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Optimizing BOLD sensitivity in the 7 T Human Connectome Project resting-state fMRI protocol using plug-and-play parallel transmission

Vincent Gras[a], Benedikt A Poser[b], Xiaoping Wu[c], Raphal Tomi-Tricot[b], Nicolas Boulant[a,*]

[a] *NeuroSpin, CEA, University of Paris-Saclay, Gif-sur-Yvette, France*
[b] *Department of Cognitive Neuroscience, Faculty of Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands*
[c] *Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, Minnesota, USA*

Abstract

The Human Connectome Project (HCP) has a 7 T component that aims to study the human brain's organization and function with high spatial and temporal resolution fMRI and diffusion-weighted acquisitions. For whole brain applications at 7 T, a major weakness however remains the heterogeneity of the radiofrequency transmission field (B_1^+), which prevents from achieving an optimal signal and contrast homogeneously throughout the brain. In this work, we use parallel transmission (pTX) Universal Pulses (UP) to improve the flip angle homogeneity and demonstrate their application to highly accelerated multi-band EPI (MB5 and GRAPPA2, as prescribed in the 7 T HCP protocol) sequence, but also to acquire at 7 T B_1^+-artefact-free T_1- and T_2-weighted anatomical scans used in the pre-processing pipeline of the HCP

*To whom correspondence should be addressed. Postal address: Commissariat lnergie atomique et aux nergies alternatives Centre de Saclay — Batiment 145 P.C. 156 — 91191 Gif-sur-Yvette Cedex, FRANCE. E-mail: nicolas.boulant@cea.fr

protocol. As compared to typical implementations of pTX, the proposed solution is fully operator-independent and allows "plug and play" exploitation of the benefits offered by multi-channel transmission. Validation in five healthy adults shows that the proposed technique achieves a flip angle homogeneity comparable to that of a clinical 3 T system. Compared to standard single-channel transmission, the use of UPs at 7 T yielded up to a two-fold increase of the temporal signal-to-noise ratio in the temporal lobes as well as improved detection of functional connectivity in the brain regions most strongly affected by B_1^+ inhomogeneity.

Keywords: parallel transmission, Human Connectome Project, calibration, universal pulse, RF shimming, ultra-high field, multi-band EPI

1. Introduction

In functional magnetic resonance imaging (fMRI), there is a growing interest in performing neuro-scientific studies at ultra-high field (UHF) to benefit from the supra-linear increase in the blood oxygenation level dependent (BOLD) signal change with the static magnetic field strength (B_0) (Yacoub et al., 2001). Following this trend, e.g. the original young adult Human Connectome Project (HCP) contains a 7 T component that targets functional and diffusion MRI with high spatiotemporal resolutions (Uğurbil et al., 2013, Van Essen et al., 2013) to study the brain's organization and some of its functions. The 7 T HCP resting state fMRI (RS-fMRI) protocol comprises a ten-fold accelerated ($\times 5$ simultaneous multi-slice and $\times 2$ in-plane acceleration) multi-band echo-planar imaging (MB-EPI, a.k.a. SMS-EPI) acquisition which allows sampling the BOLD signal at 1.6 mm spatial and 1 s temporal

resolution.

A major challenge of 7 T MRI with large volume coverage is the heterogeneity of the radiofrequency (RF) transmission field (B_1^+) which, if not corrected, would result in nonuniform flip angles and tissue contrast across the whole brain. The RF nonuniformity is due to standing wave effects that become problematic in the head at B_0 of 7 T and up, where the RF wavelength becomes comparable to the head size and falls below 13 cm. The consequence of the resulting flip-angle variation in 7 T (RS-fMRI) scans such as the ones used in the 7 T HCP study is a reduced performance in the detection of BOLD signal mostly in the inferior and temporal brain regions. Similarly affected at 7 T are the magnetization prepared rapid gradient echo (MPRAGE) (Mugler and Brookeman, 1990) and 3D variable flip angle turbo spin echo (3D-VFA-TSE, a.k.a. SPACE (Mugler et al., 2000)) acquisitions which are part of the minimal pre-processing pipeline of the HCP protocol (Glasser et al., 2013). The inherent limits of these anatomical scans yet can be compensated by providing 3 T images to complement the 7 T fMRI scans (Glasser et al., 2013) but it remains desirable to be able to conduct the entire set of acquisitions at 7 T.

In order to mitigate the problem of flip-angle inhomogeneity at UHF, the 7 T HCP has adopted a practical approach, which is to place dielectric pads (filled with calcium titanate) around the head near the regions most strongly affected. The high dielectric constant of the padding material ($\epsilon_r = 100$ or higher) notably affects the properties of the environment 'seen' by the RF waves and, if placed adequately, steers them so as to locally enhance the RF field (Webb, 2011). While effective locally, it appears extremely

challenging to achieve homogeneous RF fields over extended regions with the use of dielectric pads alone.

Parallel RF transmission (pTX) technology (Katscher et al., 2003, Zhu, 2004) is one more elaborate approach to improve flip-angle uniformity, and use of this still not wide-spread technology has recently been proposed for whole-brain RS-fMRI acquisition at the same spatiotemporal resolutions as in the 7 T HCP (Wu et al., 2019). Specifically, in this work, the MB-EPI sequence (Moeller et al., 2010, Setsompop et al., 2012, Vu et al., 2017) used in HCP was modified to enable slice-specific RF shimming. In doing so, the coefficient of variation (CV), i.e., standard deviation (std)/mean) of the whole brain flip-angle distribution, was ∼15% for pTx (with eight independent transmit channels) versus ∼24% for conventional single channel transmission (sTX) , and ∼20% if 3D whole-head RF shimming was performed (Gras et al., 2017a, Krishnamurthy et al., 2019). This proved useful in enhancing the temporal SNR especially in the regions adversely affected by voids in B_1^+. Other studies have also shown the potential of pTX technology to recover optimal signal and contrast across the whole brain at 7 T in MPRAGE (Cloos et al., 2012a), diffusion (Wu et al., 2018) as well as 3D TSE (Eggenschwiler et al., 2014, Massire et al., 2015, Beqiri et al., 2018, Gras et al., 2018) acquisitions.

However one drawback of those conventional pTX approaches is that the optimized pTX excitations or refocusing were obtained by subject-specific numerical optimization, performed 'online' (i.e., while the subject was waiting in the scanner), based on subject- and session-specific B_1^+ maps that first had to be acquired in the same session. In practice, this requires an additional

B_1^+ calibration scan whose duration amounts to at least 20 s per transmit channel for optimized B_1^+ mapping sequences, and the subsequent numerical optimization of the pTX excitation which can also take up to several minutes.

The concept of Universal Pulse design (Gras et al., 2017b) offers a solution for entirely removing the need for subject- or session-specific field mapping and subsequent on-line optimization of the RF pulses. The benefits of pTX are instead utilized in a fully automated or "plug-and-play" manner, offering more flexibility and reactivity for the operator during the exam. In contrast, full automation starting from subject-based acquired B_1^+ maps and comprising on-line RF pulse tailoring in principle is possible but to date is not available, and would still require extensive developments. Plug-and-play pTX here is done by pre-calculating RF pulses that were optimized on a series of B_1^+ and B_0 offset maps obtained from a representative sample of the adult population. The RF pulse optimization thus takes place separately from the scan session, and consists in minimizing an objective function that maximizes the average performance of the pTX excitation across the database of field maps (Gras et al., 2017a). The result of this procedure is universally valid pulses, hence the term Universal Pulses (UP).

