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Title: Improving fMRI in signal drop-out regions at 7 T by using tailored radio-frequency pulses: application to the ventral occipito-temporal cortex.

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Abstract

Object: Signal drop-off occurs in echo-planar imaging in inferior brain areas due to field gradients from susceptibility differences between air and tissue. Tailored-RF pulses based on a hyperbolic secant (HS) have been shown to partially recover signal at 3 T, but have not been tested at higher fields.

Materials and Methods: The aim of this study was to compare the performance of an optimized Tailored-RF Gradient Echo Echo Planar Imaging (TRF GRE-EPI) sequence with standard GRE-EPI at 7 T, in a passive viewing of faces or objects fMRI paradigm in healthy subjects.

Results: Increased temporal-SNR (tSNR) was observed in the middle and inferior temporal lobes, and orbitofrontal cortex, of all subjects scanned, but elsewhere tSNR decreased relative to the standard acquisition. In the TRF GRE-EPI, increased functional signal was observed in the fusiform, lateral occipital cortex, and occipital pole, regions known to be part of the visual pathway involved in face-object perception.

Conclusion: This work highlights the potential of TRF approaches at 7 T. Paired with a reversed-gradient distortion correction to compensate for in-plane susceptibility gradients, it provides an improved acquisition strategy for future neurocognitive studies at ultra-high field imaging in areas suffering from static magnetic field inhomogeneities.

1. Introduction

Since Ogawa's first measurements in 1990 [1] functional MRI (fMRI) based on the Blood Oxygenation Level-Dependent (BOLD) effect has become a widely adopted technique to non-invasively measure brain activity. It is recognized that the most appropriate pulse sequence that can provide both highest sensitivity and temporal resolution is a Gradient-Recalled-Echo Echo-Planar Imaging (GRE-EPI) sequence [2]. Functional signal originates from local susceptibility changes induced by tissue oxygenation producing a dynamically varying intensity contrast. However, EPI is also very sensitive to macroscopic field inhomogeneities causing local frequency shifts and T2* relaxation time changes. The very low bandwidth in the phase encoding direction in EPI leads to increased sensitivity to any local field offsets, producing severe geometrical distortions in the images [3,4]. Moreover, signal loss and image blurring artifacts are caused by intravoxel phase dispersion during the slice selection process, which are not refocused in a GRE acquisition. This effect is

75 localized; the signal-loss is predominantly found near tissue-bone/air interfaces, and originates from
76 the strong susceptibility differences between these two tissues [5]. In particular, the orbitofrontal and
77 medial and inferior temporal lobes have been very difficult to characterize with fMRI due to the
78 severely reduced signal in these areas.

79 Several strategies have been adopted in fMRI studies to allow a better characterization of cortical
80 regions that suffer from signal dropout. These included the shortening of the echo time and the use of
81 smaller voxel sizes [6] and/or parallel imaging [7,8] or an appropriately oriented prescription of the
82 imaging slices [9]. However, these approaches typically compromise spatial coverage. One of the most
83 effective sequence modifications to compensate for the intravoxel dephasing has been based on z-
84 shimming methods, where additional compensation gradients are added to refocus the phase dispersion
85 [10-15]. Alternative approaches proposed the use of “Tailored” Radio-Frequency (TRF) pulses [16-18]
86 that generate a particular phase distribution across the slice during excitation that is later canceled by
87 the susceptibility gradient.

88 Cho and Ro [16] have demonstrated that RF pulses with a quadratic phase variation of the
89 transverse magnetization across the slice-selection direction could reduce the signal loss caused by
90 susceptibility gradients in the human head. More recently, at 3 T, it has been demonstrated that a
91 Hyperbolic Secant (HS) pulse produces an approximately quadratic variation in the phase of the
92 transverse magnetization that can partially cancel out the linear through-slice susceptibility gradient
93 induced by the inhomogeneity fields [18], successfully recovering resting-state BOLD signal from the
94 orbitofrontal and inferotemporal regions. However, the price paid when applying this compensation
95 method is a global reduction in temporal SNR.

96 The benefits offered by fMRI at ultra-high field have been extensively reported in terms of
97 increased BOLD signal amplitude and functional SNR in brain areas not affected by susceptibility
98 gradients [19-22]. However, the magnetic susceptibility effect increases linearly with field strength
99 (B_0) [23], and has a greater impact on the macroscopic susceptibility-induced signal loss in signal-
100 dropout regions at high field strengths [24,25].

