# Whole brain, high resolution multiband spin-echo EPI fMRI at 7 Tesla: A comparison with gradient-echo EPI using a color-word Stroop task

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**Running Title**: Comparison of SE EPI and GE EPI with task fMRI at 7T

## Abstract

A whole brain, multiband spin-echo (SE) echo planar imaging (EPI) sequence employing a high spatial (1.5 mm isotropic) and temporal (TR of 2 s) resolution was implemented at 7 Tesla. Its overall performance (tSNR, sensitivity and CNR) was assessed and compared to a geometrically matched gradient-echo (GE) EPI multiband sequence (TR of 1.4 s) using a colour-word Stroop task. PINS RF pulses were used for refocusing to reduce RF amplitude requirements and SAR, summed and phase-optimized standard pulses were used for excitation enabling a transverse or oblique slice orientation. The distortions were minimized with the use of parallel imaging in the phase encoding direction and a post-acquisition distortion correction. In general, GE-EPI shows higher efficiency and higher CNR in most brain areas except in some parts of the visual cortex and superior frontal pole at both the group and individual-subject levels. Gradient-echo EPI was able to detect robust activation near the air/tissue interfaces such as the orbito-frontal and subcortical regions due to reduced intra-voxel dephasing because of the thin slices used and high in-plane resolution.

**Keywords:** BOLD, PINS, orbito-frontal, sensitivity, CNR, physiological noise

## Introduction

Functional magnetic resonance imaging (fMRI) with blood oxygenation level dependent (BOLD) contrast has been the most popular tool for the neuroscience community for more than two decades (Ogawa et al., 1990). The BOLD contrast results from the interplay between cerebral blood volume, blood flow, and oxygen consumption: all triggered by the underlying neuronal activity. The BOLD response is generated by four possible contrast mechanisms, namely extravascular dynamic/static dephasing and intravascular dynamic/static dephasing, the relative contributions of which depend on main magnetic field strength B0, spatial resolution and vessel size. It is widely accepted that the extravascular component becomes much more prominent at high field (7T or above) (Duong et al., 2003; Ogawa et al., 1993). Spin-echo (SE) based sequences refocus the static effects, and the transverse relaxation time, $T_2$, of venous blood shortens very rapidly with increasing field strength. At 7T it is very short (~10-15 ms) compared to the optimal (for gray matter) echo times (TE) of SE echo planar imaging (EPI) sequences at high field (Lee et al., 1999; Ugurbil et al., 2000). This implies that the SE EPI BOLD response at 7T originates solely from the extravascular dynamic dephasing component and thus, from capillaries and smaller post capillary vessels. Given that gradient echo (GE) EPI BOLD contrast is augmented by the dephasing from the venous blood (draining vessels), GE EPI and SE EPI have been labeled as being more sensitive and more specific to the *true* site of neuronal activation, respectively (Norris, 2012; Olman and Yacoub, 2011; Parkes et al., 2005; Uludağ et al., 2009; Yacoub et al., 2005).

Similar to BOLD contrast mechanisms, the noise characteristics of SE and GE EPI are also complex and differ from each other. Acquisition parameters (TE, voxel volume) and the field strength play a major role in the effect size of the physiological component (breathing, heart beat) of the noise. It is well established for GE EPI that with increasing field strength and voxel volume the physiological noise dominates over the thermal noise (Triantafyllou et al., 2005). Triantafyllou et al have also demonstrated almost the same behavior for SE EPI as GE EPI at 3 and 7T with different coils and spatial resolutions (Triantafyllou et al., 2009). However, in an earlier study it was suggested

that in a SE EPI experiment the ratio between physiological and thermal noise is independent of the voxel size (Yacoub et al., 2005).

Even though multiband (also called simultaneous multi-slice, SMS) imaging was first proposed (Larkman et al., 2001) around the same time as the now commonly used parallel imaging techniques (GRAPPA Griswold et al, SENSE, Pruessmann et al, SMASH (Sodickson and Manning) )(Griswold et al., 2002; Pruessmann et al., 1999; Sodickson and Manning, 1997), it took almost a decade to receive any attention and interest from the MR community (Feinberg et al., 2010; Moeller et al., 2010). Multiband imaging provided the opportunity for 2D sequences to accelerate in the slice direction by acquiring data from N slices simultaneously without the penalty of a sqrt(N) reduction in signal to noise ratio (SNR). Initially an image domain reconstruction similar to SENSE was used for multiband reconstruction (Larkman et al., 2001), however, recently the blipped CAIPIRINHA approach (Setsompop et al., 2012) has proven to be very useful in facilitating an improved reconstruction by employing the coil information in the phase encoding direction. However, one has to be careful in choosing the right combination of acceleration and shift factors (Setsompop et al., 2013).

