A procedure to prevent the formation of image and spectral Nyquist ghosts in echo-planar spectroscopic imaging is introduced. It is based on a novel Cartesian center-out echo-planar spectroscopic imaging trajectory, referred to as EPSICO, and combined with a correction of the gradient-echo phase and time shifts. Processing of homogenous sets of forward and reflected echoes is no longer necessary, resulting in an optimized spectral width. The proposed center-out trajectory passively prevents the formation of Nyquist ghosts by privileging the acquisition of the center k-space line with forward echoes at the beginning of an echo-planar spectroscopic imaging dwell time and by ensuring that all k-space lines and their respective complex conjugates are acquired at equal time intervals. With the proposed procedure, concentrations of N-acetyl aspartate, creatine, choline, glutamate, and myo-inositol were reliably determined in human white matter at 3 T. Magn Reson Med 000:000–000, 2012. © 2012 Wiley Periodicals, Inc.

Key words: echo-planar spectroscopic imaging; center-out trajectory; gradient-echo phase correction; gradient acoustic frequency

INTRODUCTION

In conventional chemical shift imaging, pure phase encoding is used to separate spatial and spectral encoding in time (1,2). When the spectral width (SW) of the observed chemical species is sufficiently narrow, echo-planar spectroscopic imaging (EPSI) may be used to encode spatial and spectral information simultaneously within an EPSI dwell time (DW) with considerable shortening of the acquisition time (3). In hybrid EPSI implementations, only one-dimensional spatial information is encoded in a single pass of the sequence (4,5) and the remaining spatial dimensions with a standard phase-encoding scheme (6,7).

Two-dimensional spatial encoding (3,8) is severely limited by the required SW. Alternated phase-encoding blips have been applied during each reversal of the readout gradient (9) or between pairs of odd and even readout gradient lobes (10). SENSE parallel imaging has been proposed to increase the resolution of the second spatial dimension while minimizing the number of required phase-encoding blips and implemented as single-shot sequence (11). Segmented spiral k-space trajectories have been applied in combination with flyback gradients (12–14) or out-in trajectory (15). However, spiral trajectories are affected by eddy currents, and the resulting discrepancies between the effective and desired trajectory may vary during the readout train (16).

Eddy currents induced by gradient switching lead to slight phase and time shifts of the even readouts (3,4). Odd and even readouts are generally treated as separate sets to avoid aliasing and subsequently added as phased spectra (11,17). In this work, we investigate the correction of gradient-echo phase and time shifts of a novel EPSI sequence with center-out k-space trajectory (EPSICO). To prevent the formation of Nyquist ghosts in image and spectrum, an integrated water template scan is acquired to determine the corrections needed to restore phasing and timing of reflected gradient echoes. The correction procedure allows for an optimal SW and can be extended to arbitrary multishot center-out sequence versions.

METHODS

EPSICO Pulse Sequence

Figure 1a depicts an EPSICO implementation with standard water suppression (WS), outer-volume suppression (OVS) modules and spoiler gradients, and a point-resolved spectroscopy (PRESS) excitation (18). After excitation of the volume of interest and a readout prephaser gradient, data are collected in the spatial-spectral k-space with axes kx, ky, and kw, corresponding to the mapping of x and y spatial, and ω spectral dimensions, with, respectively, Nx, Ny, and Nω points along these axes. Sampling is performed during the gradient plateau, lasting $N_x \times \tau_\text{v}$ with $\tau_\text{v}$ the sampling duration of one data point. A phase-encoding blip is applied during the forward readout gradient ramp time, followed by acquisition of a reflected echo. After acquiring $N_\gamma/2$ lines, a phase-encoding flyback gradient completes each DW to return to the initial k-space line.

