Rapid Full-Brain fMRI With an Accelerated Multi shot 3D EPI Sequence Using Both UNFOLD and GRAPPA

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The desire to understand complex mental processes using functional MRI drives development of imaging techniques that scan the whole human brain at a high spatial and temporal resolution. In this work, an accelerated multishot three-dimensional echo-planar imaging sequence is proposed to increase the temporal resolution of these studies. A combination of two modern acceleration techniques, UNFOLD and GRAPPA is used in the secondary phase encoding direction to reduce the scan time effectively. The sequence (repetition time of 1.02 s) was compared with standard two-dimensional echo-planar imaging (3 s) and multishot three-dimensional echo-planar imaging (3 s) sequences with both block design and event-related functional MRI paradigms. With the same experimental setup and imaging time, the temporal resolution improvement with our sequence yields similar activation regions in the block design functional MRI paradigm with slightly increased t-scores. Moreover, additional information on the timing of rapid dynamic changes was extracted from accelerated images for the case of the event related complex mental paradigm. Magn Reson Med 000:000–000, 2011. © 2011 Wiley Periodicals, Inc.

Key words: echo-planar imaging; functional MRI; UNFOLD; GRAPPA; BOLD

When complex cognitive processes are studied with functional MRI (fMRI), a goal of increasing interest in the neuroscience community, a cascade of brain signal changes is typically observed (1,2). Involvement of numerous brain areas makes whole brain coverage a high priority for cognitive brain mapping. At the same time, a voxel size no larger than the cortical thickness is preferred to improve localization and specificity. However, this combination of whole brain coverage with high spatial resolution currently reduces achievable temporal resolution to a level where complex analysis or time retrieval becomes difficult. Thus, improving the temporal resolution of fMRI acquisitions becomes a critical need for these studies.

In this work, we propose an fMRI acquisition sequence that improves the temporal resolution of an fMRI exam without losing spatial coverage. The most common approach for fast fMRI uses two-dimensional (2D) echo-planar imaging (EPI). However, the imperfect slice profile of 2D EPI increasingly becomes an issue at higher resolution. Here, instead of 2D EPI, we use a multishot 3D EPI sequence in which each excitation pulse excites the whole brain at each repetition time (TR). This eliminates slice profile issues as the encoding is achieved by a secondary phase encoding direction rather than 2D slice excitation. Multishot 3D EPI, as is also true for stack-of-spirals imaging (3), has an SNR advantage over methods using 2D EPI (4), as in both methods the whole brain is excited at once at each TR. The signal-to-noise ratio (SNR) advantage of both methods depends on the T1 of tissue of interest, the TR of the 3D and comparative 2D acquisitions, and flip angles. The benefit of 3D EPI increases as the number of k-space encodings increases (3). The disadvantages of 3D EPI include higher sensitivity to motion and flow artifacts than its 2D counterpart. In addition, we note that T1 contrast will change with respect to that obtained with 2D EPI.

With this sequence, the third dimension of the excited slab (the slice encoding direction in 2D EPI) is spatially encoded by phase encoding gradients. This turns out to offer additional opportunities for accelerated imaging, thus allowing an improved tradeoff between spatial and temporal resolution. We exploit this extra phase encoding dimension by undersampling k-space in that dimension. We use a novel combination of temporal encoding [UNFOLD—Unalising by Fourier encoding the OverLaps using the temporal Dimension (5)] and spatial encoding [GRAPPA—GeneRalized Autocalibrating Partially Parallel Acquisition (6)] to reduce image acquisition time.

In related work, Poser et al. (7) have implemented and demonstrated the use of 3D EPI with GRAPPA parallel imaging and partial Fourier capability along both kx and ky phase encoding directions and were able to demonstrate blood oxygenation level dependent (BOLD) contrast to noise advantages of highly accelerated 3D EPI over 2D EPI at 7 T. Temporal resolution of this method can further be increased by the method suggested in this article. Other accelerated whole brain sequences are 3D echo volumar imaging (EVI) (8) and 2D multislice, multiband imaging (9–11). EVI requires very high acceleration factors due to rapid T2 decay. Feinberg et al. (11) have recently published a method that uses multiplexed EPI (M-EPI) that combines 2D multiband excitation, GRAPPA parallel imaging, and SIR (Simultaneous image refocusing) multislice excitation, where they acquired full volume coverage in less than 0.5 s. Our acceleration method can be implemented in these scenarios but this is beyond the scope of this report. Lee et al. (12) have presented a novel 3D radial technique with GRAPPA for multiecho fMRI, where the radial trajectory interleaves were chosen such that reconstruction could be performed flexibly at either high temporal or high spatial resolution.