Common multiband RF pulses are the complex sums of the individual RF pulses of each of the excited slices. Therefore, the RF amplitude and power needed is linearly proportional to the number of slices excited simultaneously (Maudsley, 1980; Müller, 1988). Evidently, this poses problems for SE EPI at high field due to the high specific absorption rate (SAR) of the refocusing pulses. Recently, to overcome this SAR limitation problem, Power Independent Number of Slices (PINS) pulses (Norris et al., 2011) were introduced and have been used in a high resolution SE EPI resting state (RS) study at 7T (Koopmans et al., 2012) and for high spatial resolution DWI also at 7T (Eichner et al., 2013). Due to the periodic excitation profile of the PINS pulses, a sagittal acquisition scheme was adopted for the SE EPI RS study. We have implemented a high spatial and temporal resolution SE EPI sequence by employing standard multiband pulses for excitation and PINS pulses for refocusing, so that the acquisition in any slice orientation is possible. It is thus now possible to perform whole brain SE EPI at 7T with good spatial and temporal resolution. It is hence highly relevant to examine the relative

overall performance of GE and SE EPI at 7T in order to make an informed choice of pulse sequence for performing standard activation studies (i.e. excluding specialized studies of cortical layers or columns). We hence also implemented a matched multiband GE EPI sequence and compare here the two pulse sequences in terms of signal and noise levels, sensitivity and contrast to noise ratio (CNR) using a color-word Stroop functional paradigm. The Stroop task generates activation in a broad range of brain regions including the orbito-frontal areas where SE EPI has previously been found to outperform GE EPI at lower static magnetic field strengths and coarser spatial resolutions (Norris et al., 2002; Schwarzbauer et al., 2010). We chose to perform the experiments at a nominal spatial resolution of 1.5 mm, as this is finer than the expected width of the hemodynamic response function at this field strength for both gradient- and spin-echo (Engel et al., 1997; Norris, 2006).

## Methods

### *Acquisition*

Data were collected from 6 healthy subjects (4 male, 2 female, age 25.8±3.4) after obtaining informed consent, using a 7T Magnetom scanner (Siemens Healthcare, Erlangen, Germany) with a 32 channel head coil (Nova Medical, Wilmington, USA). Prior to the functional GE EPI and SE EPI scans, 5 matched reference scans with full FOV and without multiband acceleration were obtained for the estimation of the reconstruction kernel in the phase encoding (PE) and slice direction. Geometrical parameters were kept identical between SE EPI and GE EPI such as: FOV 224x224 $mm^2$, 69 slices, PE direction AP, in plane acceleration factor (AF) 3, multiband factor 3, bandwidth 1960 Hz/Px, resolution 1.5x1.5x1.3 $mm^3$, slice gap 15%, matrix 150x150. Table 1 shows the remaining acquisition parameters of SE EPI and GE EPI scans. Structural scans for 5 subjects were obtained using MP2RAGE (Marques et al., 2010) with the following parameters: matrix 256x240x160, resolution 1x1x1 $mm^3$, acquisition time 10:42 s, flip angles 4° and 6°, inversion times 900 ms and 3200 ms, TE 1.89 ms, TR 5000 ms, bandwidth 240 Hz/Px. The structural scan of one subject was already

available from a 3T scanner (Tim Trio, Siemens Healthcare, Erlangen, Germany) with matrix size 256x256x192, resolution 1x1x1 $mm^3$, acquisition time 5:21 s, flip angle 8°, inversion time 1100 ms, TE 3.03 ms, TR 2300 ms, bandwidth 130 Hz/Px.

In a previous study (Koopmans et al., 2012) PINS pulses were employed in a SE EPI sequence both for excitation and refocusing. This excludes slice orientations having a gradient component along the z-axis (i.e. only coronal or sagittal slice orientations are permitted) as otherwise signals from the neck region, and possibly beyond, will contribute to the aliased slice due to the infinite excitation profile of PINS pulses. In this study, we have used standard (summed) multiband pulses for excitation and PINS pulses for the refocusing of the SE sequence, enabling axial slice orientation. The phases of the individual excitation pulses have been optimized to reduce the peak power (Goelman, 1997; Hennig, 1992). PINS pulses consist of a series of RF hard pulses interleaved with slice selective gradient blips. Each individual blip de-phases the signal by 2π over the defined slice spacing creating a periodic slice profile. The amplitude of each hard pulse can be determined by a Fourier series expansion of the desired slice profile. Although periodicity seems to imply an infinite number of slices, this is in practice limited by the extent of the subject or the transmit/receive volumes of the coils. Compared to a single slice pulse, there is some increase in SAR for PINS when using the same pulse duration (Norris et al., 2011). This arises from spending some time of the RF duration only on gradient switching instead of RF transmission. However, this increase is significantly smaller than the increase in power deposition of a conventional summed multiband pulse which is proportional to the number of simultaneously excited slices. Due to slew rate limitations, PINS pulses have a relatively low bandwidth-time product (BWTP). To compensate for this, RF pulse durations of 7.68 ms were used for all RF pulses in order to achieve the desired slice thickness of 1.3 mm. This allowed for 31 PINS sub-pulses resulting in a BWTP of 1.12 which was matched to the standard multiband pulses.