101 In this study (previously reported in abstract form [26]) optimized parameters of the HS pulse
102 were obtained from Bloch simulations and tested with an EPI sequence on a 7 T MRI scanner. It was
103 hypothesized that the improved pulse could recover through-slice signal dropout in the Orbito-Frontal
104 (OF), Middle-Temporal (MT) and Inferior-Temporal (IT) regions at 7 T. To assess the performance of

this strategy in a functional study, a visual stimulation using images of faces and objects was used to elicit BOLD activity in the ventral occipito-temporal cortex [27-35] where the TRF pulse sequence is expected to provide improvement. The percent signal change and the extent of BOLD activation in the ventral visual areas in the TRF-based functional experiments were compared to those obtained with a standard GRE (Gradient Recalled Echo) EPI fMRI acquisition.

2. Materials and Methods

2.1 Subjects and MR system

Seven healthy volunteers (5 females, 2 males, ages: 25-41) participated in this study after providing written informed consent to the experimental protocol. The protocol was approved by the competent ethics committee, and in compliance with national legislation and the “Code of Ethical Principles for Medical Research Involving Human Subjects of the World Medical Association” (Declaration of Helsinki). The study was conducted on a *Discovery MR950* 7T whole body MRI system (General Electric Healthcare, Chicago, USA) equipped with a 2-channel transmit / 32-channel receive coil (Nova Medical, Wilmington, MA, USA) and a high-performance gradient system (50 mT/m maximum amplitude and 200 T/m/s slew rate).

2.2. TRF pulse optimization

Tailored hyperbolic secant RF pulses were designed using the algorithm described by Wastling et. al. [18]. A brief summary of the process is outlined below. A hyperbolic secant pulse has both amplitude $A(t)$ and phase variation $\phi(t)$:

$$A(t) = A_0 \text{sech}(\beta t) \quad (1)$$

$$\phi = \mu \ln[\text{sech}(\beta t)] + \mu \ln A_0 \quad (2)$$

for $-\frac{T}{2} < t < \frac{T}{2}$ (where T is the duration of the pulse). A_0 is the maximum amplitude, β is the modulation angular frequency, and μ is a dimensionless parameter, which controls the degree of quadratic phase induced in the transverse magnetization.

For a given set of object parameters (longitudinal relaxation time, T_1 , transverse relaxation time, T_2 , and the range of susceptibility gradients in the direction of slice selection, $G_{\text{sus,min}} < G_{\text{sus}} < G_{\text{sus,max}}$) imaging parameters (repetition time, TR , echo time, TE , slice thickness, D_z , and RF pulse duration, T) and hardware constraints (maximum obtainable gradient amplitude in the direction of slice selection,

$G_{z,max}$, and maximum RF amplitude, $B_{1,max}$) a series of Bloch simulations were performed to find the optimal value of μ which gives the most uniform signal response over the range of susceptibility gradients.

In this case pulses were designed to recover signal in brain parenchyma at 7T with $T_1 = 1940$ ms [36], $T_2 = 55$ ms [37], an expected magnetic susceptibility gradient in the slice selection direction of $-500 < G_{sus} < 500 \mu T/m$ [9,15], $TR = 2$ s, $TE = 20$ ms, $T = 5$ ms (to match the SLR pulse used in the standard sequence), slice thicknesses of 1, 2 and 3 mm, $B_{1,max} = 20 \mu T$ and $G_{z,max} = 36$ mT/m (reduced from the hardware limit to reduce mechanical vibrations and associated acoustic noise). The parameters of the optimized pulses are shown in Table 1.

The optimized TRF pulses were tested *in-vivo* by comparing the product Gradient Recalled Echo EPI, which employs a Shinnar-Le Roux (SLR) RF excitation pulse (hereafter, STD GRE-EPI), and the modified sequence that employs the optimized hyperbolic secant RF pulses (TRF GRE-EPI).

