difficult to disentangle cellular organization from iron and myelin
contribution to the T₂* contrast (Fukunaga et al., 2010). This ambiguity highlights the need
to perform further measurements based on different biophysical properties, such as
quantitative magnetization transfer (Levesque and Pike, 2009), diffusion tensor imaging
(Basser and Pierpaoli, 1996) or myelin water mapping from T₂ relaxometry (MacKay et al.,
2006). Each of these metrics shows high specificity toward myelin content, therefore
combining them together into a common space using surface-based analysis could help
studies of cortical parcellation and disentangle the effect of cyto versus myeloarchitecture in
the generation of the T₂* contrast.

Cortical thickness

A similar strip pattern along the central sulcus was observed when comparing the T₂* map
and the cortical thickness map. Notably, the posterior bank of the central sulcus, which has
thinner cortex (1.5–2 mm), was associated with slightly higher T₂*. Conversely, area V1
exhibited both thinner cortex and lower T₂*. While some regions exhibiting low or high T₂*
corresponded to regions of thick or thin cortex, the two maps are largely independent.
Spearman’s coefficient showed low spatial correlation between the two maps (p=0.0046).
Thus, we can conclude that the measured T₂* is not simply reflecting cortical thickness
differences (due to, e.g., partial volume effects).
The effect of the main magnetic field (B₀) orientation on T₂* contrast was investigated, in line with previous studies reporting B₀ dependence of T₂* magnitude and phase with respect to the orientation of fibers bundles in the white matter (Bender and Klose, 2010; Cherubini et al., 2009; Denk et al., 2011; Lee et al., 2010b; Liu, 2010; Satì et al., 2012; Schäfer et al., 2009b; Wiggins et al., 2008) or at the white/gray matter interface (Schäfer et al., 2009a). This dependence is thought to arise from highly coherent and anisotropic molecular structure of the phospholipid bilayer of the myelin sheath, which has been shown to exhibit susceptibility in vitro (Boroske and Helfrich, 1978; Scholz et al., 1984; Speyer et al., 1987). Here, given the limited amount of information on the orientation of fibers in the cortex, we explored this B₀ dependence by looking at the angle between the cortical surface and B₀. We assumed that fibers exhibit similar orientation relative to the cortical surface, within regions that are anatomically distinct on the basis of their cytoarchitecture (as defined by Brodmann areas). Our results show variable B₀ dependencies across the cortex, the highest dependency being in the primary motor cortex (BA4) where orientation-dependent variation of R₂* was 4.10 Hz (fitted using the isotropic model). In comparison, Lee et al. (2011) found ΔR₂* = 6.44 Hz+/−0.15 in the corpus callosum at 7 T (fitted using the anisotropic model). Possible explanations for a lower ΔR₂* in our experiment are that fiber bundles in the corpus callosum are more dense than that in the cortex and exhibit higher coherency, therefore creating a greater bulk susceptibility, which in turn yields greater orientation dependence with respect to B₀. This argument is supported by the study of Satì et al., in which no significant change of R₂* was found in the gray matter cortex of marmosets imaged in sphinx and supine position, whereas strong dependence was observed in the optic radiation in the white matter (Satì et al., 2012). The discrepancy between our study and the study from Satì et al. suggests that subtle R₂* changes related to B₀ orientation may only be seen in the gray matter by multiple sampling of the angle between cortical fibers and B₀, combined with subsequent modeling of the R₂* dependency using cylindrical susceptibility perturbers (Lee et al., 2010a). Comparing our results with 3 T measurements in the in vivo white matter, Bender et al. found ΔR₂* = 2.68 Hz (Bender and Klose, 2010) and Denk et al. found ΔR₂* = 1.65 Hz (Denk et al., 2011). While these two studies looked at R₂* variation in white matter, the higher cortical ΔR₂* found here likely comes from the higher field strength (7 T versus 3 T). ΔR₂* estimated independently in each hemisphere seemed fairly reproducible in some areas, although important differences were observed in BA2-3, BA7, BA9-11, BA18-19, BA23, BA42 and BA45-47 (ratio >2 between left and right hemisphere). This variability can be accounted by the relatively low number and uneven distribution of θz values sampled in some areas; hence, reducing the number of θz values by a factor of two further reduced the robustness of the fit. For example, if in one Brodmann area we observe a cluster of θz values, the corresponding area in the other hemisphere may exhibit a different pattern of θz due to differences in the geometry of the folding pattern, resulting in a different bias in the R₂* fit calculated for each hemisphere. Another source of inter-hemispheric variability is the presence of B₀ inhomogeneities in lower brain regions and close to the sinuses, which yielded unreliable estimate of R₂*. A third explanation is that the actual microstructure might be different in the two hemispheres of a given Brodmann area, as been shown, e.g., in the auditory cortex (Sigalovsky et al., 2006).