### *Reconstruction and registration*

The reconstruction was performed offline in MATLAB. First, both the reference data and the multiband data were unfolded in the phase encoding direction with the GRAPPA

algorithm (5x4 kernel) (Griswold et al., 2002). Then, multiplexed slices were unaliased with the SENSE-GRAPPA algorithm (3x2 kernel) (Blaimer et al., 2006). The mean of the reconstructed EPI volumes was coregistered to the corresponding anatomical scan using an in-house developed distortion correction and coregistration algorithm for each subject (Visser et al., 2010), which simultaneously estimates the transformation matrices in all directions, non-linear in the AP PE direction (deformation due to EPI) and linear in the other directions (rigid-body) (Studholme et al., 2000). The degree of distortion and the corrected mean images for SE EPI and GE EPI for a representative subject can be seen in Figures 1 and 2, respectively.

***Functional task and analysis***

The functional task was the same for SE EPI and GE EPI scans: the color-word interference Stroop task, which is widely used by the neuroscience community and known to induce consistent (de-)activation in the whole brain and especially in orbito-frontal regions. For each trial (1.5 s) two words were presented above each other on a gray screen (in text: blue, red, green or yellow), the one below in black and the one above in color (blue, red, green, or yellow). The subjects were told to press a button when the meaning of the word in black (below) was matched by the color of the above word, regardless of its meaning. There were 10 ON blocks (30s, 20 trials) in each run with an initial 20 s and 10 other (10 s) OFF blocks in-between. During the OFF blocks subjects were told to fixate on a red cross at the center of the screen. The total duration of each run was 7 minutes and the order of acquisition was alternated between subjects to counter balance habituation effects. Thus, three subjects started with SE EPI scan and then GE EPI while the other three first performed the task while being scanned with GE EPI and then SE EPI.

The functional analysis was carried out with FEAT (v5.98, http://www.fmrib.ox.ac.uk/fsl/) with the following preprocessing steps: spatial smoothing (3mm kernel), drift removal, MCFLIRT motion correction and prewhitening. Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 and stage 2 (Beckmann et al., 2003; Woolrich et al., 2004; Woolrich, 2008). Z (Gaussianised T/F)

statistic images were thresholded using clusters determined by Z>2.3 and a (corrected) cluster significance threshold of P=0.05.

The temporal signal to noise ratio (tSNR) maps were corrected for different TRs of SE and GE EPI to obtain sequence efficiency. In other words, tSNR of a voxel is its mean divided by the standard deviation and the square root of the TR of the sequence. Contrast to noise ratio (CNR) maps were obtained from the z-score statistical maps considering the accurate transition of individual subject results to the group level (with FLAME 1+2).The regions having higher z-score (for both contrasts combined) for one modality compared to the other one were mapped for both GE and SE EPI. The individual subject and group results were masked with the brain masks obtained from the mean EPI image and the MNI template, respectively.

## Results

Reconstructed SE EPI and GE EPI single time point images of a representative subject are shown in Figure 3. SE EPI suffers from reduced signal intensity at the centre of the brain due to B1 inhomogeneity, whereas it is superior to GE EPI in recovering the signal in the orbito-frontal areas. The signal losses can also be observed from the mask (see the first slice of the GE EPI and central regions of SE EPI) applied to the tSNR maps of the corresponding slices shown in Figure 4. GE EPI has higher tSNR with respect to SE EPI in the whole brain for the single subject case and in the group average.

Figure 5 shows that the superior tSNR of GE EPI also translates to higher functional sensitivity compared to SE EPI. Number of (de)activated voxels and the maximum z-scores in the group level are listed in Table 2. GE EPI is able to detect whole brain activation (red-yellow) and deactivation (blue) including in problematic regions such as the orbito-frontal regions and hippocampus. However, SE EPI surprisingly has comparable sensitivity within the visual cortex. For comparison, the activated regions where GE EPI and SE EPI perform better in terms of CNR are plotted in Figures 6a and 6b respectively. Except for some parts of the visual cortex and (superior) frontal pole, GE EPI has higher CNR. In addition, the signal change ($\Delta S$) and the noise ($\sigma$) levels for

SE and GE EPI can be seen in Figure 7. GE EPI has considerably higher signal change but also higher noise in the visual areas.