Three fMRI datasets (each one of 30 volumes preceded by 6 dummy scans) were acquired axially on one subject (female, 26 y.o.) with both STD GRE-EPI and TRF GRE-EPI and covered the inferior region of the brain, where magnetic susceptibility gradients are known to be particularly severe [5]. In each dataset slice thickness was varied (1 mm, 2 mm and 3 mm, with slice spacing of 3 mm, 2 mm and 1 mm, respectively, so that slice locations matched across different runs). Acquisition parameters, common to all acquisitions and both sequence types, were: $TE = 20$ ms, $TR = 2000$ ms, flip angle (FA) = 69° , acquisition matrix size = 128×128 ; FoV = 256 mm, ASSET (Array Spatial Sensitivity Encoding Technique) acceleration factor = 2, echo-spacing = 612 μs , slice acquisition interleaved bottom-up, phase encoding direction Anterior to Posterior (A>>P), number of slices = 16.

For each run the temporal SNR (tSNR, measured as the per-voxel temporal mean over the temporal standard deviation of the EPI series) was calculated after motion correction with MCFLIRT [38] and temporal filtering (FWHM = 100 ms). At each slice thickness, the tSNR maps from STD ($tSNR_{STD}$) and TRF GRE-EPI ($tSNR_{TRF}$) were compared by computing the percentage tSNR difference, $\delta tSNR$:

$$\delta tSNR = \frac{2(tSNR_{TRF} - tSNR_{STD})}{(tSNR_{TRF} + tSNR_{STD})} \times 100 \quad (3)$$

Positive values of $\delta tSNR$ indicate higher tSNR in the TRF acquisition.

2.3. Task-fMRI imaging protocol

On the other six healthy subjects, fMRI datasets were acquired during visual stimulation with

STD GRE-EPI and TRF GRE-EPI.

Twenty slices were placed axially in the inferior region of the brain, covering all portions of the temporal lobes and the inferior-middle portion of the occipital lobe. Slice prescription was maintained the same throughout each subject's exam in both STD GRE-EPI and TRF GRE-EPI acquisitions. Acquisition parameters were common to both sequences: TE = 20 ms; TR = 2000 ms; flip angle (FA) = 69°; slice thickness = 1.9 mm (in these experiments the TRF GRE-EPI pulse was therefore optimized for slice thickness = 1.9 mm); slice spacing = 0.1 mm; acquisition matrix size = 128x128; FoV = 256 mm, ASSET acceleration factor = 2, echo-spacing = 612 us, slice acquisition interleaved bottom-up, phase encoding direction Anterior-to-Posterior, A>>P. During acquisition, the subjects' heart rate and respiration were recorded with a plethysmograph and a respiratory belt, respectively.

The first 6 volumes of fMRI acquisitions were discarded in analysis to obtain the steady-state regime, and were followed by the collection of 120 volumes of functional data.

In addition to the functional scans, two additional EPI scans (one using the TRF GRE-EPI, one using the STD GRE-EPI) were acquired on each subject, maintaining the sequence parameters as described above, but reversing the phase gradient polarity (i.e., in this case it was set to P>>A). After discarding 6 dummy volumes to ensure a steady state signal, as above, 5 volumes were acquired for these additional scans, and were used to estimate B0 field maps for the geometrical distortion correction of the EPI sequences as described in section "Data processing and analysis" below.

2.4. T1-weighted anatomical imaging

For all subjects, structural images for anatomical reference were acquired using a T1-weighted Fast Spoiled Gradient Recalled (FSPGR) sequence with receiver bandwidth (RBW) = 50kHz, inversion time (TI) = 450ms, TR = 6ms, TE = 2.2ms, FA = 12°, ASSET acceleration factor = 2, voxel size = (1x1x1) mm³.

2.5. Functional paradigm: Face-Object (F-O) visual stimulation

A visual stimulus involving the presentation of images of faces and objects was designed to elicit functional activity in the occipital-temporal visual areas. Neuroimaging studies have shown stronger activity for human face identification than for other kinds of objects in the occipitotemporal cortex [28,29,39-41] and the anterior temporal lobes [42]. The visual stimulation used in this study

incorporated 20s blocks of grayscale images (n=16 images per block) of either human faces unknown to the subject (F), or random everyday objects (O). These blocks were interleaved with 20s blocks of blank periods (B), where no images were shown. Subjects passively viewed three epochs of the blocks series (B-F-B-O), which gave a total acquisition time of 240s for each functional run.