Regions that were particularly affected by the orientation dependence were BA4 (primary motor cortex), BA3 (primary somatosensory cortex), BA17 (primary visual cortex V1), BA42 (auditory association cortex) and BA44/45 (Broca’s area). Interestingly, those regions are also known to be heavily myelinated (Barbier et al., 2002; Duyn et al., 2007; Sigalovsky et al., 2006). In addition to myelin content, we might hypothesize that myelinated fibers are coherently oriented in these areas, hence yielding the orientation dependence reported in previous white matter studies. To verify this hypothesis, we compared our map of B₀
dependence ($\Delta R_2^*$) with a map of fractional anisotropy (FA) generated from 1 mm isotropic diffusion tensor imaging (DTI) data acquired at 3 T in six other healthy subjects (McNab et al., 2011). FA is a measure of the anisotropy of water diffusion, and sometimes indicates the level of orientational coherence within a bundle of myelinated fibers (Beaulieu, 2002). FA was mapped along the mid-surface of each individual, normalized to the same fsaverage template and averaged across subjects. Fig. 6 shows the $\Delta R_2^*$ map and the FA map with an overlay of the PALS-B12 Brodmann areas. Higher $\Delta R_2^*$ (i.e., higher $B_0$ dependence) is associated with higher FA in BA4, and lower $B_0$ dependence is associated with lower FA in BA2. Note that some regions show high FA without systematic higher $B_0$ dependence. This could be explained by the methodology that was used here: FA was estimated voxelwise and then mapped on the surface, whereas $\Delta R_2^*$ was estimated for the whole Brodmann area (including thousands of vertices). Hence, it is possible that within each vertex fibers showed high coherence and low amount of crossings (hence high FA), but within some Brodmann areas the orientation of fibers may have been different, therefore yielding low $\Delta R_2^*$.

**Effect of blood vessels**

Radially penetrating vessels may have influenced $T_2^*$ dependence with respect to $B_0$ (Petridou et al., 2010). This effect may have been emphasized due to the anisotropic shape of our voxel size (Denk et al., 2011). However, the venous blood volume fraction is only about 3% in the human cortex (Buxton et al., 2004), suggesting that the contribution of blood vessels to the $B_0$ dependency is marginal (Lee et al., 2010a; Petridou et al., 2010). Hence, we think that blood vessel only marginally contributed to the $B_0$ dependence in the cortex, and that the primary reason for this dependence was myeloarchitecture features. Future studies should be conducted to investigate the contribution of blood vessels to the $B_0$ dependence, e.g., studies employing carbogen – a mixture of carbon dioxide and oxygen gas that increases blood flow and therefore reduces deoxyhemoglobin concentration.

**Limitations and future studies**

We used anisotropic voxels in order to acquire the entire cortex in a reasonable scan time while maintaining high in-plane resolution (300x300 $\mu$m). Anisotropic voxels suffer from more severe partial volume effects in the through-plane direction. Thus cortical regions parallel to the image slice are worst affected and may also show a larger effect of coherently oriented cortical veins. In future, EPI-based multi-echo measurements (Zwanenburg et al., 2011) may accelerate acquisition enough to allow use of more isotropic voxels, provided that distortion correction is applied as required.

$T_2^*$ mapping of the cortex may be useful in the diagnosis of disease, as well as understanding pathogenesis, disease progression and the monitoring of treatment. It may help to quantify changes in iron concentration related to healthy aging (Hirai et al., 1996) or to pathologies such as Alzheimer Disease (Benveniste et al., 1999) and multiple sclerosis (Craelsius et al., 1982). The good spatial correspondence between our $T_2^*$ map, the $B_0$ dependence map, Brodmann map and regions of high myelin content suggests that $T_2^*$ and $B_0$ dependence mapping could provide useful information for studying the cytoarchitecture (Brodmann, 1909; Economo and Koskinas, 1925) and myeloarchitecture (Flechsig, 1920; Geyer et al., 2011) in the cortex, and guiding the development of cortical atlasing and parcellation methods (Eickhoff et al., 2005; Van Essen, 2005; Zilles, 2004).

One specific application of $B_0$ dependence analysis is the exploration of fiber orientation within the cortex, previously described using DTI (Anwander et al., 2010; McNab et al., 2011). While $B_0$ orientation dependence in the white matter can potentially help to study features of axonal organization, we believe that studying $B_0$ orientation dependence in the
gray matter potentially has some relevance, as it might reveal new features of cortical fiber
distribution and monitor re-myelination in diseases (e.g., multiple sclerosis).