To better cope with inter-subject variability of the B_1^+ profile, UPs are often designed by considering a broader class of pTX excitation modes than RF shimming, namely *dynamic* RF shimming (Padormo et al., 2016). Here, the capabilities of pTX are more fully exploited in that dynamic RF shimming pulses take advantage of the transmit-sense (Katscher et al., 2003) concept to homogenize the flip angle distribution. One potential weakness with such types of excitation yet is the possible increase in the excitation du-

ration as compared to standard RF shimming, with impact on the response of off-resonant spins but which can be taken into account in the pulse optimization (Grissom et al., 2006). The most prominent examples for this are 2D spokes excitation (Saekho et al., 2006, Setsompop et al., 2008) and 3D k_T-points (Cloos et al., 2012b) which apply small "gradient blips" in between a series of selective or non-selective pulses, so as to spatially modulate the flip angle phase of each subpulse and yield an overall more homogeneous flip angle distribution within a slice or across a volume. Importantly, as shown by Tse and colleagues in recent work at 9.4 T (Tse et al., 2016), the 2D multi-spoke dynamic RF shimming technique can be extended to generate pTX multi-band RF pulses that simultaneously excite multiple slices.

In this work, we report on the design of multi-band Universal Pulses to conduct HCP-style RS-fMRI studies at 7 T. As in the original 7 T HCP, the RS-fMRI was acquired using a 2D SMS sequence with factor-5 slice acceleration. We also show that a complete shift towards 7 T acquisitions is possible, with additional pTX-UP enabled T_1- and T_2-weighted anatomical scans that can be incorporated in the preprocessing pipeline. The excitation pulse of the MB-EPI sequence was replaced by bipolar two-spoke (MB-5) UPs, the non-selective square pulses of the SPACE acquisition by a scalable (Eggenschwiler et al., 2014, Gras et al., 2018) 9-k_T UP, the adiabatic inversion preparation pulse of the MPRAGE sequence by a 9-k_T inversion UP, and the small FA square pulse of the FLASH readout module of the MPRAGE sequence by a 7-k_T UP. This pTX-UP implementation of the RS-fMRI protocol is compared experimentally on five healthy adults with the same protocol played with standard pulses and single channel transmission (sTX), without and with

dielectric pads. Using retrospective flip angle simulations based on measured subject-specific B_1^+ maps, the benefit of the UP integration into the RS-fMRI protocol in terms of signal homogeneity is compared with subject and slice specific RF shimming strategies. Temporal SNR (tSNR) is quantified based on the measured EPI time-series of each volunteer. A seed-based analysis of the default mode network (DMN) is also reported to evaluate the gain in terms of functional connectivity estimation.

2. Material and Methods

All experiments were performed on a 7 T Siemens Magnetom MRI system (Siemens Healthineers, Erlangen, Germany, software baseline VB17A and step 2.3 pTX) equipped with an eight-channel pTX system (1kW per channel), and SC72 body gradient coil (nominal slew rate 200 mT/m/ms and 40 mT/m maximum amplitude). The vendor-provided head-coils were used: 8Tx-32Rx for pTX acquisitions, 1Tx-32Rx for the sTx reference experiments (both from Nova Medical, Wilmington, MA, USA). The implementation of the HCP resting-state fMRI protocol used custom MB-EPI, MPRAGE and SPACE sequences to enable pTX and UPs integration. Measurements were performed on 5 healthy adult subjects (2 women) and were divided for each one of them into three one-hour sessions, run on different days, to cover the pTX and the sTX operation modes with and without dielectric padding. The dielectric pads were based on a calcium titanate ($CaTiO_3$) suspension (Webb, 2011) and were 0.5 cm thick and 10 cm long (square form). Two such pads were placed against the subjects ears. For the acquisition in sTX, the standard RF transmitter adjustment procedure provided by the scan-

ner's manufacturer was used. In pTX, this calibration step was disabled and the transmitter adjustment was specified by the UPs used in the respective sequences, as detailed below. Adherence to the SAR guidelines was ensured by real-time SAR supervision using a Virtual Observation Point (VOP) model (Eichfelder and Gebhardt, 2011) of the SAR distribution in the head that was implemented using home-made routines and electromagnetic simulations provided by the coil vendor. After experimental phantom validation on the scanner, the VOPs were augmented by safety factors to account for RF coil modelling imperfections, inter-subject variability in the peak SAR value (Garrec et al., 2016, Boulant et al., 2018) and uncertainties in the directional coupler measurements of the TX Array system (Gumbrecht, 2013), resulting in a total safety factor of 2.3 (Boulant et al., 2018). The study was approved by the local ethics committee and all volunteers gave written informed consent.

2.1. MRI protocol

The MRI acquisition consisted of a 30 min resting-state (RS) fMRI protocol, followed by T_1- and T_2-weighted anatomical scans using the MPRAGE and the SPACE sequences, respectively. An interferometric turbo-FLASH B_1^+ mapping protocol (5 mm isotropic resolution, repetition time [TR] = 20 s, acquisition time [TA] = 4 min 40 s) (Fautz et al., 2008, Brunner and Pruessmann, 2009) and multiple gradient recalled echo (GRE) protocol (2.5 mm isotropic resolution, TR = 8.4 ms, 3 echoes, echo times [TE] = 2.7, 4.2, 6 ms, TA = 30 s) were also added in order to quantitatively assess the B_1^+ and ΔB_0 distributions for each subject and each acquisition mode.

The RS-fMRI part used a 15 min fat-suppressed MB-EPI acquisition ap-

plied twice, with the in-plane phase encoding direction being flipped during the second run (AP followed by PA). Subjects were instructed to keep their eyes open and focus on a red fixation cross on a black screen. EPI acquisition parameters were : 90 axial slices of 1.6 mm thickness with no gap, standard sinc excitation (time-bandwidth product = 3.2, Hanning window apodization), nominal flip angle = 45°, TR = 1 s, voxel size = $(1.6\,\mathrm{mm})^3$, in plane field of view (FOV) = $(208 \times 208)\,\mathrm{mm}^2$, multi-band slice acceleration factor = 5 with blipped-CAIPIRINHA FOV/3 inter-slice shift, in-plane GRAPPA acceleration factor = 2 with 52 autocalibration lines (ACS) acquired separately using the fast low angle excitation echo-planar technique (FLEET) (Polimeni et al., 2016), partial Fourier acquisition = 7/8, readout bandwidth = 1832 Hz/pixel, fat saturation with nominal flip angle = 80°. Online image reconstruction was performed with the implementation of the MGH blipped-CAIPI MB-EPI C2P (www.nmr.mgh.harvard.edu/software/c2p/sms), which uses sequential application of Slice-GRAPPA (Setsompop et al., 2012) with leak-block (Cauley et al., 2014) and GRAPPA (Griswold et al., 2002).