We briefly explain both UNFOLD and GRAPPA and then explain how we use them jointly. UNFOLD belongs to the
class of techniques (13–16) that exploits the significant $k$-space signal redundancy from frame to frame that occurs in temporally dynamic applications. Temporal encoding strategies introduce a time-varying signal phase modulation between consecutive frames. This phase shift then tags the aliased components that contribute to the dynamic variability of pixels in images formed from subsampled $k$-space. In particular, UNFOLD decreases the number of samples needed to reconstruct the $k - t$ space data by leveraging the assumption that the temporal encoding of the aliased dynamic pixels makes the aliased components separable from the unaliased signals of interest in the temporal frequency spectrum. GRAPPA is a parallel coil imaging reconstruction technique that supports self-referencing. A sufficient number of lines in the center of $k$-space are acquired at the spatial-domain Nyquist sampling rate, to model reconstruction coefficients for the unacquired lines. Those coefficients are estimated from those fully sampled lines and then in turn used to estimate the unaliased lines, thus allowing speedup through reduced sampling of $k$-space.

In the approach reported here, GRAPPA is applied with UNFOLD along the secondary phase encoding direction. We use an acceleration factor of 4 in the high-spatial-frequency coordinates of $k_z$ space through this combined approach. As a $k_z$ plane in the 3D Fourier domain is acquired at each TR, undersampling in this direction directly reduces the total scan time for each volume (7). The scan time, in principle, can be further shortened by undersampling in the phase encoding direction, $k_y$, to reduce the readout time. However, this does not improve the time resolution substantially as a minimum echo time (TE) is required for the mean BOLD signal to form, which imposes a minimum time between the radiofrequency (RF) excitation pulse and the readout gradients. But, the inplane susceptibility artifacts can be reduced by the shortened readout time due to a reduction in off-resonance effects, whereas the through-plane artifacts will be unaffected (17).

We compare our accelerated 3D multishot EPI sequence with both standard 2D EPI and nonaccelerated multishot 3D EPI sequences. We tested our sequence with both block design and event-related fMRI paradigms. For the block design study, we used apericif visuo-spatial stimuli. For the event-related design, we used a self-paced complex mental task involving multiplication and comparison of numbers. We showed that under the same experimental setup and imaging time, the temporal resolution improvement with our sequence yields (a) similar activation regions for both the block design and event design fMRI paradigms but with slightly increased $t$-scores using a standard hemodynamic response function (HRF) analysis method and (b) more information on the temporal behavior of the complex cognitive processes from the accelerated images for the case of event-related complex mental paradigms. We also show that this information can be used to help identify the timing of cognitive processes when we use an alternative analysis method (finite impulse response (FIR)) that is more sensitive to temporal information in the data.

**MATERIALS AND METHODS**

**Data Acquisition**

Figure 1 shows the pulse sequence diagram for each TR. An RF pulse that excites the whole field of view (FOV) was applied at each TR. As the whole brain is excited at each TR, a small flip angle calculated from the Ernst equation was used to optimize the signal intensity. The phase encoding ($y$) and frequency encoding gradients ($x$) were exactly the same as standard 2D EPI. Unlike 2D EPI, an additional phase encoding gradient (highlighted in red) was applied in $z$. At each TR, the area of the $z$-phase encoding gradient was adjusted to traverse a corresponding specified $k_z$ plane in the 3D frequency domain. This process was repeated for each $k_z$ plane required. In nonaccelerated multishot 3D EPI, therefore, the number of TRs was determined directly by the desired FOV coverage and resolution along $z$.