The center-out trajectory of the first DW covers the upper half of the $k_xk_y$-plane. After TR (repetition time), the sequence is repeated with inverted polarities of the phase-encoding gradient to record the lower tile (Fig. 1b,
FIG. 1. EPSICO sequence. a: Double-shot implementation depicted with seven lines per DW ($n_{co} = 7$). After WS, OVS preparation, and PRESS excitation, the first forward echo (blue) is acquired at $t = T_E$ followed by six gradient reversals with six phase-encoding blips (orange). After seven echoes, a phase-encoding flyback (hashed) rewinds the six phase-encoding blips. The second DW begins with a reflected echo centered at $T_E + T_v$ (green). b: The resulting trajectory samples the upper half of the $k_xk_y$-plane (segment 1) and during the second shot the lower half (segment 2). c: Semilog plot of the gradient acoustic spectrum ($n_{co} = 7$) after single-sided Fourier transform of the readout (blue) and phase-encoding (orange) gradients. The forbidden acoustic frequency range of the gradient coil (TIM Trio AS092) is highlighted (tool for the estimation of gradient acoustic under Siemens IDEA VB17 available from corresponding author upon request). d: Time representation of the third segment trajectory (first DW: solid lines, second DW: dotted lines) of a four-shot EPSICO acquiring a $16 \times 16$ matrix by skipping every other line ($n_{co} = 4$). e: Fourth segment samples missing lines. Black circles indicate the center of the $k_xk_y$-plane at $k_v = jw_v$. Broken lines are placed at $k_y = 0$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
segment 2). Acquisition of the central k-space line is skipped in the second shot by adding a prephaser blip in the $k_y$-direction.

To accommodate the narrow SW resulting from multiple gradient-echoes per DW, the carrier frequency of the excitation and readout modules is shifted to the center of the observed metabolic region, typically between the water and fat $^1$H resonances. The required minimum SW is thus about 4 ppm limiting the maximum DW duration $\tau_{sw} = 1/2$ SW to about 2 ms at 3 T. The maximum double-shot EPSICO image acquisition matrix at 3 T is limited to $16 \times 14$. Larger matrices are accomplished by segmentation into multiple shots. Figure 1d presents the k-space trajectory of the third segment of a four-shot EPSICO. Mitigation of spatial-spectral convolution is ensured by privileging the acquisition of $n_{seg}$ lines near the k-space center at $t = TE$ (echo time), where $n_{seg}$ is the number of segments. Thus, the first line of the fourth segment is directly positioned below that of the third segment (Fig. 1e). The amplitude of phase-encoding blips is increased by $n_{seg}/2$. Other lines are acquired with a delay, $k_y = \{j - 1\}$ from the $j$-th DW, where $j \in \{1, \ldots, N_x\}$ is the dimensionless DW index, $v \in \{1, \ldots, n_{co}\}$ the data point index within a DW, and $n_{co} = N_x/n_{seg}$ the number of center-out lines per DW.

In all EPSI implementations, care must be given to the frequency-dependent loudness caused by rapid switching of trapezoidal gradients (19,20). The gradient acoustic spectrum of the readout gradient is dominated by a resonance at $n_{co}/(2\tau_{sw})$, characterizing the EPSICO sequence pitch (Fig. 1c). Other harmonics are observed at $l/(2\tau_{sw})$ with $l \in \{2, 4, 6, 8, \ldots\}$ for even $n_{co}$ values and with $l \in \{1, 3, 5, 7, \ldots\}$ for odd $n_{co}$ values.

### Gradient-Echo Phase and Time Shifts

Effects of eddy currents resulting from periodic switching of readout gradients were determined by a separate template scan of the strong ubiquitous water signal. This scan corresponds to the first segment of the EPSICO sequence without WS, phase-encoding blips, and flyback gradients.

Figure 2 demonstrates the effect of eddy currents on an even readout (reflected) of a standard EPSI scan with a $128 \times 128$ spatial matrix ($n_{seg} = 128$, $n_{co} = 1$). After reflection of the even readout, visual inspection reveals a slight time shift, $\Delta t$, of the echo center (Fig. 2b) with respect to that of the odd readout (forward in Fig. 2a). Following Fourier transform along the readout dimension, a plot of the angle difference between the two echoes follows a linear function with a slope equal to $2\pi \Delta t / (N_x \tau_y)$. The center position at $\xi = N_x/2$ is crossed with a phase shift $\Delta \phi$, where $\xi \in \{0, \ldots, N_x - 1\}$ is the position index. Correspondingly, the reflected readout is corrected with

$$c = \exp\left(-i \frac{2\pi \Delta t}{N_x \tau_y} \left(\xi - \frac{N_x}{2}\right) + \Delta \phi\right),$$

where $i$ is the imaginary unit. The small number of points in EPSICO readouts limits the determination of a slope by comparison of the angle in hybrid space, as routinely performed in echo-planar imaging (21). Hence,
phase and time shifts were determined by comparison of the echoes in k-space with a two-parameter nonlinear fit. The reflected readout, \( S(k) \), was Fourier-transformed along \( k_x \), shifted and phased in hybrid space, then transformed back to yield a corrected signal:

\[
S_{\text{corr}}(k_x) = r \cdot FT^{-1}[c \cdot FT_x(S(k_x))].
\]  

The scaling factor \( r \), accounting for transverse relaxation, is the ratio of the maxima of the echoes.