The stimuli were presented on a 32-inch display screen (NordicNeuroLab, Bergen, Norway) positioned at the rear of the scanner bore, and subjects observed them through a mirror attached to the head coil. Subjects were instructed to keep their eyes open and fixate on the center of the screen. Stimuli were identical during both STD-GRE-EPI and TRF-GRE-EPI but the order of scans was varied across subjects in order to avoid a systematic task-performance bias.

2.6. Data processing and analysis

All functional brain data were pre-processed and analysed in FEAT of FSL v6.0 (<http://fsl.fmrib.ox.ac.uk/fsl/>) [43]. First, each time-series was corrected for head motion using MCFLIRT [38]. To remove temporal drifts, a temporal filter (FWHM=80s) was applied, followed by a pre-whitening process. The BOLD response was modeled using separate explanatory variables (EVs) for the two stimulus types. A standard Gamma Hemodynamic Response Function (HRF) (mean lag=6s, standard deviation=3s, phase=0s) was convolved with each of the EVs and a General Linear Model (GLM) analysis that included motion parameters as nuisance regressors was performed for each voxel. To minimize the detrimental contribution of the physiological fluctuations of the fMRI time series, the respiration and cardiac signals were added in the GLM as additional explanatory variables, after appropriate temporal undersampling to match the MR sampling rate and taking into account the slice acquisition timings.

For each of the scans, three z-score contrast maps were computed:

- Faces>Baseline contrast (F>B), where F-blocks were analyzed against B-blocks;
- Objects>Baseline contrast (O>B), where O-blocks were analyzed against B-blocks;
- Images>Baseline contrast (I>B), where F-blocks and O-blocks were taken together and compared to B-blocks.

The z-statistical maps were thresholded using clusters determined by $z > 3.09$, with a corrected significance cluster threshold of $p < 0.05$ [44].

In order to set ROIs in a reproducible manner and obtain a reliable analysis, the Montreal National Institute 152 (MNI152) brain was registered to individual subjects' spaces via a three-step registration pipeline compensating for the severe geometrical distortions that occur in EPI, especially at high field [4]. First, distortion fields were obtained with the reversed gradient approach [45]: the first five baseline volumes from a P>>A phase encoding acquisition were isolated and averaged. The same was done for the five volumes of the corresponding A>>P phase encoding scan. Both volumes were processed with the *topup* command from FSL [43] to obtain distortion fields (independently for the TRF GRE-EPI and the STD GRE-EPI) and these were used to correct the corresponding fMRI data. Second, a boundary-based registration algorithm [46] was applied to register the distortion-corrected STD and TRF GRE-EPI images to the high-resolution structural scans (FSPGR) of each subject. Third, a 12-DOF affine registration was used to compute the transformation matrix that allowed co-registration of the FSPGRs with the standard T1 MNI152 brain.

Such transformation matrices allowed mapping regions-of-interest (ROIs) of a standard structural atlas onto each subject's EPI scans. Ten ROIs were considered to cover all regions of the occipital and temporal lobes in the analysis. These regions were obtained from nineteen areas of the Harvard-Oxford Cortical Structural Atlas [47], which were mapped to each subjects' raw EPI space, according to Table 2.

Signal analysis was performed on a per-subject basis directly in "native" EPI space (i.e. no distortion correction was applied) to avoid confounding effects in the analysis. From the pre-processed, temporally filtered data, temporal SNR (tSNR) was estimated using the first 10 baseline volumes in each functional acquisition and was calculated voxel-wise as the ratio of the temporal mean to the temporal standard deviation in the series. tSNR maps from STD ($tSNR_{STD}$) and TRF GRE-EPI ($tSNR_{TRF}$) were compared by computing the percentage tSNR difference, $\delta tSNR$, as in equation (3). In addition, the voxel-wise percent BOLD signal change, PSC, was calculated. PSC was defined as the difference between the average of seven time points after the peak of the response 6s after the stimulus onset (Son) and the average of seven time points of the previous blank block 6s after the stimulus was turned off (Soff), normalized by the baseline signal average (S) calculated from the first 10 time-points of the time series. In short: $PSC = (Son - Soff) / S$. The per-voxel PSC was calculated separately for the three contrasts F>B, O>B and I>B.

The regional PSC was computed for each subject as the average PSC in the significant voxels in each ROI. The regional active volume was defined as the number of active voxels in each ROI. The percentage PSC difference, δPSC , and the percentage active volume difference, δAV , were calculated in a similar manner as in equation (3) for each ROI. The δAV was also computed in additional ROIs comprising all voxels where $\delta\text{tSNR} > 50\%$, for each subject.