We first divide $k$-space into inner (low-frequency) and outer (high-frequency) regions. The $k_z$ planes in the inner region are acquired at full density as in standard 3D imaging. In the outer region, we acquire only one out of every four planes, which we can conceptualize as every other odd-indexed plane. The fully sampled planes are used to estimate the GRAPPA coefficients. In the standard UNFOLD acquisition, $k$-space is shifted by $\Delta k$ between consecutive time frames. As we will see, because of our joint use of GRAPPA with UNFOLD, we shift by two $k_z$ planes ($2\Delta k$) at even time frames. Thus, half of the odd indexed $k_z$ planes are acquired at the odd time frames and the other half are acquired at the even time frames. The even indexed $k_z$ planes were never acquired but rather were reconstructed as described below. An illustration with 50 $k_z$ planes is shown in Fig. 2, where at each volume, only 17 $k_z$ planes (7 $k_z$ planes at the center of $k$-space and 10 $k_z$ planes at the outside) are acquired using the scanner.

**Image Reconstruction**

For fully acquired $k$-space data, the images were reconstructed in a standard fashion, using a 3D inverse Fourier...
3D EPI with UNFOLD and GRAPPA

FIG. 2. Subsampling pattern in $k_z$ for FOV of 150 mm with a resolution of 3 mm. Dark gray (red in color) $k_z$ planes are acquired using the sequence. Those planes are used to reconstruct the light gray (green in color) planes using the UNFOLD algorithm. Then, the black $k_z$ planes are reconstructed from the dark gray (red in color) and light gray (green in color) planes using the GRAPPA algorithm. The $k_z$ planes at the center of the $k$-space are acquired for all time frames to use as reference planes for GRAPPA reconstruction. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Transform and a Nyquist ghost correction method (18), where the latter is required because of sampling errors inherent to all EPI acquisitions. For the UNFOLD+GRAPPA acquisitions, Fig. 3 depicts the flow chart for the reconstruction process. We first start by correcting for any instabilities or drifts by phase aligning the frames along time. Then, the missing odd indexed $k_z$ planes are reconstructed using UNFOLD. In this step, a low-pass filter with a cut-off frequency, selected as described in the next paragraph, is applied on a voxel-by-voxel basis along the temporal dimension of the 4D $k-t$ data to filter out the dominant near Nyquist rate component (i.e. the aliased near DC (Direct current) component of the undesired aliasing voxel).

An important parameter in the UNFOLD reconstruction, as mentioned in the previous paragraph, is the cut-off frequency for the temporal filter used to remove aliasing. A well-chosen bandwidth is required to remove the aliased near-DC component of the undesired aliasing voxel. On the other hand, this temporal filtering induces temporal coherence which lowers the temporal resolution. The cut-off frequency was chosen after analyzing a dataset acquired using the unaccelerated 3D EPI sequence. A heuristic method of determining this parameter was adopted; we performed a visual inspection of the temporal spectrum in the unaliased dataset of all voxels which would alias in the accelerated datasets, and determined that the majority of their frequency content was consistently below $\pm 8\%$ of the Nyquist frequency. As with the UNFOLD scheme this frequency range will alias to be centered at $\pi$, we designed our filter to cut-off at $0.92\pi$ using a filter design method described below.

As filtering is only done along the temporal direction, the time series of each voxel can be filtered independently to reduce computer memory requirements and it is straightforward to distribute this aspect of the whole volume reconstruction across multiple parallel computing nodes.

The output of the UNFOLD reconstruction produces a $k$-space dataset that has data in odd numbered $k_z$ planes in the outer regions of $k_z$ space as described earlier. This dataset, along with the four reference planes acquired as described above is then processed at each time point using the GRAPPA reconstruction algorithm. Specifically, first a Fourier Transform was applied along the $k_z$ dimension to transform the data to the $x-ky-k_z$ domain. Then, for each $k_x-k_y$ plane (i.e. for each x), a 2D GRAPPA matrix calculated from the reference data was applied to estimate the remaining missing $k_z$ planes, using a $2 \times 3$ GRAPPA kernel.

