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Wideband MR Echo Planar Imaging: A High Temporal/Spatial Resolution Neuro-architecture study of Rodent Brain

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Abstract

Latest simultaneous multi-slice (SMS) methods greatly benefit MR efficiency for recent studies using parallel imaging technique. However, these methods are limited by the requirement of array coils. The proposed Coherent Wideband method, which employs an extended field of view to separate multiple excited slices, can be applied to any existing MRI instrument, even those without array coils. In this study, the Coherent Wideband echo-planar imaging method was implemented on 7T animal MRI to exhibit comprehensive enhancements in neuro-architecture, including diffusion tensor imaging (DTI) and functional MR studies (fMRI). Under the same scan time, the time-saving effect can be manipulated to increase the number of averages for DTI SNR improvement, reducing fractional anisotropy difference by 56.9% (from 0.072 to 0.041) and the deviation angle by 64% (from 25.3° to 16.2°). In summary, Coherent Wideband EPI will provide faster, higher resolution, thinner slice, or higher SNR imaging for precision neuro-architecture studies.

Introduction

Magnetic resonance imaging (MRI) ¹ technology is a non-invasive diagnostic tool that reveals not only changes in cerebral blood oxygen saturation ^{2,3} but also pathways in nerve fibers. ⁴⁻⁶ However, compared with computed tomography and positron emission tomography, MRI has a markedly lower time resolution.

Consequently, numerous acceleration techniques were born in pursuit of greater MRI throughput. Simultaneous multi-slice (SMS) imaging is an acceleration technique which enhances imaging efficiency by simultaneously exciting and acquiring multiple slices. Müller first proposed the concept in 1988 and used the Fourier shift theorem to develop multi-frequency selective radiofrequency pulses for SMS ⁷. This led to the proposal of Hadamard-encoded RF pulses, which Souza et al. utilized to separate simultaneously acquired slices. ⁸ Glover et al. took a similar approach, utilizing encoded RF pulses in their phase-offset multi-planar (POMP) technique. ⁹ These earliest SMS methods didn't shorten MR scan time due to the extra phase-encoding steps or excitations needed in their design. However, they facilitated the development of future SMS techniques in the next few decades.

Modern SMS methods can be divided into two categories according to their hardware dependency. The majority of SMS methods belong to the first category, which utilizes additional hardware to provide

necessary spatial information to separate simultaneously acquired slices. Multi-channel coils were first proposed and used by Larkman to acquire multiple excitations.¹⁰ Afterward, Breuer used a combination of RF and multi-channel coils for multi-slice imaging.¹¹ Furthermore, Setsompop et al. combined controlled aliasing in parallel imaging with echo-planar imaging to match multi-excited image signals with standard signals.^{12,13} These SMS techniques hugely advanced the research in fields of functional MRI (fMRI) and diffusion tensor imaging (DTI)^{14,15}. Numerous studies successfully proved the benefits of applying SMS techniques instead of other techniques, such as increasing analysis bandwidth¹⁶ or enhances image resolution.¹⁷

However, all aforementioned SMS methods suffer from hardware-induced artifact problems like g-factors and slice leakage due to the usage of multi-channel coils.¹⁸ Since small animal pre-clinical apparatuses generally possess fewer coils, the noise will be even more severe. From this aspect, non-hardware based SMS approaches are essential to provide neural dynamics in pre-clinical studies.

Weaver *et al.* first proposed the approach to achieve simultaneous multi-slice imaging acceleration without extra hardware in 1988.¹⁹ The multi-excited signals can be separated by applying an extra gradient during spatial encoding, but this addition results in severe image blur. Therefore, Wu *et al.* developed the Multi-frequency excited Wideband (ME-Wideband)²⁰ method on gradient sequences for blur mitigation, improving Wideband image quality to the standard level. Since most current SMS techniques use additional hardware, non-hardware based SMS techniques are more commonly referred to as “Wideband” techniques to emphasize the difference.^{21,22}

For dynamic functional studies, Setsompop et al. applied Weaver’s technique to EPI and referred to it as Blipped-Wideband.¹² Naturally, Blipped-wideband suffers from the same blurring problem. For blur mitigation, the ME-wideband technique is applied to EPI in this paper. We adapt ME-wideband to EPI sequence, the “Coherent Wideband” technique is proposed to optimize wideband EPI images. Coherent Wideband, consisting of novel refocusing gradient sequence and precise phase alignment, provides faster, higher resolution, thinner slice imaging, or higher signal-to-noise pre-clinical imaging for precision neuro-architecture studies. Experimental results prove the advantages of Coherent Wideband against previous Wideband methods and demonstrate the benefits of this technique in fields of pre-clinical DTI and fMRI researches.