## Discussion

SE EPI at high field is challenging to perform mainly due to SAR limitations leading to partial brain coverage and/or increased TR. SE EPI with multiband approaches only exacerbate the SAR problem as the RF power per unit time linearly increases with the acceleration factor. Power deposition of PINS pulses is independent of the number of multiband slices, currently making them a natural option for SE EPI at 7T. Another limitation related to the hardware rather than the safety limits is the peak voltage which also increases linearly with the flip angle and the number of slices. In this study, in line with previously reported RF peak power reduction methods (Auerbach et al., 2013; Goelman, 1997; Hennig, 1992) we optimized the phases of the multiplexed slices along the lines of (Wong, 2012) and achieved a 26% decrease in the RF peak amplitude. The low signal intensity observed at the center of SE EPI images is caused by B1 inhomogeneity which is a typical feature of high field. Even though for this specific study the Stroop task does not show activation close to the center of the brain, this issue should be resolved by recent advances in SMS parallel transmission (Poser et al., 2013) or better RF shimming (Katscher and Börnert, 2006; Van de Moortele et al., 2005).

The possible acceleration in one direction is determined by the independent information (i.e. reconstruction power) that is available from the coil channels in that specific direction. The reconstruction power can be transferred from the PE direction to the multiband direction with the blipped CAIPIRINHA (Setsompop et al., 2012) approach by shifting the slices with respect to each other in the PE direction in a controlled fashion and thus maximizing the distance between aliased voxels. This would allow higher acceleration factors in the multiband direction. Alternatively, one can accelerate in the PE direction by skipping some of the PE lines periodically as in this study. In this case, the shortened readout train also results in slightly lower TR but the real benefit is the

reduced EPI distortion. Furthermore, the minimum achievable TE potentially decreases and provides the opportunity, especially for GE EPI, to diminish dropout and signal loss due to intra-voxel spin dephasing with shorter TEs (Frahm et al., 1993; Olman and Yacoub, 2011; Robinson et al., 2008; Schmidt et al., 2005) or indeed to acquire multi-echo data (Poser et al., 2006; Speck and Hennig, 1998).

The color-word Stroop task is a stable and consistent fMRI paradigm generating robust BOLD activation in many brain regions including the orbito-frontal areas (Zysset et al., 2001). As expected, SE EPI and GE EPI detected activation at the same locations but with different cluster sizes. Owing to its higher functional sensitivity, GE EPI has larger cluster sizes and higher z-scores in almost the whole brain. One of the surprising results of this study is the significant activation observed with GE EPI in the frontal and sub-cortical regions. Several studies have hypothesized and shown the poor performance of GE EPI within regions prone to susceptibility artifacts (Norris et al., 2002; Schwarzbauer et al., 2010). On the other hand, GE EPI has been the workhorse of fMRI research and thus many methods to cope with and reduce those susceptibility related artifacts have been investigated. Z-shimming (Glover, 1999) and tailored RF pulses (Glover et al., 1998; Stenger et al., 2000) help to reduce dephasing in the slice direction. Data quality can also be improved by just optimizing/adjusting the slice orientation (Deichmann et al., 2003). Two studies at 3T reported the benefit of increasing spatial resolution, especially by reducing the slice thickness with comparable (with respect to SE EPI) GE EPI activation in the temporal lobe and orbito-frontal cortex (Schmidt et al., 2005) and increased functional contrast in the amygdala (Robinson et al., 2008). In the light of the mechanisms described above, the activation observed with GE EPI near air/tissue interfaces results from a combination of high spatial resolution (thinner slices) and higher sensitivity at 7T.