Experiments

**MRI Measurements**

Experiments were performed with an eight-channel head coil on a 3 T GE EXCITE scanner with a maximum gradient...
of 40 mT/m and maximum slew rate of 140 T/ms. The FOV was $192 \times 192 \times 150$ mm$^3$, with a matrix size of $64 \times 64 \times 50$, resulting in an isotropic 3-mm resolution. For 3D EPI sequences, a 2D RF pulse (19) was used with a flip angle of 15°, and the readout bandwidth was 100 kHz. The flip angle for the 2D EPI sequence was set at 90° to have a fair comparison. The TE was chosen as 30 ms for all experiments. A sagittal orientation was selected to optimize the coil sensitivity distribution for GRAPPA. The acquisition orientation was as follows: 3D encoding direction: left–right, EPI-readout direction: anterior–posterior, and phase encoding (EPI-blip) direction: superior–inferior.

Three different sequences were applied to each subject chosen so that we could compare our proposed accelerated 3D method to both 2D EPI and 3D EPI.

1. A standard 2D EPI sequence with full $kt$-space coverage, where we acquired exactly $64 \times 64$ $k$-space points for each of the 50 planes, resulting in a TR for the whole volume of 3 s.

2. A multishot 3D EPI sequence with full $kt$-space coverage, where we acquired exactly $64 \times 64 \times 50$ $k$-space points for each time frame. For each RF excitation, we acquired 64 EPI readout lines. This led to a TR of 60 ms between RF pulses. As we acquire 50 $k_z$ planes, again 3 s were required to acquire all of $k$-space.

3. Accelerated 3D EPI with spatial and temporal encoding along the $z$ direction. $k$-Space points ($64 \times 64$) for 17 $k$-space planes were acquired at each time frame, reducing the acquisition time to 1.02 s per volume. TR was also 60 ms for this sequence.

The sequences were also used in phantom studies for SNR measurements.

fMRI Paradigms

We tested each sequence using two different fMRI paradigms. Institutional review board (IRB) approval was obtained for both studies, and informed consent was obtained for all subjects.

- **A periodic block design paradigm.** Visuospatial-motor task: subjects were exposed to visual quadrants with high-contrast random noise patterns and asked to focus on a center dot. A finger motion scheme was exerted in the left or right hand when the visual wedge was active in the upper left or upper right quadrants, respectively. Block lengths of the stimulating quadrants varied between 5 and 15 s. Noise patterns changed at a frequency of 5 Hz. In a total imaging time of 3 min, 60 volumes were acquired at full $kt$-space coverage using both 2D EPI and 3D EPI and 171 volumes were acquired using the accelerated 3D EPI method. This visuospatial-motor task was tested on six healthy volunteers.

- **Event related paradigm.** The second paradigm was an event-related, self-paced, audio-visual fMRI study solving arithmetic problems. They were presented, by randomly chosen auditory or visual stimuli, simple multiplication problems followed by an incorrect result (example: $4 \times 5 = 23$). They indicated by a button press if the incorrect product presented was (a) close to the correct solution, (b) too big, or (c) too small. Stimulus events lasted between 4 and 8 s depending on subject response time, while the inter-stimulus interval was kept at 2 s. In a total imaging time of 10 min, 200 volumes were acquired at full $kt$-space coverage with both 2D EPI and 3D EPI and 588 volumes were acquired with accelerated 3D EPI. The event-related multiplicity paradigm was tested on 4 healthy volunteers.

For all experiments, the first five volumes were discarded because of significant intensity fluctuation before a steady state was reached. To make a fair comparison between the sequences, scan time was taken as a constant for all the experiments. For the block design paradigm, the scan time was set to 180 s whereas for event-related paradigm it was set to 600 s.

Data processing and statistical analysis were computed with the SPM8 software. Spatial preprocessing consisted of realignment (rigid transformation) and 3D smoothing with a full width at half maximum kernel size of 8 mm. Conventional analysis was performed for the block design paradigm, using a stimulus onset vector convolved with the HRF. With the event-related design experiments, a FIR method (20) presented with a window length of 12 s was chosen with a train length (order) of 12 bins for the accelerated 3D EPI acquisition (1.02 s) and four bins for full 3D EPI acquisition (3 s). Parametric regressors were applied for the corresponding values of the number size effect (logarithm of effective correct product size). T-Score thresholds were kept at $P < 0.001$ for the HRF analysis, and at $P < 0.05$ corrected for the FIR data. Activation maps were overlayed on the corresponding mean BOLD image.