Apart from these possible applications, $B_0$ dependence in the cortex has some impact in
relaxometry studies, where $T_2^*$ is used as a biomarker or to develop parcellation methods.
As demonstrated here, $T_2^*$ is influenced by the angle between cortical fibers and $B_0$
orientation. Hence, it is possible that spurious apparent boundaries and/or apparent change
in tissue contrast within a homogeneous region (on the basis of its cellular organization)
would result from a pure $B_0$ orientation dependence effect. For instance, the recent study
of Sati et al. showed drastic $R_2^*$ change within the optic radiation in marmosets images in
supine versus sphinx position (Sati et al., 2012), and other studies showed changes in the
human pyramidal tract (Bender and Klose, 2010) and corpus callosum (Wiggins et al., 2008)
depending on the orientation of the head. Future studies should aim at developing methods
to correct for this orientation dependence, allowing to estimate a more intrinsic $T_2^*$ value
(i.e., not depending on subject’s orientation in the scanner). One possibility would be to
estimate the angle between fiber bundles and $B_0$ from DTI measurements, and then derive a
spatial map of $B_0$ dependence associated with a correcting factor to be applied to $T_2^*$
measurements. This correcting factor could be calculated from models of field perturbations
(Schäfer et al., 2009a; Wharton et al., 2009; Yablonskiy and Haacke, 1994). Although more
challenging, robust and precise in vivo measurements of fiber bundles orientation in the
cortex were shown to be feasible thanks to the use of highly parallelized phased-array
receive coils (McNab et al., 2011) and increased magnetic field strength (Heidemann et al.,
2010).

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Fig. 1.
The effect of the main magnetic field ($B_0$) orientation on $T_2^*$ contrast was investigated on the basis of the radially and tangentially oriented fibers penetrating into the cortex. $T_2^*$ was sampled at 50% depth across the whole cortex, surface-smoothed with a 3 mm kernel and then plotted against $\theta_z$ (angle between the normal vector on the mid-surface and $B_0$). Here we used the surface of each individual (not the fsaverage surface). A map of $\theta_z$ is shown for one subject.
Fig. 2.
A. First (6 ms) and last echo (45 ms) of a FLASH T$_2^*$-weighted image in a representative subject. B. T$_2^*$ map computed voxelwise from 12 echoes using least-squares fitting of the log of the data vs. echo time. C. Adjusted R$^2$ assessing the goodness of T$_2^*$ fit.
Fig. 3.

A. $T_2^*$ maps sampled at 50% depth, surface-smoothed with 5 mm kernel, normalized to the fsaverage template, averaged across subjects ($N=8$) and displayed on the inflated surface. B. Map of significant differences between $T_2^*$ in each vertex and the median value ($p<0.0001$, corrected for FDR). Lower $T_2^*$ is noticeable in the primary sensorimotor (“1”), visual (“2”) and auditory areas (“3”). Higher $T_2^*$ is noticeable in the superior and middle frontal sulci (“4”) and in the anterior and posterior cingulate (“5”). Missing or low $T_2^*$ values in the lower brain region (“6”) are due to poor coverage or through-slice susceptibility artifacts.
Fig. 4.
Lateral left view of the averaged $T_2^*$ map with an overlay of the PALS-B12 Brodmann atlas, which represents regions with specific cytoarchitectonics. The thickness map was computed from the 3 T MPRAGE data and averaged across subjects. The curvature map shows the distribution of gyri/sulci across the cortex. Strips of lower $T_2^*$ are noticeable on both sides of the central sulcus (arrows) and correspond to a larger cortical thickness. Distribution of $T_2^*$ resembles subdivisions of the Brodmann areas, with homogeneous regions of lower $T_2^*$ corresponding to e.g. BA1 (primary somatosensory), BA4 (primary motor), BA19 (visual) and BA42 (auditory). The bar graph shows $T_2^*$ values averaged across subjects for each hemisphere (error bars correspond to SD). Significant differences between hemispheres were assessed using a Student’s $t$-test and significance levels are displayed as *: $p<0.05$; **: $p<0.005$. 

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Fig. 5.
A. $R_2^*$ versus $\theta_z$ in two regions of the cortex defined by the Brodmann atlas (BA2 and BA4). For visualization, $R_2^*$ values were averaged by bins of 2 $\theta_z$ across all subjects (hence 45 bins in total). Standard deviation is displayed as light blue. Fitting curve is overlaid in red and fitting parameters are indicated at the top left of each figure. B. Dependence towards $B_0$ across Brodmann areas. $R_2^*(\theta_z)$ was fitted for every vertices within each Brodmann area, and the resulting $\Delta R_2^*$ is displayed for each area. The maximum $B_0$ dependence occurred in the primary motor cortex, with $\Delta R_2^*$=4.10 Hz. The bar graph shows quantitative values of $\Delta R_2^*$, with error bars corresponding to the 95% confidence bounds. C. Comparison of $\Delta R_2^*$ estimates across hemispheres.
Fig. 6.
Map of $B_0$ orientation dependence ($\Delta R_2^*$) and fractional anisotropy (FA) map estimated from DTI data, normalized to the same fsaverage template and averaged across subjects ($N=6$). Higher $\Delta R_2^*$ is associated with higher FA in BA4 (motor cortex), and lower $\Delta R_2^*$ is associated with lower FA in BA2 (sensory cortex), suggesting higher coherence of myelinated fibers in the motor cortex. Note that the field of view was reduced in the DTI acquisition, due to acquisition time constraints, precluding the study of the whole cortex.