Materials and Methods

Pulse sequence and imaging parameters

This paper proposes the “Coherent Wideband” technique, consisting of a novel refocusing gradient sequence and precise phase alignment. This study introduced a method that employs expanded field of view (FOV) to acquire image signals from simultaneously-excited slices without extra hardware, then utilizes separation gradients so that image signals undergo phase shifts. Although additionally applied separation gradient and expanded FOV can separate image signal from different slices on the image domain, they also cause residual artifacts or “N/2 ghosting” artifacts. To eliminate these artifacts, an accurate phase alignment method is introduced by this study.

Coherent Wideband EPI Sequence

For EPI sampling, extra separation gradient pulses were applied along the z-direction to achieve phase shift in signals and corresponding image separation. For two-fold excitation (acceleration factor, $W=2$), each k -line exhibits an extra phase of $\pi/2$, which results in a FOV/2 shift on the image.

According to the ME-wideband equation by Wu, signal strength and phase vary by this separation gradient applied as describe in Eq1&2.

$$S'(k_x, k_y) = S(k_x, k_y) \times \left(\int_{z_1}^{z_2} \exp(i\gamma G_z \tau) dz \right) \quad \text{Eq.1}$$

$$\left(\int_{z_1}^{z_2} \exp(i\gamma G_z \tau) dz \right) = (z_2 - z_1) \times \text{sinc}\left(\gamma G_z \tau \left(\frac{z_2 - z_1}{2}\right)\right) \times \exp\left(i\gamma G_z \tau \left(\frac{z_2 + z_1}{2}\right)\right) \quad \text{Eq.2}$$

A gradient is required to separate two adjacent planes, which further reduces the signal strength in wideband MRI. Blipped-CAIPI method²³ and ME-Wideband²⁰ have suggested that refocusing gradients can be applied to recover signal strength.

Fig.1 shows multiple wideband EPI sequence designs, including blipped wideband EPI, ME-wideband EPI, and Coherent Wideband EPI. ME-wideband EPI is the EPI version of ME-Wideband, while Coherent Wideband EPI is its optimization. In blipped wideband EPI, accumulated separation gradient causes severe signal attenuation. While ME-wideband EPI partially mitigates such attenuation, the rapidly switching refocusing gradient leads to additional eddy current artifact. The optimized Coherent Wideband design keeps the isochromatic spin in phase in each pair of separation gradients, minimizing signal attenuation, phase deviation, and eddy current artifacts. (See Fig.1 (d), (e) & (f)) The phase plots of Coherent Wideband shows the phase shifts between 0 and $\pi/2$ which causes an N/2 shift on the image domain. The following section will demonstrate how an accurate phase alignment process addresses this issue.

Fig. 1. Pulse sequences of multiple wideband EPI

(a) Blipped Wideband EPI Sequence with constant separation gradients. (b) ME Wideband EPI Sequence with refocusing gradient. (c) Coherent Wideband EPI sequence with bipolar refocusing gradient. (d) Phase plots of multiple EPI sequences. (e) Signal Magnitude of various EPI sequences. (f) Zoom in View of Signal Magnitude

Zero phase $N/2$ artifact mitigation: EPI Reconstruction

EPI images suffer from $N/2$ artifacts due to rapidly switching gradient and resulting odd-even echo phase errors. Since these artifacts overlaps with multi-slice images in Wideband EPI applications, $N/2$ ghost removal is the priority of our image reconstruction. Proper phase corrections can be done to reduce $N/2$ ghost by measuring the gradient data set in Fig. 2a & 2b.²⁴ However, ghost artifacts are still visible due to k-space signal asymmetric. The zero-phase compensation method based on Ordidge *et al.*²⁵ improves the phase adjustment process, facilitating the symmetricity of k-space signal and reducing the ghost factor from 6.3% to 3.1% (Fig. 2c). Nevertheless, for the case of wideband EPI, the phase difference caused by additional separation gradient should also be considered. The next section will elaborate on this extra phase alignment process.

Fig. 2. EPI Phase Alignment.