RESULTS

Figure 4 illustrates sample images acquired with each of the different sequences. The 3D EPI images had fewer in slice artifacts but they are more $T_1$-weighted compared with 2D EPI. They also show more coverage in fronto-orbital and temporal lobes because of reduced through-plane signal loss in 3D EPI. As expected because of the undersampling, the accelerated 3D EPI images have slightly more artifacts (shown by the red arrow) in the 3D slice encoding direction compared with nonaccelerated 3D EPI.

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<td>For the phantom studies, 3D EPI had a slight tSNR advantage compared with 2D EPI. The tSNR drop of 3D EPI UNFOLD GRAPPA compared with 3D EPI is a result of the undersampling in $k$-space and is</td>
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consistent with the SNR equation (SNR \( \propto \) voxel size \( \times \sqrt{\text{number of measurements/BW}} \)). The SNR advantage of multishot 3D EPI did not translate to the in vivo studies due to increased susceptibility of 3D EPI to motion and flow artifacts, and we observed that 2D EPI had slightly better tSNR values for both gray and white matter. The difference between the tSNR drop calculated using the above SNR equation and the experimental values may be explained by physiological noise.

Figure 5 shows SPM (Statistical Parametric Mapping) analysis results for the block design experiment for three different sequences. The activated regions correspond to the case where upper right quadrant is active with a noise pattern which requires a right-hand finger tapping from the volunteer. In all cases, similar activation regions were observed. Table 2 gives a comparison between all sequences in terms of number of activated voxels, t-scores in motor and visual cortex, and the percentage signal change of BOLD activation. Although 3D EPI UNFOLD GRAPPA has a lower tSNR and percentage signal change, it resulted in better t-scores when compared with fully acquired 2D EPI and 3D EPI sequences. The statistical power gained by acquiring three times as many time samples with the accelerated 3D sequence more than compensated for the lowered tSNR, in agreement with previous studies (7,11). The number of activated voxels was similar for the three sequences.

<table>
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<tr>
<th>Sequence</th>
<th>TSNR phantom (per unit t)</th>
<th>TSNR GM (per unit t)</th>
<th>TSNR WM (per unit t)</th>
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<tbody>
<tr>
<td>2D EPI</td>
<td>102.1 (58.94)</td>
<td>65.2 (37.64) ± 4.1</td>
<td>74.4 (42.95) ± 3.1</td>
</tr>
<tr>
<td>3D EPI full</td>
<td>111.8 (64.54)</td>
<td>54.7 (31.58) ± 3.1</td>
<td>61.8 (35.68) ± 2.9</td>
</tr>
<tr>
<td>3D EPI UNFOLD + GRAPPA</td>
<td>68.2 (66.86)</td>
<td>43.8 (43.2) ± 4.1</td>
<td>48.9 (48.3) ± 4.6</td>
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</table>

For the phantom studies tSNR values are given as the median tSNR over voxels. For the in vivo studies, tSNR values in gray (GM) and white matter (WM) are given separately as the mean of the median tSNR (over voxels) ± variance over six different volunteers. Also tSNR per unit time calculated as tSNR divided by the square root of the acquisition time is reported in parantheses.
FIG. 5. SPM results showing the activation regions calculated for the visuospatial-motor task (block design) using standard HRF analysis for (a) standard 2D EPI (TR = 3 s), (b) multishot 3D EPI (TR = 3 s) and (c) accelerated 3D EPI (TR = 1.02 s). For this example, the activation corresponding to a right-hand finger tapping and a visual stimuli at the upper right wedge is shown. For all the three sequences, the same brain regions were found to be active.

HRF activation regions corresponding to the auditory regressor (product size effect) for the event-related multiplication paradigm are shown in Fig. 6. The regions for nonaccelerated 3D EPI (top) and 3D EPI UNFOLD GRAPPA (bottom) acquisition are projected on to the mean images of each sequence. Both maps show strong activation in the auditory cortex as expected. However, the activation map for nonaccelerated 3D EPI does not feature numerous areas typically recruited during mental arithmetic, whereas the accelerated 3D EPI sequence shows strong activation in such regions.