Hardware eddy-current compensation of long-range time constants may be limited during submillisecond gradient switching, and a related field drift may be observed (22). This effect was assessed by comparing two forward echoes separated by \( 2\tau\) (i.e., acquired with equal gradient polarity) to extract an apparent frequency offset, \( \Delta v \).

Averages of \( \Delta v \), \( \Delta \phi \), and \( \Delta t \) were computed by weighting the fitted parameters by the integral of the echo magnitude of the template scan at each DW. The phase correction was achieved according to

\[
S_{\text{corr}}(x, k_y, k_w) = \begin{cases} 
\exp(-i2\pi k_0\Delta v) \cdot FT_x(S(k_x, k_y, k_w)) & \text{if forward} \\
\begin{align*}
C & \cdot \exp(-i2\pi k_0\Delta v) \cdot FT_x(S(k_x, k_y, k_w)) \\
C & \cdot \exp(-i2\pi k_0\Delta v) \cdot FT_x(S(k_x, k_y, k_w)) \\
\end{align*}
\text{if reflected}
\end{cases}
\]  

followed by Fourier transform along the \( k_y \)-axis (21), yielding a spectroscopic time-domain map.

Magnetic field inhomogeneity progressively dephases signal, resulting after few DWs, into noticeable image distortions in the phase-encoding direction. In this work, an alleviation of these effects was attempted by applying a time-domain gaussian apodization:

\[
S_{\text{sim}}(x, y, k_w) = \exp\left(-\left(\frac{k_w}{b}\right)^2\right) \cdot S(x, y, k_w),
\]

where \( b \) denotes the full-width at half-maximum of the resonance frequency histogram in Hertz. The field map was determined by fitting the phase of the unsuppressed water signal at short \( k_w \). Processing was developed with Matlab (MathWorks, Natick, MA).

**Data Acquisition**

The EPSICO sequence was implemented at 3 T with up to seven lines per DW on a TIM Trio (Siemens, Erlangen, Germany) with a circularly polarized head coil.

The water template scan was acquired during one of four dummy scans. Subsequently, a water reference scan was acquired with one average. The water template and reference scans were performed without WS and with the carrier frequency centered on the water resonance (4.7 ppm). Four dummy scans were repeated with WS, realized by three gaussian pulses with 60-Hz bandwidth before the acquisition of the water-suppressed signal (23). During water-suppressed scans, the carrier frequency was centered at 2.8 ppm (except for WS pulses kept on water resonance). In vivo, the water-suppressed signal was accumulated with an exor phase-cycling scheme (24) in four steps for spin-echo excitation and 16 steps for PRESS (25). The total duration, including \( n_d \) dummy scans, one water reference scan, and \( n_{av} \) water-suppressed accumulations was

\[
T_{\text{tot}} = TR(2n_d + n_{av}(1 + n_{av})).
\]

Phantom measurements were performed with a 1 L spherical phantom, 100 mM sodium acetate (Act), and 100 mM lithium lactate (Lac). A healthy woman volunteer (age 31 years) was examined after informed consent had been obtained following guidelines of the Max Planck Institute and local ethics committee. Prior to measurement, the volunteer was informed about the high pitch and measurement loudness (26), asked if she suffered from tinnitus (27), and provided with earplugs and headset for ear protection (19,28). To avoid contamination by fat signal from the scalp, four OVS slabs were automatically placed around the volume of interest. The PRESS excitation module (TE = 30 ms) was compared to spin echo (6,12,29) allowing TE = 10 ms.

For absolute quantification of in vivo metabolite concentrations, the time-domain spectroscopic data, including the water reference scan, were processed voxel-wise with LCModel (30). Metabolite basis sets (31–34) were simulated with Gamma (35) based on chemical shifts and coupling constants of alanine, Act, aspartate, choline, creatine, \( \gamma \)-aminobutyric acid, \( \alpha \)/\( \beta \)-glucose (anomer ratio 36:64), glutamine, glutamate, glutathione, Lac, myoinositol, N-acetyl aspartate, N-acetylaspartylglutamate, phosphocholine, and taurine (36).