The T_1- and T_2-weighted acquisitions were in sagittal orientation, isotropic resolution of 0.8 mm, FOV = $(256 \times 224 \times 208)\,\mathrm{mm}^3$ (read, phase and partition axes) and a GRAPPA acceleration factor of 2 in the phase encode direction. Other parameters were: TR = 2.6/3.0 s, MPRAGE inversion time = 1.1 s, echo spacing (ES) = 10.2/8.6 ms, readout bandwidth = 240/370 Hz/pixel, flip angle = 4°/Mugler's approach (Mugler, 2014, Mugler et al., 2000) respectively for the MPRAGE and SPACE acquisitions.

2.2. Design of parallel transmission Universal Pulses

Dynamic RF shimming with spoke (slice-selective) and k_T-point (non--selective) pulses use a simple and low-dimensional parameterization of the RF and gradient waveforms. It consists of i) the different RF shimming weights, defined by the time integral of the RF shim sub-pulses, and ii) the transmit k-space (Cloos et al., 2012b) displacement vectors, i.e. the time integral of the interleaved magnetic field gradient blips along the three axes. In this framework, efficient non-linear constrained optimization algorithms can be applied to attempt finding the best possible dynamic RF-shimming solution (Hoyos-Idrobo et al., 2014).

The UPs used for the MB-EPI, the MPRAGE and the SPACE acquisitions in pTX were designed offline on a database $\mathcal{B}$ of measured subject-based B_1^+ and ΔB_0 maps of size $N_{\mathcal{B}} = 10$ (5 female), acquired in a separate study (Gras et al., 2017a). The UP design consisted in evaluating the subject-specific objective $\epsilon_{\text{tailored}}$ (typically a measure of the mean deviation of the flip angle distribution across the region of interest) on every subject of the database and computing the mean objective across this database. The UP-objective ϵ_{UP} may thus be written as:

$$\epsilon_{\text{UP}}(p) = \frac{1}{N_{\mathcal{B}}} \sum_{j \in \mathcal{B}} \epsilon_{\text{tailored}}(\mathcal{S}_j, p), \tag{1}$$

where p denotes the dynamic RF shimming parameterization to be optimized, and $\epsilon_{\text{tailored}}(\mathcal{S}_j, p)$, the evaluation of the subject-based objective on subject $\mathcal{S}_j$ of the database for the parameterization p. Hence, without any additional difficulty, hardware (RF power and gradient slew rate limits) and safety (SAR) constraints can be enforced explicitly for the UP design following exactly the same methodology used for a subject-tailored pulse design. This

was implemented using the active-set non-linear constrained optimization algorithm (Hoyos-Idrobo et al., 2014), available in the optimization toolbox of MATLAB (R2016b, the Mathworks, Natick, MA). The hardware constraints were i) the peak RF amplitude limit (170 V per TX channel at the coil plug), ii) the average RF power limit per TX channel (3 W), iii) the total average RF power limit (16 W) and iv) the maximum slew rate of the magnetic field gradient coils (200 mT/m/ms). The SAR thresholds were expressed in terms of global and local SAR limits of 3.2 W/kg and 10 W/kg respectively (International Electrotechnical Commission, 2015).

For the design of the non-selective UPs (SPACE and MPRAGE sequences), the subject-tailored objective was defined as the normalized root mean square (NRMS) deviation of the flip angle distribution $\alpha(r)$ from the target flip angle α_{T}, calculated across the brain (region $\mathcal{R}$), i.e.:

$$\epsilon_{\mathrm{tailored,3D}} = \frac{1}{|\alpha_{\mathrm{T}}|}\left(\frac{1}{|\mathcal{R}|}\sum_{r\in\mathcal{R}}\left(\alpha(r)-\alpha_{\mathrm{T}}\right)^2\right)^{\frac{1}{2}}, \tag{2}$$

where $|\mathcal{R}|$ and r denote the number of brain voxels of the B_1^+ map and the spatial coordinates, respectively. For the design of the slice-selective UPs (MB-EPI sequence), the objective was formulated as a weighted NRMS deviation from the target flip angle across the brain with the slice-dependent weighting function:

$$w(r) = \exp\left(-d_0^{-1}\max\left(0, d(r,\mathcal{P}) - \frac{\theta}{2}\right)\right) \tag{3}$$

where $\mathcal{P}$ denotes the median plane of the considered slice, $d(r,\mathcal{P})$ the Euclidean distance from r to $\mathcal{P}$, θ the slice thickness, and $d_0 = 1\,\mathrm{cm}$. The

objective in this case for a single slice thus is given by the equation:

$$\epsilon_{\text{tailored,2D}} = \left(\frac{1}{\sum_{r\in\mathcal{R}} w(r)} \sum_{r\in\mathcal{R}} w(r)\ (\alpha(r) - \alpha_{\text{T}})^2 \right)^{\frac{1}{2}}. \tag{4}$$

We note here that taking $d_0 = 0^+$ leads to the weighting function $w = 1$ for $r \in \mathcal{P}$, which is the conventional way of designing slice-specific spokes pulses. Taking into account all voxels in $\mathcal{R}$, and letting the flip angle deviation have an (exponentially) decreasing weight as the distance from the slice of interest, promotes robustness of the pulse against variations in the slice positions and small tilts. Likewise, taking $d_0 = \infty$, leads to $w = 1$ everywhere and the 2D objective converges to the 3D objective in that case. The choice of a 1 cm soft threshold was found to offer a good compromise between excitation performance and robustness.

In equations 2 and 4, for all but the inversion pulse, the flip angle distribution $\alpha(r)$ was computed using the small tip angle approximation (Pauly et al., 1989a). This approximation provides a linear relationship between the RF weights and the flip angle (Boulant and Hoult, 2012) which is valid for up to moderate target flip angles or for symmetric pulses (Pauly et al., 1989b, Eggenschwiler et al., 2014, Gras et al., 2018). For the inversion pulse, this approximation being not valid, $\alpha(r)$ was obtained by numerical integration of Bloch's equations (Bloch integration). For the computation of $\alpha(r)$, relaxation effects during the pulse were neglected.

For the design of the MB-EPI UPs, coherent summation of the slice-specific RF pulses within each multiband slice group was assumed for simplicity to ensure that peak RF amplitude of the multiband waveforms of any slice group did not exceed the hardware peak power limit. This has a sim-

ple and tractable implementation as it involves only a reasonable number of constraints per multiband slice group (the product of the number of transmit channels by the number of spokes). For this particular scenario (8 transmit channels, two spokes and MB-5), the subsequent optimization of the global (consistent across all transmit channels and spokes) RF phase offsets between the different slices of the same multiband slice group (Wong, 2012) returned a reduction of peak amplitude of 20%.

Owing to the smooth variation of the B_1^+ field and the weighting function in the 2D objective above, RF coefficients and spokes-placement in k-space (Dupas et al., 2015) were optimized for every other slice only (45 slices among 90) and the same parametrization was attributed to the adjacent slice (Wu et al., 2013, Tse et al., 2016). To comply with the multiband acceleration (here of 5), the spoke placement optimization was done concurrently for all slices of a multiband group (the set of slices excited simultaneously). Finally, the bipolar two-spoke pulses were designed with a subpulse duration of 2180 µs and a total pulse duration of 4800 µs (excluding the slice selection rewinder). Prior to designing the bipolar spokes, the gradient delay was characterized on phantom using sub-µs precision and compensated for by manipulating the RF phase of the second spoke (Gras et al., 2017c). As shown also elsewhere (Tse et al., 2016), characterizing and correcting for this delay with such precision is a necessary ingredient for multi-bipolar spoke applications away from the iso-center. Unipolar designs, where both slice selection gradients share the same polarity, are inherently insensitive to these imperfections but they have less spectral bandwidth due to a longer duration and are more prone to peripheral nerve stimulations due to the

additional gradient lobe.