3. Results

3.1. HS pulses at 7 T

The results of simulations that led to the optimization of the TRF pulses are reported in Table 1 and Supplementary Material Fig. 1. In particular, a uniform slice profile was obtained at all thicknesses ($|M_{xy}|/M_0$).

The signal variation as a function of through-plane susceptibility gradient, calculated by Bloch simulations is shown in Fig. 1. It is noted that for the 1 mm slice the uniformity is markedly reduced.

The magnitude of the STD GRE-EPI and TRF GRE-EPI, and the calculated δtSNR of two representative slices (S1 and S2) from data acquired at three different slice thicknesses are displayed in Fig. 2. The TRF GRE-EPI runs had higher tSNR in regions around the inferior temporal and orbito-frontal lobes compared to the STD GRE-EPI runs. From all voxels showing positive δtSNR , the TRF acquisitions had, on average, 82.6% higher tSNR compared to the STD acquisition at a slice thickness of 3 mm. The gain in δtSNR decreased with decreasing slice thickness (56.1% and 35% for 2 mm and 1 mm slice thickness, respectively). The average tSNR loss observed in the TRF sequence outside the recovery regions was 70.6%, 59.1% and 52.6% at 3 mm, 2 mm and 1 mm slice thickness, respectively.

3.2. fMRI analysis

In the fMRI experiments with visual stimulation, a slice thickness of 1.9 mm was used. The optimized values of μ and β of the HS pulse were 2.950 and 2961 Hz, respectively. The RF pulse bandwidth was 3236 Hz. The conventional SLR pulse used in the STD-EPI acquisition had a bandwidth of 712 Hz and a duration of 5 ms.

Fig. 3 shows the δtSNR maps obtained from all six subjects, in two representative slices. In all subjects, localized regions that showed recovery of signal included the anterior and ventral portions of the temporal lobes and the orbital frontal cortices. From all voxels showing positive δtSNR , the TRF

acquisitions presented, on average, a $(59\pm7)\%$ higher tSNR compared to the STD acquisition. However, in all other brain voxels there is a loss of $(61\pm3)\%$ in tSNR. Considering the whole brain mask, tSNR was on average lower in the TRF than in STD sequence: $(-29\pm8)\%$.

Fig. 4 (A) shows the δ PSC in all ROIs from the three fMRI contrasts. Generally, the average PSC across all subjects was higher in the TRF run than in the STD. The Friedman test, followed by Nemenyi post-hoc test, were used to evaluate the statistical significance of each of the results. For Occ Pole, IntraCalc, Lingual, Lat Occ, Fusiform, ST Gyrus and IT Gyrus, the PSC in TRF GRE-EPI was significantly higher in at least one functional contrast (see asterisks in Fig. 4 (A)). The regional δ AV averaged across all subjects is displayed in Fig. 4 (B). However, this difference did not reach statistical significance in any of the functional contrasts tested. Yet, when this analysis was restricted to voxels showing a δ tSNR $> 50\%$, the δ AV was positive in all subjects for all functional contrasts (Fig. 5). Examples of functional maps with improved activation extent and/or statistics in areas of signal recovery are shown in Fig. 6.

4. Discussion

4.1. HS pulses at 7 T

In this work, HS pulses with optimized parameters [18] were used for GRE-EPI acquisitions at 7 T. Our results show that regions suffering from severe signal dropout in standard GRE-EPI due to strong susceptibility differences at tissue-air interfaces have larger tSNR when using the Tailored-RF approach. These results were consistent across a range of slice thicknesses (Fig. 2). The recovered signal was localized in the temporal lobe (anterior and ventral portions) and the orbital-frontal cortex and was observed in all subjects (Fig. 3). As predicted [18,19], tSNR losses were found in most of the other brain regions that are not affected by through-plane susceptibility effects. Therefore, there is an advantage of using a tailored HS pulse in regions where there is an inhomogeneity leading to at least a 50% loss of signal.