**RESULTS**

**Phantom Measurements**

The signal obtained by periodic reversal of gradient echoes is affected by eddy currents (37,38) and prone to the formation of Nyquist ghosts both in the spatial domain (21) and in the spectral domain (39). Figure 3 demonstrates the correction of these effects in a high-resolution EPSI measurement (\( n_{co} = 1 \)). A conventional reconstruction of the forward echoes (even DW) yields a spectrum with halved SW (17,29). The spectrum of a selected voxel reveals a strong water peak at 4.7 ppm (Fig. 3a, left) with no distinguishable water Nyquist artifact. It can be verified by integrating the center region of the spectrum to display a water map (Fig. 3a center) and then integrating the sides of the spectrum to obtain a Nyquist map (Fig. 3a right). Reflected echoes (odd DW) would yield a second set with halved SW as in spatial-spectral oversampling (17,29).

When combining forward (odd DW) and reflected (even DW) echoes into one mixed dataset, the resulting SW is doubled (Fig. 3b). A Nyquist peak forms at 4.7 ppm – SW/2. This artifact is more pronounced on the sides of the Nyquist map where readout phase differences are larger (Fig. 2c). After phase and time correction, the water Nyquist ghost disappears (Fig. 3c).

In the water map, patterns of signal drop-outs are visible. Comparison of these patterns with the field map (Fig. 3d, insert) suggests a correlation. After applying a time-domain gaussian apodization (full-width at half-maximum 3.9 Hz), the water map is nearly free of signal drops and the Nyquist map is comparable to that obtained with forward echoes only (Fig. 3d).
The number of phase-encoding lines per DW was progressively increased from 2 to 7 (Fig. 4). With even \( n_{co} \) values, EPSICO samples the center lines of k-space as synchronized forward echoes at each DW. This drastically reduces the formation of water Nyquist ghosts as seen in the uncorrected maps. In Fig. 4a, the phase-encoding blips skip large portions of k-space lines \((n_{seg}/2)\) lines thus avoiding typical N/2 image ghosts (21).

With odd \( n_{co} \) values, phase-correction and time-domain apodization effectively reduces the formation of water Nyquist ghosts (Fig. 4f). Without phase correction, the magnitude spectrum of the selected voxel reveals Nyquist ghosts for all resonances of Act (singlet 1.9 ppm) and Lac (quartet 4.1 ppm, doublet 1.3 ppm). After phase correction, the ghosts are no longer visible, except a subtle residual ghost at 2.8 ppm for \( n_{co} = 7 \) (Fig. 4f). With only one accumulation, the Lac quartet is detected with a nominal voxel volume \( V \geq 0.5 \text{ mL} \) (Fig. 4c–f), and the doublet is resolved by all protocols \( V \geq 0.06 \text{ mL} \).

**In Vivo Measurements**

Figure 5 compares the double-shot EPSICO of a supraventricular axial slice acquired with spin-echo and PRESS excitation modules. Despite four OVS slabs, spectra on the left side are contaminated by fat signal from the scalp. With spin-echo selection, this is additionally observed in the upper row. LCModel quantifications of the selected voxel \((x,y = 7,8)\) were performed with simulated basis sets without accounting for relaxation differences of water and metabolites. After subtraction of the macromolecule baseline, which was more pronounced at the shorter TE (40), signal-to-noise ratio (SNR) of about 10 was estimated for both spin echo and PRESS (Fig.
5b). The full-width at half-maximum of spin-echo signals (0.084 ppm) was larger than that of PRESS (0.065 ppm). With spin-echo excitation, the concentration estimates were about 12% lower than with PRESS. The concentration of glutathione was estimated to 0.92 mM with spin echo and not detected with PRESS. The Cramér–Rao lower bound of the glutamine concentration exceeded 20% both with spin echo and PRESS.

DISCUSSION

The formation of Nyquist ghosts resulting from gradient-echo phase and time shift of the reflected echoes is significantly reduced when the center line of k-space is acquired with the same gradient polarity. Phase-encoded EPSICO measurements acquired with an even number of phase-encoding lines per DW are nearly free of water.
Nyquist ghosts ($n_{co} = 2, 4, 6$ in Fig. 4a,c,e). With the center-out trajectory, one-half of the $k_xk_y$-plane is sampled per DW (Fig. 1). In the case of even $n_{co}$ values, peripheral lines, although acquired toward the end of DW, are also sampled with the same gradient polarity as that of their complex conjugates. This requires the introduction of phase-encoding flybacks imposing only a minimal timing penalty.