Figure 7 illustrates the results of FIR analysis of 2D EPI, nonaccelerated 3D EPI and 3D EPI UNFOLD GRAPPA sequences. This graph shows the results from one representative subject. Similar results were obtained with all participants. In this graph, FIR bins corresponding to voxels from brain areas related to audio input (auditory cortex), number recognition (intra parietal sulcus) and button press (motor cortex) were averaged and plotted against time. For both sequences in all three regions, an HRF curve can be observed. The peak of the HRF curve for the nonaccelerated 3D EPI occurs cumulatively at the third FIR bin (6 s after the start of an event) for all three regions. On the other hand, with an accelerated 3D EPI sequence (TR = 1.02 s), it is possible to distinguish the peaks corresponding to these three events. The effect of long auditory stimuli can be seen consistently in both sequences as the auditory response is stronger than the shorter button press and intraparietal sulcus activation. Also, it should be noted that the right-hand side of the graph corresponding to the second event is hard to interpret as the order of audio and visual stimuli is randomized, which distorts the temporal consistency.

The increased temporal resolution in the 3D EPI GRAPPA + UNFOLD data results in an overall much more informative picture, in contrast to the temporal resolution of the full dataset that is insufficient to capture rapid dynamic changes intrinsic to the complex mental task.

DISCUSSION

Although we observed improved t-scores with block design paradigms acquired with our accelerated multishot 3D EPI sequence, the real benefit is more evident when a complex mental task is studied in an event-related design. With an accelerated sequence, not only we were able to observe a better activation map using a standard HRF analysis but we were also able to gain more information about the timing of events with a more complex analysis (FIR). Techniques to take advantage of this information to achieve time retrieval of complex mental processes (21) will be investigated in future work. With the emergence of fMRI analysis using machine learning tools (22,23) and state space analysis (24), increased temporal resolution will also be helpful in providing more highly temporally resolved data.

A major problem in fMRI studies is that the small signal changes from neural activity are vulnerable to physiological noise, such as respiration and heartbeat. Therefore, in this respect, another potential advantage of increased

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<th>Table 2</th>
<th>fMRI Activation Analysis Comparing the Three Different Sequences for the Visuospatial-Motor Task (Block Design).</th>
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<tr>
<td></td>
<td>Activated voxels</td>
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<tr>
<td>2D EPI</td>
<td>261 ± 8.2</td>
</tr>
<tr>
<td>3D EPI full</td>
<td>268 ± 8.4</td>
</tr>
<tr>
<td>3D EPI UNF. + GR.</td>
<td>272 ± 9.2</td>
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Number of active voxels, relative amplitude of the BOLD signal to the mean signal (dSignal) and maximum t-scores in visual cortex (VC) and motor cortex (MC) are given. We did not observe a statistically important difference between the quadrants, so only the right upper quadrant is reported here.
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FIG. 6. SPM results showing the HRF analysis (auditory regressor) for the event-related multiplication task using: (top) 2D EPI (TR = 3 s), (middle) multishot 3D EPI (TR = 3 s) and (bottom) accelerated 3D EPI (TR = 1.02 s). Activation regions are projected on to the mean images in sagittal (left column) and coronal (right column) views. All three sequences show strong activation in the auditory cortex (blue arrows) and motor cortex (green arrows); however, primarily, the accelerated sequence reveals activation in the cortical regions responsible for number recognition and processing (red arrows).

temporal resolution is the ability to more correctly estimate and remove physiological noise from the data. For whole brain imaging with high spatial resolution, breathing artifacts can be estimated and removed but with a TR = 1.02 s we are not yet able to compensate for artifacts associated with cardiac activity. A highly accelerated single shot 3D EVI (25) may be better suited for this goal by reducing TR to the 100 ms range. However, EVI will be limited in how many $k_z$ planes can be acquired because of the rapid $T_2$ decay. This decay causes excessive signal blurring along the slow secondary phase encoding direction, and hence is difficult to apply for fMRI without high acceleration factors. By contrast, a sequence that uses temporal sub sampling (UNFOLD) combined with multiband excitation and simultaneous refocusing (11) might enable an increase in temporal resolution to a level where physiological artifacts can be removed.