Multiple N/2 ghost correction method is implemented in (a), (b) & (c). The uncorrected N/2 ghost artifact is shown in (a.3). The artifact is partially removed by the linear correction method in (b.3), and thoroughly removed by the zero-phase compensation method in (c.3).

Slice Dependent Phase Alignment: Wideband Reconstruction

The Wideband technique utilizes additional separation gradients to separate simultaneously-excited images. These gradients introduce different amount of phase to signals depending on the spatial location of the excited slices, which also contributes to N/2 artifacts as shown in Fig.3 (a). Therefore, this extra phase must be measured and compensated to ensure image quality. Ideally, this phase (Fig.3 (b)) can be calculated with the given sequence design, and phase correction can be done accordingly to remove ghost artifacts. However, the actual phase value is affected by the inhomogeneity of magnetic field and eddy currents, so remnant artifacts could still be observed after phase correction with theoretical phase values, as shown in Fig. 3(c). To ensure precise phase correction for Wideband image reconstruction, the gradient measurement method proposed by Beaumont²⁶ is applied in this study to determine the magnitude and phase of signals, as shown in Fig. 3(d). As Fig. 3(e) demonstrates, the ghost artifacts are no longer visible after phase correction with measured phase values.

Fig. 3. Slice Dependent Phase Alignment.

Separation gradients induce phase shift in k-space which leads to N/2 artifacts on the images shown in (a). The artifacts were partially corrected by theoretical phase as shown in (b) & (c). By applying the measured phase, precise offset compensation for Wideband images was ensured as shown in (d) & (e).

Animals

In this study, pre-clinical scans were performed on the male healthy Sprague Dawley rat model (200-300g, N=6 in this study) from National Taiwan University Laboratory Animal Center. Pre-clinical experimental procedures were approved by the Institutional Animal Care and Use Committee of National Taiwan University (NTU). All animal experimentation was done with institutional approval and followed NTU guidelines.

MR Parameters

All experimental data used in this study was obtained on the Bruker 7T MRI system by a volume coil (Biospec 70/30, PV5.1, Bruker BioSpin MRI GmbH, Ettlingen, Germany).

- *Rodent brain structure study: High temporal resolution*

Coherence Wideband EPI achieves 2-fold acceleration for rodent brain scan. The scan parameters are as follows: For conventional Spin-Echo EPI, TR/TE = 3000/75 ms, matrix size = 96x192, slice thickness = 1mm, resolution = 0.26 x 0.26 mm², bandwidth = 250 kHz, the number of averages = 120, and the total time is 6 mins. For 2-fold acceleration Coherent Wideband EPI, TR / TE = 1500 /75 ms, cutting the scan time to 3 min.

- *Rodent brain structure study: High spatial resolution*

Another usage of Coherent Wideband EPI is enhancing image spatial resolution under the same scan duration. The scan parameters are as follows: For traditional Spin-Echo EPI, TR/TE = 1000/75 ms, matrix size = **80x80**, slice thickness = 1mm, resolution = 0.31 x 0.31 mm², bandwidth = 500 kHz, the number of averages = 40, and the total time is 6 m 40 s. For 2X-spatial resolution Coherent Wideband EPI, matrix size = **160x160**, TR/TE = 500/75, and the resulting scan duration is also 6 min 40 s.

- *Rodent diffusion Tensor image: High temporal resolution*

The parameters for EPI-based Spin-Echo DTI are as follows: FOV = 2.5x5.0 cm², slice thickness = 1mm, matrix Size = 96x192, TE = 75ms, and the number of averages = 40. TR = 5000 ms for standard EPI and 2500 ms for Coherent Wideband EPI, so the respective scan time is 43 min 20 s and 21 min 40 s.

- *Rodent diffusion Tensor image: SNR enhancement*

The time-saving advantage of the Coherent Wideband technique can also elevate image SNR by doubling the number of average for precision medicine study. In this study, the Spin-Echo DTI scan consists of 1 null-image and 12-direction diffusion gradients. The scan parameters are as follows: FOV=2.5x5.0cm², slice thickness = 1mm, TE = 75ms, $\Delta/\delta = 8/3$ ms, b-value = 1500s/mm². TR = 5000 ms for standard EPI and 2500 ms for Coherent Wideband EPI. Since Coherent Wideband EPI is two times faster, the number of average is increased from 40 to 80 **while total scan time remains constant at 43min 20s.**

- *Rodent diffusion Tensor image: Thinner Slice*

For higher Z-axis resolution, Coherent Wideband EPI provides thinner slice imaging to delineate finer details of brain neuro-architecture. The parameters are as follows: For conventional EPI, slice thickness = 1 mm, average number = 20, **number of slices = 12** and TR = 5000; for Coherent Wideband EPI, slice thickness = 0.5 mm, number of average = 20, **number of slices = 24** and TR = 2500. The duration of both scans is 32 m 30 s.