The pTX UP MPRAGE acquisition used k_T-point pulses (Cloos et al., 2012b) for the 4° excitation and 180° inversion pulses, as described in ref. (Gras et al., 2017a). The excitation used 4° flip angle (800 µs total duration with 7 gradient blips of 40 µs each) while the 180° inversion pulse lasted 4000 µs (9 subpulses of 400 µs each). The sTX pulse implementation used a standard 700 µs-long square pulse for the 4° excitation and a standard 10 ms hyperbolic-secant adiabatic pulse for inversion.

The pTX UP SPACE acquisition was based on a unique scalable (Eggenschwiler et al., 2014) k_T-point pulse (9 subpulses, total duration = 1100 µs), consistently with the methodology proposed in ref. (Gras et al., 2018). The leading excitation pulse was implemented using the same k_T-point pulse, but scaled to produce a 90° flip angle and with 90° phase offset to satisfy the Carr-Purcell-Meiboom-Gill (CPMG) condition. Scalability of the refocusing pulses, was enforced by exploiting symmetries and applying a dedicated optimization routine (Gras et al., 2018). This allowed using a unique k_T-point pulse to implement the entire array of non-selective pulses of the variable flip angle TSE readout and the preceding 90° excitation. The sTX implementations of the SPACE acquisition used standard 500 µs- and 700 µs-long square pulses for the 90° excitation and the variable flip angle TSE readout respectively.

2.3. Analysis of pulse performance and additional simulations

The RF pulse performance was assessed post-hoc by performing voxel-wise Bloch simulations using the B_1^+ and B_0 offset maps that were acquired on each subject in addition to the (f)MRI scans. The CV of the flip angle

and the MR signal were calculated across the brain. The interest of analyzing the signal homogeneity (as the ultimate measure of interest in practice) in addition to the flip angle (the physical parameter that drives the RF pulse optimization) is to take into account the non-linear dependence of MR signal with the flip angle. The MR signal was computed for a representative pair of T_1/T_2 values for brain white matter at 7 T, namely 1300/60 ms.

For the MB-EPI sequence, to provide a comparison of the proposed two-spoke UP design with the volume (global) (Krishnamurthy et al., 2019) and slice-specific RF shimming (Wu et al., 2019) (one-spoke pulses), additional sets of simulations were performed in which the bipolar two-spoke design was replaced with the (simpler) one-spoke design (pulse duration 4520 µs), with otherwise identical design parameters as for the 2-spoke UPs): i) a set of 45 slice-specific *universal* RF-shims using the database of B_1^+ and B_0 offset maps and the UP objective, ii) a set of 45 slice-specific and subject-tailored (Wu et al., 2019) RF-shims per subject, and iii) a global ($d_0 \to \infty$) subject-tailored RF-shim over the whole head, per subject.

The gain in robustness with respect to slice position and inclination provided by the weighted least-squares approach (see Equation 4) was also tested through the following simulation. The 45-slice UP design for the MB-EPI protocol was repeated with a weighted-least squares soft threshold d_0 (see Equation 3) of 1 mm (instead of 10 mm). The coefficient of variation of the flip angle (45 slices merged together) of both sets of pulses was then computed for different values of slice position offsets (up to 20 mm) and slice inclinations (rotation about the right-left axis of up to 20°).

2.4. fMRI pre-processing and temporal SNR calculations

The MB-EPI data were first motion-corrected using FSL McFLIRT (Jenkinson et al., 2002). The two 900-volume series (with AP and PA phase encoding directions) of each session were then distortion-corrected based on FSL Topup (Andersson et al., 2003). The temporal SNR was then calculated for each voxel, subject and session by taking the mean of the corresponding time-series divided by its standard deviation, after linear de-trending and removal of the first 10 volumes to reject the transient spin evolution towards steady-state from the analysis. The tSNR maps were then registered to the Montreal Neurological Imaging (MNI152) template by using the FSL FLIRT affine registration tool with 12 degrees of freedom (Jenkinson and Smith, 2001), aided by the T_1-weighted anatomical scan. This allowed computation of an average tSNR map across subjects and generation of inflated cortical surface representations by using PySurfer (https://github.com/nipy/PySurfer). In order to provide a common ground and not bias the comparison of sTX versus pTX, the same (pTX) T_1-weighted scan was used for the registration.

Analysis of the resting-state data

After motion correction, distortion correction and registration as described above, the time varying signals associated to each voxel were standardized to display a unit-variance, detrended and band-pass filtered (0.01-0.1 Hz) (Goelman et al., 2017). The 6 motion parameters (3 for translation, 3 for rotation) of the time-series realignment procedure and physiological noise related confounds were regressed out using CompCor (Behzadi et al., 2007).

Correlated BOLD fluctuations were identified using the seed-based approach, by selecting a voxel in the brain (seed) and calculating the correlation

between its associated signal and all other voxel time-series. For the present analysis, the seed was a spherical volume of 8 mm in diameter located in the posterior cingulate cortex (center coordinates: $[0, -50, 26]$ on the MNI152 template). For all voxels across the brain, the Pearson correlation coefficient relative to this seed was then calculated and mapped onto inflated cortical surfaces using nilearn (Abraham et al., 2014).

In the resting brain, The BOLD signal in the posterior cingulate cortex is known to correlate with the one observed in the inferior parietal and medial prefrontal cortices as well as the temporal cortex (Raichle et al., 2001, Vincent et al., 2006), thus characterizing the so-called default mode network. The aim of this analysis hence was to reproduce this finding on a subject-by-subject basis and compare the correlation maps between acquisition modes. The hypothesis here is that a better BOLD sensitivity translates into higher correlations in this seed-based analysis of the DMN.

3. Results

3.1. Comparison of image quality

Figure 1 provides a comparison of the MB-EPI, MPRAGE and SPACE acquisitions obtained in subjects 1 to 5 in pTX versus sTX. All sTX acquisitions display signal losses in the temporal lobes, of which one coronal section is shown in the figure. For the MB-EPI acquisition, this signal loss directly affects BOLD sensitivity as the SNR and tSNR naturally scale with the MR signal. The introduction of $CaTiO_3$ dielectric pads (second rows in a)-c)) somewhat reduces but does not eliminate the signal loss. For the SPACE acquisition, which makes use of an optimized flip angle train to enable long