FIG. 7. SPM results showing the FIR analysis (auditory regressor) for the event-related multiplication task using: (top) 2D EPI (TR = 3 s), (middle) multishot 3D EPI (TR = 3 s) and (bottom) accelerated 3D EPI (TR = 1.02 s). For each sequence, FIR bins corresponding to areas related to auditory input, number recognition, and button press are plotted along time.
One problem that arises with subsampled phase encoding in accelerated EPI sequences is increased Nyquist ghosting. Especially for long fMRI scans, methods that rely on a reference scan can be unreliable in the presence of system instabilities. Here, we used a self-referenced Nyquist ghost correction (18) to solve this problem, without requiring an extended EPI echo train. Unreliability of reference scans in long fMRI experiments was also the main reason that we preferred a self-referenced parallel imaging method. GRAPPA was used instead of SENSE (26), as less auto-calibration data are needed in this low resolution scenario.

The sequence might be further accelerated by subsampling the reference planes and using UNFOLD to reconstruct the missing reference planes. However, we observed severe reconstruction artifacts along $z$ after the GRAPPA reconstruction was applied with this approach. Also, it is possible to acquire (7) the reference data at the start of the scan and use it throughout. This will reduce the acquisition time (calculated to be a reduction from 1.02 s to 780 ms in this specific case) and would also allow acquisition of more reference planes at the start. However, in our setup, during a total scan time of 10 min for each exam, we experienced a significant change in the auto-calibration data between the start and end of the acquisition. Possible reasons for this are scanner bore heating (27) and magnetic field disruption from external electromagnetic sources (28). Another approach to potentially increase temporal resolution is to use PRESTO (Principles of Echo Shifting using a Train of Observations) (29). However, unless higher acceleration along the phase encoding direction can be achieved, the empty space between the RF pulse and the readout gradient is currently not long enough to make use of PRESTO with our setup. PRESTO might be a viable option for a longer echo time or a smaller magnetic field.

The temporal resolution can also be increased by reducing the spatial coverage using an oblique trajectory. A standard eight-channel head coil was used in this work, and therefore a sagittal orientation was selected to optimally use coil sensitivities to accelerate along the slice encoding direction. Using a head coil with distributed coil sensitivities along all three dimensions should enable an oblique FOV orientation. In this case, the number of acquired $k_z$ planes could be reduced while still covering the entire brain.

Partial Fourier methods (30) could also be used in either the phase encoding, $k_x$, or the slice encoding, $k_z$, direction to reduce the scan time. In a previous work (31), we applied partial Fourier in conjunction with UNFOLD for a multishot 3D EPI sequence. However, our experiments showed that when a small number of reference lines was used, significant image artifacts were observed because of phase inconsistencies and susceptibility artifacts.

It should be noted that although the whole volume is acquired in 1.02 s for the accelerated sequence, some part of the temporal frequency spectrum is lost in the UNFOLD filtering process. This filtering will introduce correlations in the time domain that will reduce the effective temporal resolution which will depend on the width of the filter. In our case, 8% of the spectrum was removed which reduces the temporal resolution to 1.1 s.

Our current accelerated 3D EPI approach will require some modification to enable its use in real-time fMRI, as the typical reconstruction times are in the range of 10 min for a long fMRI study. In particular, the UNFOLD filtering should be done using a more sophisticated filter design implemented via a difference equation in the time domain, and both the GRAPPA and UNFOLD reconstructions should be parallelized, to achieve reasonable reconstruction time. This has been implemented in more recent versions of the Fast Imaging Library (32) used in this work, and is a subject of future work.

**CONCLUSION**

A multishot 3D EPI sequence accelerated along the secondary phase encoding direction using UNFOLD and GRAPPA was implemented to improve the temporal resolution of complex fMRI studies. Compared with traditional 2D EPI and 3D EPI methods, our experiments with a block design fMRI paradigm showed that the increased temporal resolution achieved by our 3D EPI UNFOLD GRAPPA sequence improved the sensitivity of the reconstructed images to BOLD activation. Moreover, our results from event-related studies imply that this increased temporal resolution gives richer information about complex neural processes in cognition and in particular furthers our knowledge about the temporal schedule of such processes.

**ACKNOWLEDGMENTS**

The authors thank Bruno Madore, Ph.D., for valuable comments and discussions.

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