In this study, the HS pulse amplitudes were not high enough to act adiabatically and therefore remain susceptible to the effects of B1 inhomogeneities (which are particularly severe at 7 T). However, the SLR pulse used in the conventional EPI approach is also not in adiabatic regime, so the comparison between the techniques is fair. The Specific Absorption Rate (SAR) for TRF was higher than for STD GRE-EPI and it varied with slice thickness: at 2 mm thickness the SAR was higher in the TRF by a

factor of two. Yet it is important to consider that a GRE-EPI sequence is an inherently low-SAR sequence and, in our fMRI experiments, the average SAR never exceeded 0.5 W/kg. Therefore we do not expect that SAR could be a severely limiting factor for the most common fMRI studies even with different scanning parameters, i.e. at higher flip angles.

EPI acquisitions suffer not only from signal dropouts originating from through-plane susceptibility differences, but also from in-plane local susceptibility gradients that cause image distortions. Deichmann et al. [9] suggested that by optimizing the imaging slice orientation and by using of a z-shimming preparation block it is possible to reduce the local signal losses. Yet, this approach might limit brain coverage because it requires tilting the imaging slices in such a way to redistribute the susceptibility gradients. The reversed gradient EPI approach is a more flexible method that also estimates field maps for distortion correction [45]. It was designed primarily for spin-echo EPI schemes which refocus signal dephasing with a 180° pulse, hence theoretically devoid of signal losses related to through-plane dephasing. In standard GRE-EPI the reversed gradient approach is thus likely to be suboptimal in signal drop-off regions. Therefore, TRF GRE-EPI should improve the reversed gradient distortion correction method, although this aspect was not directly examined in the current study.

Future studies should aim to recover the signal in regions with severe susceptibility artifacts without sacrificing the SNR in areas that are not affected by signal dropout would be desirable. Improved TRF GRE-EPI implementations might explore the use of slice-dependent excitation pulses: for each slice, the range of expected susceptibility gradients used to optimize the excitation pulse could be extracted from a simple B0 map (used as a calibration scan) so that differently tailored RF pulses could be used at different locations. This more flexible approach would relax the rigid constraint that the current implementation imposes on the choice of whether to use either a standard or a TRF GRE-EPI scheme.

4.2. Considerations on *in-vivo* fMRI

The occipital-temporal pathway is traditionally associated with face perception and recognition processes of the brain. In this study we used visual stimuli involving images of faces and objects, which elicited the largest BOLD responses in the posterior portions of the inferior visual cortex in accordance with the literature [31,33,40]. In these regions the TRF BOLD signal was significantly improved for most fMRI contrasts analyzed. Although there is evidence of activation recovery at an

individual level, both techniques showed similar activation patterns. Active voxels did not significantly extend to regions with the highest signal recovery in the inferior temporal lobes with the TRF acquisition, despite the higher tSNR. Our results also showed that the performance of the TRF sequence in areas not affected by susceptibility artifacts was not hampered in terms of z-statistics even though tSNR was lower. The statistical power in the assessment of the different BOLD fMRI performance of TRF and STD GRE EPI might have been limited by the small number of subjects and the short acquisition time of each condition: a larger dataset might enable a better evaluation of the differences between the two sequences. We also point out that that our experiments do not demonstrate that the measured performance can be generalized to different experimental setups.

The use of TRF GRE-EPI could provide more pronounced improvement in the study of more complex mechanisms such as image-invariant face recognition, which have been observed in a face-selective region in the anterior temporal lobe [48-51]. As described by the authors of those studies, one of the major difficulties in imaging this area is the severe signal drop-off in conventional GRE-EPI acquisitions, which can be recovered by TRF GRE-EPI (Fig. 3). Other regions that might benefit from TRF GRE-EPI are the medial temporal lobe and the prefrontal cortex [52-54]. The improved tSNR of TRF-EPI around areas with high magnetic susceptibility gradients, together with the higher resolution capabilities of 7 T imaging [55], have the potential to aid presurgical planning in temporal lobe epilepsy patients [56], both in assessing the risk of postsurgical deficits and in determining the site of seizure onset.

5. Conclusion

This study validated the use of the TRF approach at 7 T [18,26] in a functional MRI study targeting the ventral occipito-temporal cortex. With respect to conventional GRE-EPI using SLR pulses, this sequence improved tSNR bilaterally in the MT and IT lobes as well as in the OF cortex, where through-plane susceptibility gradients most often hamper the imaging quality. In addition, increased BOLD sensitivity was observed in regions involved in face perception, which suggests that TRF GRE-EPI could be a suitable technique for fMRI studies targeting the temporal lobes at 7 T.