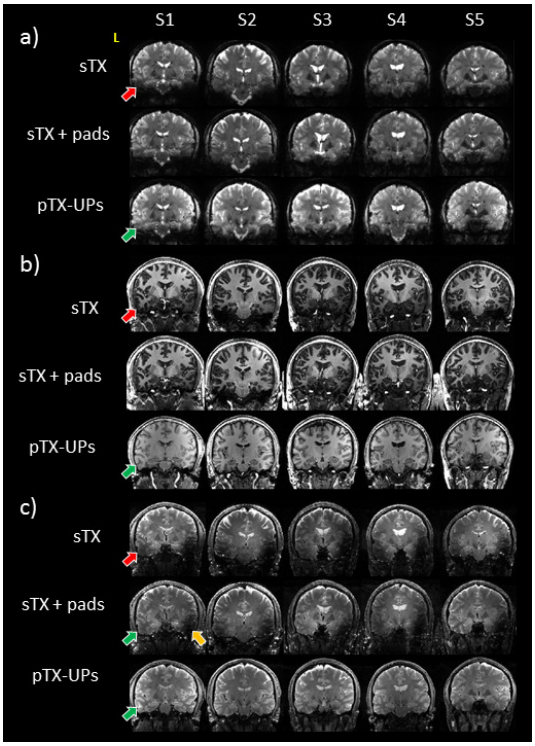

Figure 1: Image comparison comparisons for the different acquisition modes and sequences. EPI with MB=5 (a), b) MPRAGE and c) SPACE acquisitions obtained in subjects 1 to 5 in sTX (with and without dielectric padding) versus pTX are provided. For all subjects (S1 to S5), a marked signal loss is present in both sTX acquisitions (top and middle rows in a-c) in the temporal lobes (red arrows). For all subjects, such signal loss or contrast deterioration is absent in the pTX UP acquisitions (bottom row), as indicated by the green arrows. The dielectric pads (clearly visible in the MPRAGE and SPACE images) were able to compensate for the signal drop in all subjects, mostly in the left temporal lobe. As can be seen for instance in the SPACE acquisition of S1, the favorable influence of the dielectric pad however was clearly asymmetric as it was not able to restore a good contrast for the right temporal lobe (orange arrow).

TSE readouts, the flip angle heterogeneity severely degrades the signal and the contrast in lower brain regions. As confirmed by the flip angle analysis that follows, with pTX and universal k_T-point pulses, the flip angle error is reduced to a level that is sufficient to obtain T_2-weighted 3D images free of B_1^+ artifacts. In the MPRAGE images, the improvement with UPs was less pronounced because the preservation of the gray-white matter contrast is mostly governed by the quality of the inversion preparation. In sTX, we observed that the hyperbolic-secant adiabatic inversion pulse provided good inversion efficiency over the whole brain, with the exception of a small portion of the cerebellum or the temporal lobes in some subjects. The major image imperfection that remains in the T_1-weighted scans in sTX thus is a signal drop in regions of low B_1^+, more detrimental to SNR than image contrast. As a general rule for MPRAGE, a smaller flip angle for the FLASH readout leads to stronger contrast, but a weaker signal (Gras et al., 2016). As a result, undershot FLASH excitations in sTX results in a stronger gray-white matter contrast, but a weaker SNR than observed in the pTX acquisitions.

3.2. Assessment of RF pulse performance by simulation

Figure 2 provides a comparison of the functional and anatomical images that were obtained in one representative subject with the three acquisition modes (pTX UPs, sTX and sTX with dielectric pads) evaluated in this study. For the coronal plane that is displayed, the associated flip angle distribution obtained retrospectively in simulation using the RF pulse definition and the subject-specific B_1^+ and ΔB_0 maps is shown on the right side. The flip angle profile in sTX displays flip angle values ranging from 30% to 110% of the target value. Using pTX UP slice-specific two-spoke multi-band (for

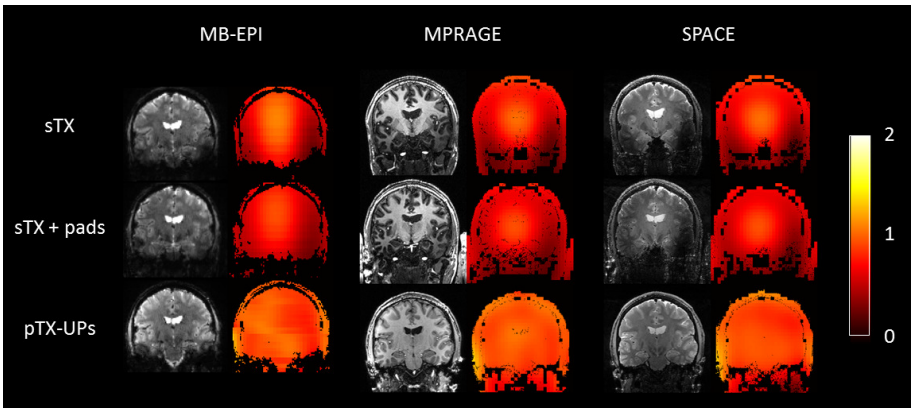

Figure 2: Coronal views for one representative subject of the MB-EPI, MPRAGE and SPACE images with corresponding simulated flip angle simulations. For every scan, the underlying flip angle distribution (obtained by retrospective simulation from the measured subject-specific B_1^+ and ΔB_0 distribution) is displayed in units of the nominal FA distribution. Even in the presence of dielectric pads, the sTX acquisition mode displays a strong flip angle heterogeneity, with values ranging from 30% up to 110% the nominal flip angle (respectively the 1%- and the 99%-quantiles of the flip angle distribution in the brain). This heterogeneity is largely removed in the pTX-UP acquisition mode.

MB-EPI) and volume-selective k_T-point pulses (for the MPRAGE inversion and FLASH pulses, and the SPACE excitation and refocusing pulses), much greater homogeneity of the excitation profiles is achieved.

The CV of the flip angle and the MR signal for $T_1/T_2 = 1300/60\,\text{ms}$ across the brain (i.e. the region of interest) with respect to the mean flip angle is reported in Table 1. These were computed for the 45° slice-selective pulses of the MB-EPI acquisition, the 4° non-selective pulse used in the MPRAGE sequence and the 90° excitation pulse used in the SPACE sequence. The statistical significance of the flip angle and the signal heterogeneity reductions (pTX UP versus sTX) was also quantified using paired t-tests. For all se-

	pTX UPs		sTX		sTX+pads	
	FA	Signal	FA	Signal	FA	Signal
MB-EPI	9-11	4-6	22-24	15-17 (2.10^{-5})	20-22	14-17 (8.10^{-5})
MPRAGE	7-9	8-10	”	22-25 (7.10^{-6})	”	21-23 (3.10^{-6})
SPACE	8-11	9-13	”	34-40 (3.10^{-5})	”	35-41 (4.10^{-6})

Table 1: CV (in percent) of the flip angle (FA) and the MR signal (best case − worst case over 5 subjects) for the MB-EPI, the MPRAGE and the SPACE HCP-style protocols at 7 T. For the sTX acquisition mode, relative homogeneity is consistent for all sequence types given that pulses involved in those sequences do not use the dynamic RF shimming principle. The values displayed in parenthesis are p-values of statistical paired t-tests performed on the signal NRMS deviation between the pTX UP acquisitions and the sTX acquisitions.

quences, the CV of the MR signal was statistically significant ($p < 2 \times 10^{-5}$). While the CV of the flip angle typically exceeds 25% in sTX, the UP approach allows to restore an excitation uniformity at least as good as typically seen on a clinical 3 T system (13%) with standard transmission hardware (Boulant et al., 2008). Using pTX UPs, the CV of the MB-EPI signal ranged from 4% to 6% while it always exceeded 14% using sTX. For the 3D T_1-weighted and T_2-weighted anatomical scans, the signal's CV was below 13% in pTX while it often exceeded 25% in sTX with and without dielectric padding. The dielectric pads were helpful in compensating for the B_1^+ drop in their vicinity (the left and right temporal lobes) but, this had a minimal impact on the CV, the latter criterion being a global performance measure.