Furthermore, the formation of Nyquist ghosts is effectively prevented both in metabolite maps and individual spectra with the correction of phase and time shifts of reflected gradient echoes. This is possible without additional scan time using phase correction derived from a water template scan obtained during dummy scans while reaching steady state.

The combination of phase and time shift correction with an even number of phase-encoding lines per DW prevents the formation of Nyquist ghosts. The full Cartesian sampling of EPSICO may be averaged with exor phase cycling to further eliminate spurious signal contributions (41). Thus, forward and reflected echoes may be reliably quantified in one single analysis. Repetition with opposite gradient polarities (39), flyback echo-planar readout (42), or spatial-spectral oversampling acquisition (11,17) is no longer necessary.

High-resolution EPSICO maps reveal patterns of signal drop-outs related to magnetic field inhomogeneity but without observable distortion of the maps as commonly observed in echo-planar imaging images (21). During the short DW, the magnetic field inhomogeneity does not sufficiently dephase the signal (43), and significant voxel displacement only occurs after a few DWs. Although these effects may be mitigated by a multifrequency image reconstruction (21), phases and amplitudes of late DWs are irreversibly contaminated. Time-domain gaussian apodization effectively limits the appearance of patterns of signal drop-outs in maps.

The center-out EPSI measurement presents the advantage of a fast water reference scan lasting $(n_{co} + n_{seg})/C2$ TR and enables to allocate more time for signal averaging of the water-suppressed metabolite signal with a full phase-cycling scheme (44).

A comparison of the spectra obtained with spin echo at $TE = 10$ ms (Fig. 5b) and PRESS at $TE = 30$ ms (Fig. 5c) emphasizes the increase of macromolecular baseline signal at very short $TE$. To improve the conditions for determining the baseline, efforts were made to keep the SW at least 3.8 ppm wide, such that the $^1H$ resonances from methylene (1.3 ppm) and methyl groups (0.9 ppm) of mobile lipids and from residual water were adequately sampled.

Nevertheless, lower estimates of metabolite concentrations were obtained at $TE = 10$ ms than at 30 ms. This

**FIG. 5.** Volunteer measurements with double-shot EPSICO (TR = 1.7 s, 48 averages in 3:00 min, $n_{co} = 6$ lines per DW, $n_{seg} = 2$, $N/N_c = 12/512, 17 \times 17 \times 17 \text{ mm}^3$, $V = 4.91 \text{ mL}$, $T_{20}/T_{20}/T_{20} = 15/300/1830 \mu$s, SW = 4,433 ppm). Spin-echo excitation (TE 10 ms) and PRESS (TE 30 ms) are compared. a: Slab-width of first sagittal (spin-echo and PRESS) and second coronal (PRESS) refocusing pulses, $12 \times 12$ voxels field of view (grid), $6 \times 6$ voxels volume of interest (dashed box), mosaic display of spin-echo (blue), and PRESS (green) magnitude spectra. Residual fat signals from scalp are due to insufficient OVS (four OVS slabs). LCModel analysis with simulated basis sets determined in the selected voxel (highlighted in purple) the following concentrations in mM: (b) with spin-echo, creatine (3.26 ± 4%), glutamate (4.39 ± 5%), N-acetyl aspartate (5.29 ± 4%), myo-inositol (2.72 ± 6%), phosphocholine (0.72 ± 6%), and glutathione (0.92 ± 14%), and (c) with PRESS, creatine (3.43 ± 4%), glutamate (5.72 ± 8%), N-acetyl aspartate (6.12 ± 3%), myo-inositol (3.25 ± 7%), and phosphocholine (0.78 ± 5%). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
may be in part related to the relaxation of water in white matter, as the signal of water trapped between the myelin sheaths has a shorter $T_2$ and will contribute more to the water reference signal at shorter TE (45,46).

In considering the acoustic noise generated by the EPSICO sequence at 3 T, sensitivity changes of human hearing above 1000 Hz (20) should be taken into account when increasing the number of lines per DW, to prevent hearing loss or persisting tinnitus (27,47,48).

CONCLUSIONS

We have introduced a procedure that mitigates inherent limitations of the SW in EPSI by combining forward and reflected readouts and efficiently prevents the formation of spurious peaks and image ghosts. The combination of a robust Cartesian center-out trajectory with an even number of phase-encoding lines per DW, phase cycling, phase correction of reflected echoes, and optionally time-domain apodization, as integrated in EPSICO, constitutes a simple procedure to speed up spectroscopic imaging while robustly preventing the formation of ghosting artifacts.

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