- *Rodent resting functional MRI: 1/2 short TR*

High sampling MR speed is one of the unmet demands for resting fMRI researches (N=6). For investigating the quick dynamic change in fMRI, wideband EPI is utilized to improve temporal resolution in each measurement. The TR of Coherent wideband is shortened from 2 s to 1 s, and the sampling point for each fMRI study is increased from **120 to 240** for better statistical significance of functional analysis under the same scan time. The alternative is to shorten the acquisition time for **120** points from 6min to 3min to fit the user's need.

MR Analysis

Diffusion Analysis

The k-space data of the wideband images were reconstructed in Matlab (Math Works, Natick, USA). The DSI Studio (<http://dsi-studio.labsolver.org>) was used to perform Diffusion Tensor analysis and calculating the eigenvalues for each pixel. After selecting different ROIs, their respective Fractional Anisotropy (FA), Mean Diffusivity (MD), and other values can be calculated to determine their directivity and diffusivity^{27,28}, and then eigenvectors can be used to calculate the direction and angle of the pixel²⁹.

Reproducibility Study

Even with the same scan parameters and conditions, different repetitions of the same DTI scan may derive different FA and fiber orientation due to thermal and systematic noise²⁹. Therefore, high SNR is required for DTI to reduce the variance of analysis results and consistently track neuro-structures. To observe the reproducibility rise for SNR-enhanced DTI results, these DTI scans will be repeated twice to calculate their FA difference and deviation angle between repetitions.

Resting MRI analysis

Resting functional MR image analysis was performed using REST toolbox (<http://www.restfmri.net/forum/>), with SPM 12 (Wellcome Department of Cognitive Neurology, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>). Default preprocessing pipeline was used to perform all the preprocessing steps, including slice-time correction, and then spatially smoothed. Physiological and other spurious noise were estimated and then removed together with the aforementioned motion artifacts by band-pass filtering (chosen band 0.001Hz-1Hz). The ROIs were defined and used as a SEED, and functional ROI connected to each Segment. For first-level analysis, the residual BOLD time course was extracted from each ROIs and Pearson's correlation coefficients were computed between each pair of ROIs.

Data availability

The image data generated and presented in this study are available from the corresponding author on reasonable request.

Results

Do **not** include a **Results** section.

Discussion

Do **not** include a **Discussion** section.

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Figures

Figure 1

Pulse sequences of multiple wideband EPI (a) Blipped Wideband EPI Sequence with constant separation gradients. (b) ME Wideband EPI Sequence with refocusing gradient. (c) Coherent Wideband EPI sequence

with bipolar refocusing gradient. (d) Phase plots of multiple EPI sequences. (e) Signal Magnitude of various EPI sequences. (f) Zoom in View of Signal Magnitude

Figure 2

EPI Phase Alignment. Multiple $N/2$ ghost correction method is implemented in (a), (b) & (c). The uncorrected $N/2$ ghost artifact is shown in (a.3). The artifact is partially removed by the linear correction method in (b.3), and thoroughly removed by the zero-phase compensation method in (c.3).

(a) Images with Separation Gradient

Ghost Factor = 99.6% Ghost Factor = 98.7% Ghost Factor = 99.8%

(c) Images reconstructed by theoretical phase compensation

Ghost Factor = 9.2% Ghost Factor = 8.3% Ghost Factor = 10.8%

(e) Images reconstructed by measured phase compensation

Ghost Factor = 4.1% Ghost Factor = 3.4% Ghost Factor = 3.9%

Figure 3

Slice Dependent Phase Alignment. Separation gradients induce phase shift in k-space which leads to $N/2$ artifacts on the images shown in (a). The artifacts were partially corrected by theoretical phase as shown in (b) & (c). By applying the measured phase, precise offset compensation for Wideband images was ensured as shown in (d) & (e).