The simulated flip angle homogeneity of the two-spoke versus the one-spoke pulse designs for the pTX-enabled MB-EPI sequence is provided in

objective	#spokes	FA	Signal
universal	2	9-11	4-6
	1	12-16	5-8 ($p = 0.047$)
tailored s.s.	1	9-12	3-5 ($p = 0.8$)
tailored global	1	17-20	6-8 ($p = 0.005$)

Table 2: NRMS deviation (in percent) of the flip angle (FA) and the MR signal (best case − worst case over 5 subjects) for the slice-specific universal 2-spoke, tailored slice-specific (s.s.) and global RF shims, and universal 1-spoke pulse designs. Using universal 2-spoke pulses, the signal NRMS deviation is significantly lower than with universal 1-spoke pulses ($p = 0.047$). The same comparison with tailored 1-spoke pulses yet gives $p = 0.8$, i.e. no statistical evidence that the universal 2-spoke design outperforms the tailored 1-spoke design.

Table 2. The universal 2-spoke design (the one evaluated experimentally in this work) is comparable in performance with the tailored 1-spoke design ($p = 0.8$), applied in another study (Wu et al., 2019). This raises the question whether a 1-spoke *universal* design, simpler than the 2-spoke universal design, would be sufficient. In simulation, the 1-spoke UP design indeed yields a significantly better signal CV than the sTX acquisition (5-8% versus 14-17%, $p = 0.047$), but a poorer homogeneity as compared to the two-spoke universal or 1-spoke tailored design (3-6%). Hence for one subject, the flip angle CV exceeds 16%, that is, a signal uniformity that is superior to that observed on a clinical 3 T system (Boulant et al., 2008). The subject-specific global RF shim on the other hand returned flip angle CVs of 17% up to 20%..

The robustness of the multiband UPs with respect to a shift in the slice positions or an inclination of the slices is showed in Figure 3. As expected,

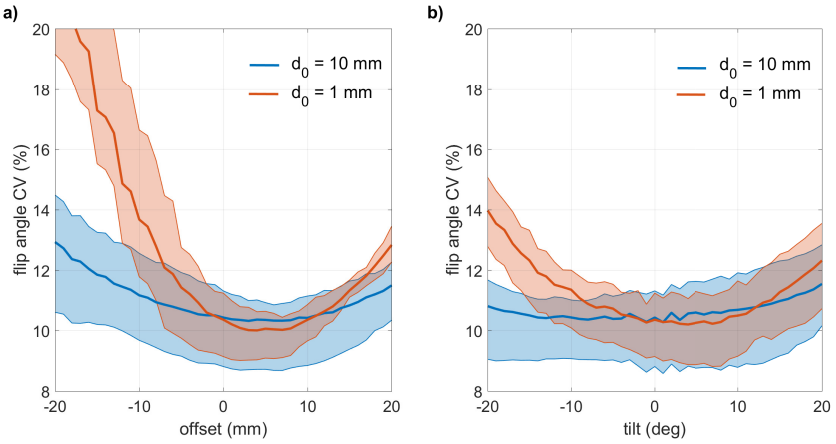

Figure 3: Simulation of the flip angle CV (45 slices pooled together) as a function of a) the slice shift and b) the slice inclination (about the right-left axis) for the universal pentaband pulses designed with a weighted least-squares parameter d_0 (see Equation 3) of 1 mm (red curve) and 1 cm (the proposed design parameter, blue curve). For each plot, the thick line and the two enclosing lines represent the mean, the minimum and the maximum of the CV across the five subjects.

the set of pules obtained with the 1 cm soft-threshold perform better than the other with respect to a variation in the position or the inclination of the slice. Note that d_0 =1 mm practically leads to no weighting since the spatial resolution of the B_1^+ maps is 5 mm. This result also indicates that the tolerance of the universal MB-EPI pulses designed in this study can be considered as high as 2 cm for the slice position offset and 20° for the slice inclination. Indeed, for both cases, the CV in flip angle does not exceed 13%.

3.3. Temporal SNR

Projections of the tSNR maps onto cortical surfaces for each subject are shown in Figure 4. In each subject, tSNR of the pTX UP scans exceeds that of the sTX acquisitions, without and with pads), which is consistent with

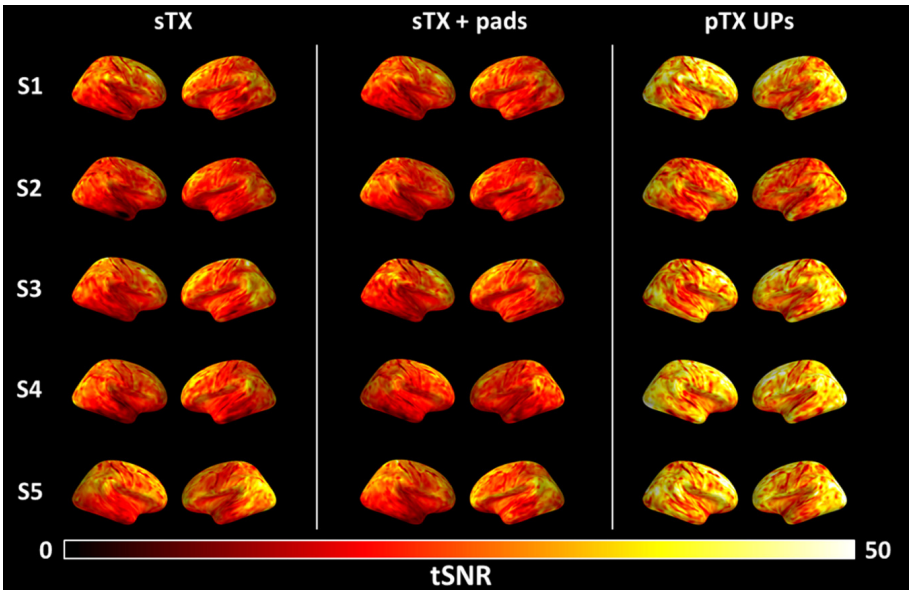

Figure 4: Cortical surface projection of the tSNR maps obtained for the left and right hemispheres for subjects 1 to 5 (top to bottom) and for the three different setups (left to right). Using pTX and UPs, a higher tSNR can be achieved over the cortex consistently throughout all subjects.

the flip angle simulations reported above. Additionally, a comparison of the average (across the five subjects after normalization to the MNI152 template) temporal SNR maps is displayed in Figure 5a. A marked tSNR gain with pTX can be seen, in particular in the temporal, occipital and parietal lobes, where the transmit efficiency of the RF coil in sTX is weaker. This is also demonstrated by the ratio maps (Figure 5b) which reveal tSNR gains of up to 100% between the pTX and the sTX acquisitions. On average across all subjects and over the whole brain, the tSNR gain using UPs amounted to 25%.