With regards to differences between SE EPI and GE EPI for fMRI, the measure of interest is CNR rather than tSNR or activation cluster size. The CNR difference maps in Figure 6 reveal that in general, GE EPI is superior to SE EPI with the exception of some parts of the visual cortex and frontal lobe. When further investigated, we found that GE EPI has higher signal change but also higher residuals (Figure 7) which explains the

comparable CNR of GE EPI and SE EPI in the visual cortex. The difference in contrast between SE EPI and GE EPI at high field is generally attributed to the fact that GE EPI BOLD signal is formed by all the 4 contrast mechanisms whereas only the extravascular dynamic averaging plays a role in SE EPI BOLD signal. This argument is also regarded as the proof for SE signal being strongly weighted by microvascular contribution and, thus being more specific to the true activation site. A recent study (Budde et al. 2013) showed that the ratio of micro- to macrovascular signals is around 0.6 for GE EPI and between 0.75 and 1.02 for SE EPI at 9.4 T. These values are much smaller than previous simulation results (Uludag et al. 2009) and will only be smaller at 7T. The possible reasons are listed as the $T_2$* weighting (due to the EPI readout), $T_2$ values not being as short as previously reported (Harmer et al. 2011) and inflow effects due to the limited FOV. In the same paper, it has also been demonstrated that shorter readout times and longer echo times increase the microvascular contribution to the SE signal. The protocol used in our study makes it possible to reduce the possible artifacts associated with SE EPI by acquiring whole brain SE EPI data (effectively eliminating inflow effects) at 7T. Furthermore, the potential SNR increase from the MB excitation can be traded off for acceleration in the PE direction giving shorter readouts and hence higher in plane acceleration factors. The echo time can also be increased if needed as with MB acceleration volume TR is not a limiting factor any more.

The physiological and BOLD noise of SE EPI and GE EPI are comprised of different effects. The non-$T_2$ effects contribute a small portion of the SE EPI signal and mostly originate from CSF and inflow effects (Yacoub et al., 2005), e.g., the region pointed with the arrow in Figure 7 suffers from the noise coming from the arterial blood. It can be argued that the mechanisms causing the lower SE EPI BOLD signal are also responsible for reducing the physiological fluctuations, hence the almost homogeneous noise profile for SE EPI (c.f. figure 7). The high noise level and the signal change in the visual areas for SE and GE EPI suggest that non-task related BOLD noise contributes to the overall noise. GE EPI noise is greatest in gray matter. This is to be expected, because for GE EPI with increasing field strength and voxel dimensions, the physiological noise dominates over the thermal noise (Triantafyllou et al., 2005). The increased noise of GE EPI suggests that the physiological noise (pulsation, breathing)

compartment still contributes to the overall noise. In fact, both GE EPI and SE EPI data with this specific resolution fall under the physiological noise regime as previously demonstrated (Triantafyllou et al., 2009; Yacoub et al., 2005).

In conclusion, the whole brain comparison of multiband SE EPI with a matched multiband GE EPI protocol using the Stroop task revealed that GE EPI has higher CNR in most brain areas and can detect activation near air/tissue interfaces due to the reduced intra-voxel dephasing with such high resolution at 7T. The whole brain, high spatial and temporal resolution multiband SE EPI sequence with transverse slice orientation was possible at 7T using PINS pulses when combined with conventional multiband excitation. All previous studies comparing SE and GE EPI at 7T to date were confined to the visual cortex, owing to the limited FOV posed by TR/SAR limitations of SE EPI which may have compromised the generality of those results. This study exhibits convincing evidence that GE EPI is favorable to SE EPI for whole brain high resolution studies at 7T and has important implications for functional connectivity studies or cognitive paradigms/experiments where activation is more widespread.

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## Table Captions

Table 1. Acquisition Parameters of SE EPI and GE EPI

Table 2. Group level cluster sizes and maximum z-scores for GE and SE EPI

## Figure Captions

Figure 1. Three slices from (a) anatomical T1, (b) SE EPI mean raw and (c) distortion corrected volumes. The frontal and occipital regions benefit the most from distortion correction. Note the improvement in areas depicted by the yellow arrows.

Figure 2. Three slices from (a) anatomical T1, (b) GE EPI mean raw and (c) distortion corrected volumes. The frontal and occipital regions benefit the most from distortion correction. Note the improvement in areas depicted by the yellow arrows.

Figure 3. GE EPI and SE EPI single time point images of a representative subject.

Figure 4. Single subject and group average tSNR maps in arbitrary units. GE has, in general, higher tSNR.

Figure 5. Z-score maps of the Stroop task for GE EPI and SE EPI *for a representative single subject and at the* group level. Two contrasts, activation (red-yellow) and deactivation (blue) are shown. Overall, GE EPI has higher sensitivity compared to SE EPI.

Figure 6. Comparison of SE EPI and GE EPI CNR (in z-scores). a) Activated regions (both contrasts) with GE EPI having higher z-scores. b) Activated regions (both contrasts) where SE has higher z-scores.

Figure 7. Signal change (ΔS) and noise (σ) levels for SE and GE EPI in arbitrary units for four representative slices. In general, GE EPI has higher signal change and noise compared to SE EPI. The arrow in the top slice of SE noise column depicts the noise introduced by the arterial blood.