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7. Authors' Contribution

Rua C: Project development, data collection and data analysis.
Wastling SJ: Project development and data collection.
Costagli M: Project development, data collection and data analysis.
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Biagi L: Project development and data collection.
Cosottini M: Project development and data management.
Del Guerra A: Project development.
Tosetti M: Project development and data management.
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8. Compliance with Ethical Standards

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Conflict of Interest: MRS is employed by General Electric Healthcare. GJB receives honoraria for teaching from General Electric Healthcare, who also part fund a PhD studentship. GJB acts as a consultant for IXICO.
Statement of human rights: All procedures involving human participants were in accordance with the ethical standards of the competent ethics committee and with the 1964 Helsinki declaration and its later amendments.
Informed consent: Written informed consent was obtained from all individual participants included in the study.

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Figure captions:

Fig. 1 Simulated normalized steady state gray matter voxel signal as a function of through-slice susceptibility gradient for the optimized HS pulses at different slice thicknesses: 1 mm (blue), 2 mm (red) and 3 mm (yellow)

Fig. 2 STD GRE-EPI (first row) and TRF GRE-EPI (second row) and δt SNR in percentage (third row) on two different slices (S1 and S2) of one subject at three different acquisition resolutions: (A) slice

thickness = 1 mm, (B) slice thickness = 2 mm and (C) slice thickness = 3 mm. In plane resolution was (2x2) mm² for all acquisitions

Fig. 3 Percent $\delta tSNR$ in all subjects in two acquired slices covering the Temporal Lobe (TL), Orbital Frontal (OF) and Fusiform Cortex (FC) where signal drop-out is, in general, particularly severe

Fig. 4 Average percent differences in BOLD signal change (δPSC) and active volume (δAV) across all subjects in the 10 defined ROIs (error bars represent inter-subject standard error) for the contrasts F>B, O>B and I>B. Positive percent differences indicate higher values in TRF GRE-EPI than in STD GRE-EPI. For each subject and in each region, the average regional PSC was obtained from all the active voxels of the corresponding functional contrast. Statistical significance was evaluated with the Friedman test followed by post-hoc Nemenyi test for each ROI and contrast independently. Asterisks indicate statistically significant results ($p < 0.05$)

Fig. 5 Average percent δAV in voxels with $\delta tSNR > 50\%$. The number of active voxels in signal recovery areas was higher in TRF GRE-EPI than in STD GRE-EPI, in all subjects for all functional contrasts

Fig. 6 Examples of functional activation maps for the contrasts I>B and F>B in two different contiguous slices for Subjects 1, 4 and 6. In green overlay, voxels with $\delta tSNR > 50\%$ are also shown (bottom row). Yellow dotted circles indicate example regions that show improved activation extent and/or statistics in areas of signal recovery in TRF GRE-EPI

Table 1

	Slice thickness (mm)		
	1	2	3
μ	1.45	3.00	3.95
β (Hz)	2757	3073	3621
Bandwidth (Hz)	1703	3406	5109
A_0 (μ T)	6.11	9.79	13.27

Table 1: Optimized parameters of the TRF pulses for the three simulated slice thicknesses.

Table 2

ROI	Harvard-Oxford Cortical Structural Atlas Structures
Occ Pole	occipital pole
SupraCalc	supracalcarine cortex
IntraCalc	intracalcarine cortex
Lingual	lingual gyrus
Lat Occ	lateral occipital cortex, superior division lateral occipital cortex, inferior division
Fusiform	temporal fusiform gyrus, anterior division temporal fusiform gyrus, posterior division temporal occipital fusiform cortex occipital fusiform gyrus
ST Gyrus	superior temporal gyrus, anterior division superior temporal gyrus, posterior division
MT Gyrus	middle temporal gyrus, anterior division middle temporal gyrus, posterior division middle temporal gyrus, temporooccipital part
IT Gyrus	inferior temporal gyrus, anterior division inferior temporal gyrus, posterior division inferior temporal gyrus, temporooccipital part
Temp Pole	temporal pole

Table 2: MNI-derived ROIs defined for each subject.

Fig. 1

Fig. 2

Fig. 3

Fig. 4

(A)

(B)

Fig. 5

Fig. 6