In this study, we used a different, standard, (pre) processing pipeline (FSL

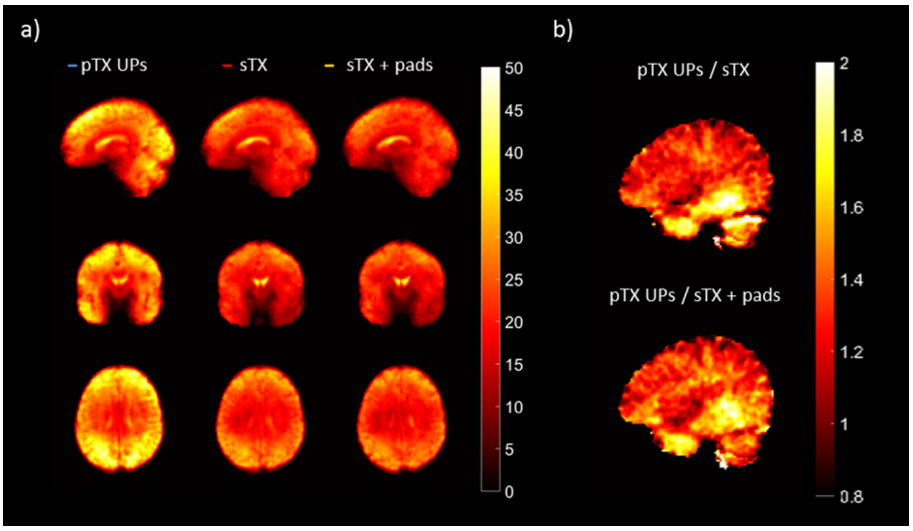

Figure 5: Average tSNR data. a) Three-plane view of the average (across all five subjects) tSNR map for the pTX UP (left column), in sTX (middle column) and sTX with dielectric pads (right column) acquisitions. Averaging was performed after normalization to the MNI152 standard space. b) tSNR ratio maps of pTX/sTX and pTX/sTX with pads shown for one sagittal slice through the right temporal lobe, showing a considerable tSNR enhancement in that region for the UP approach.

for realignment and distortion correction, nilearn for normalization and denoising) than the one defined in the HCP protocol (Van Essen et al., 2013), and in which the T_2-weighted scan was not employed for registration and segmentation. However, for the HCP data analysis framework, the contrast uniformity enhancement enabled by UPs for the T_2-weighted acquisition (see Figure 1) could be beneficial to improve the quality of the segmentation. In this study, We found for instance that the registration to the MNI template using FSL (with default processing parameters) was more robust if the pTX- rather than the sTX-MPRAGE acquisition was selected as the input anatomical image. We shall note however that a more thorough and expert use of the software could have improved the robustness of the registration with the sTX-MPRAGE acquisition.

3.4. Resting-state analysis

Figure 6 reports the seed-based analysis of the DMN performed on all subjects and for all setups. Here, stronger time-correlations between the posterior cingulate cortex and the temporal cortex can be seen in the data acquired with pTX UPs. This observation is consistent with the reported tSNR increase in the same regions. However, due to the small number of subjects involved in this study, no statistical analysis of the increased time-correlation was performed. It is also interesting to note a more pronounced left-right symmetry in the pTX UP results, which conforms to the description of the DMN as a symmetric network in the literature (Smith et al., 2009).

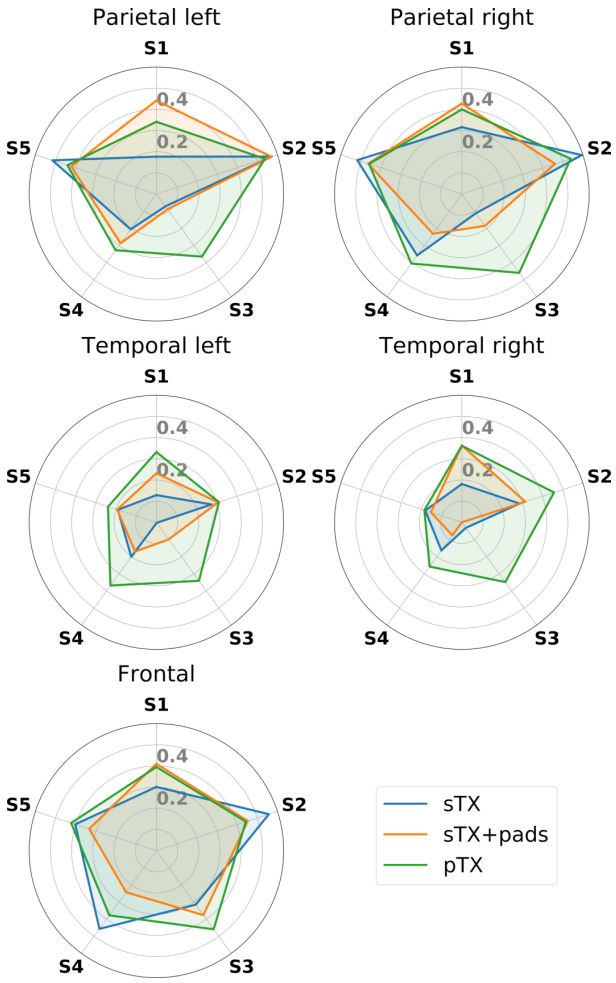

Figure 6: Radar plots of the time-correlation coefficient between the posterior cingulate cortex (seed) and the DMN-associated left parietal, the right parietal, the left temporal, the right temporal and the frontal regions for the five subjects (S1-S5) and the three acquisition modes (sTX, sTX+pads and pTX). Although below significance level due to the small number of subjects involved in this study, this result strongly suggests that higher levels of correlation can be seen in the pTX acquisition mode, in particular in the left and right temporal regions.

4. Discussion

Parallel transmission has long been advocated as promising technology to tackle standing wave effects at UHF, and enormous progress has been made in the past decade. But to date, the cumbersome operation and need for time-consuming calibrations typically result in these precious resources to be underused in actual application studies. The UP approach circumvents these limitations as it allows for a scanner operation that is no different from a sTX exam. A parallel here can be drawn with another proposed plug and play pTX approach (Cloos et al., 2016), which yet relies on the MR fingerprinting (MRF) concept. The major philosophical difference from UP lies in how the RF field inhomogeneity is dealt with: UPs tackle it at the excitation stage whereas the plug and play MRF technique resolves it at the reconstruction stage by disentangling its effects from the rest of the data. While the latter has shown promising results for quantitative MRI, it is yet not clear how the same framework could be leveraged to fMRI. The UP concept on the other hand is theoretically compatible with any type of MRI acquisition.

As shown in a previous work (Gras et al., 2017b), slightly superior pTX excitation performance can be achieved with full subject-specific RF pulse calibrations (Gras et al., 2017b). Another price to pay with UPs is the increased SAR and power demands engendered by their broadband behavior to be robust versus the variability of the B_0 offset across subjects (Gras et al., 2017b). The MB-EPI bipolar spoke UPs implemented in this work saturated the peak 10 g SAR of our VOP model (safety factor of 2.3) as well as the peak and total average power constraints, while the MPRAGE and SPACE acquisitions still left a factor of around 2 in TR to manoeuvre with. Consid-

ering the integration of pTX into a clinical setting, however, the incremental performance gain of subject-tailored pulses would probably not outweigh the additional effort of calibrating B_1^+, performing computationally expensive online pulse calculation and other complex pTX-related steps. As an indication of the time that would be needed to perform the calculations (any other operation than the pure pulse optimization taken aside) for this specific protocol in pTX with subject-tailored pulses (slice-specific RF shimming for the MB-EPI sequence and same k_T-point parameterization as for the UPs for the MPRAGE and SPACE sequences), the RF pulse computation times on a DELL Precision 7510 (processor Intel Core i7-6820HQ, 16 Gb of RAM) were 10 s, 48 s and 104 s for the MB-EPI, the MPRAGE and the SPACE sequences respectively. These times were returned for 100 iterations of our optimization algorithm (active-set) and 4 initial random k-space trajectories (for the k_T-points), which is an acceptable trade-off between performance and computation time, yet in our experience with low chances to return the global optimum. In addition, the subject-specific approach is prone to errors from any imprecision of the B_1^+ measurement, which is a particular risk in rapid B_1^+ mapping (Pohmann et al., 2016). Finally, the subject-specific approach relies on B_0 offset and B_1^+ maps that are typically obtained once at the beginning of the examination, and so any subsequent patient motion will impose further errors. The UP approach effectively removes this risk and provides robust universally applicable dynamic RF shims that are pre-calculated from a set of high-quality calibration data. Interestingly also, the use of UPs provides an additional layer of RF safety in that they can be extensively validated with prior phantom scans (e.g. by temperature mapping). Session-specific

subject-tailored RF pulses, as they do not exist until the actual scan occurs, do not allow such extensive RF safety tests and so their compliance with the IEC guidelines can only be assessed by means of numerical SAR simulations (the ones giving rise to the VOP model).

In this work, plug and play pTX acquisitions were characterized for the specific example of the HCP-style 7 T whole-brain resting-state fMRI protocol, by an excitation uniformity of significantly lower CVs than in standard sTX operation without and with dielectric pads. The excitation uniformity of the slice-selective and non-selective UPs that enable plug-and-play pTX were in fact comparable to the B_1^+ uniformity of a volume coil at 3 T, where RF field inhomogeneity in the brain is not considered obstructive to clinical use. We furthermore verified experimentally that the improvement in the excitation uniformity translated into a gain in tSNR and in a more robust measurement and analysis of the signal correlations in the resting brain. This is illustrated by the seed-based DMN result (Figure 6) which displayed stronger correlations with the use of pTX UPs than in sTX. One may naturally expect that this sensitivity gain translates directly to task-based fMRI.

For the MB-EPI acquisition, as shown in 2, we found in flip angle simulations that the proposed UP two-spoke design was comparable in performance with the subject-tailored slice-specific RF shimming (one-spoke design) that was recently proposed in HCP-style RS-fMRI scans at 7 T (Wu et al., 2019), and outperformed the subject-tailored volume RF shimming approach. Moving to a one-spoke slice-specific UP on the other hand resulted in significantly impaired excitation quality and robustness across subjects. Here, one subject had a flip angle CV above 16% for the UP RF shimming scenario. As a re-

sult, the key advantage of using the UP technique for conducting HCP-style RS-fMRI experiments at 7 T is that it combines the excitation performance typical of subject-tailored slice-specific RF shimming for SMS-EPI with the simplicity of use of sTX. While the first requirement is important to fully exploit the SNR and sensitivity gain at high field, the second is fundamental for the pTX technology to be embraced by new potential users. In the following, we mention some of the limitations that one should be aware of before switching to pTX UPs, and propose directions to mitigate them.

Adopting the proposed plug-and-play pTX framework can impose some restrictions on the protocol preparation, in particular for the MB-EPI case. Indeed, for the 2D case, since the two-spoke UP parameters (spokes RF amplitudes and locations in the transmit k-space) are optimized for a fixed slice position, these slice positions, in principle, cannot be modified for the acquisition. To mitigate this, we have proposed a weighted least-squares optimization procedure that promotes some robustness with respect to slice placement. This strategy not only gives a tolerance with respect to the actual position of the slices, but also some tolerance in the slice inclination. As a consequence, it also promotes robustness in terms of flip angle stability in case of motion. Furthermore, by increasing the value of the soft-threshold d_0 (in this study, it was set to 1 cm), it is possible to select a desired degree of robustness, naturally at the expense of performance in the ideal setting. Note here that the MPRAGE and SPACE acquisitions, as well as any 3D sequence, using non-selective dynamic RF shimming pulses, do not have this limitation at all. Hence, for those acquisitions, the position and orientation of the field of view can be set arbitrarily.

The fact that the design of UP is dependent of the flip angle that is targeted can appear as another obstacle, in particular if the latter parameter is supposed to be varied across experiments. We shall note however that the MB-EPI spokes pulses being designed by using the small tip angle approximation, reasonably valid up to 90° (Boulant and Hoult, 2012), different flip angles can be targeted by simply scaling the RF waveforms of the pulses. The repetition time of the sequence can be changed as long as the RF power and SAR limits are fulfilled. Just as in sTX acquisitions, the pulse duration likewise can be adjusted to accommodate these constraints, without having to recalculate the pulses, yet with increased penalty with respect to B_0 robustness. To provide more optimal solutions, different sets of pulses with different energy loads but identical duration could also be designed. The small tip angle and refocusing pulses in the MPRAGE and SPACE sequences being scalable as well, the same reasoning holds for the 3D anatomical scans.

The fact that the UP framework requires the adoption of bipolar 2-spoke pulses to preserve the same quality of excitation as the subject-tailored slice-specific RF shim does not impose a significant penalty in terms of the time-efficiency of the pulse, since the only excitation time overhead amounts to twice the ramp duration of the slice selection gradient. However, a limitation of the current implementation, and which does not exist for 1-spoke pulses, is that the slices could not be tilted (although this functionality can be desirable in practice, e.g. to maximize brain coverage with a minimum number of slices). This limitation is due to the way the gradient delay correction was performed, namely the application of a slice-dependent RF phase offset to the second spoke RF pulse (Gras et al., 2017c). This strategy unfortunately

does not allow slice tilting unless the gradient delay is the same for the x, y and z gradient coils. This however can be overcome in future work by adopting a more general correction strategy which consists in encoding the gradient delay correction in the second spoke k-space location rather than in the second spoke RF phase, by using so-called trim-blips (Oelhafen et al., 2004).

Conclusions

Calibration-free pTX was successfully implemented in the entire HCP RS-fMRI protocol at 7 T, including anatomical scans, by means of slice-specific bipolar two-spoke SMS-UPs (MB=5) and non-selective k_T point UPs. The flip angle homogeneity reported in this study with universal slice-specific two-spoke MB-EPI pulses (9 to 11% across 5 subjects) is comparable to the flip angle homogeneity obtained with subject-tailored slice-specific RF shim pulses. With this work, we report for the first time a plug and play utilization of a multi-transmit multi-receive RF coil for whole-brain BOLD fMRI at ultra-high field which, for MB-EPI, gives access to the same quality of excitation as subject-tailored slice-specific RF shimming without deviating from simple routine scanning. As compared with the single transmission mode, with and without dielectric pads, a noticeable gain in tSNR (up to 2-fold in B_1^+ deprived regions) resulting into a higher sensitivity for the BOLD-induced neural activity, and an improved contrast uniformity in whole-brain anatomical scans were reported.

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Competing interests

CEA has filed provisional patent applications directed to this technology.

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