Multi-Echo Coarse Voxel Acquisition for Neurofeedback fMRI

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Abstract

"Real-time" functional magnetic resonance imaging (fMRI) is starting to be used in neurofeedback applications, enabling individuals to regulate their brain activity for therapeutic purposes. These applications use two-dimensional multi-slice echo planar or spiral readouts to image the entire brain volume, often with a much smaller region of interest (ROI) within the brain monitored for feedback purposes. Given that such brain activity should be sampled rapidly, it is worthwhile considering alternative fMRI pulse sequences that trade spatial resolution for temporal resolution. We developed a prototype sequence localizing a column of magnetization by outer volume saturation, from which densely sampled T2* decays are obtained at coarse voxel locations using an asymmetric gradient echo train. For 5 x 20 x 20 mm voxels, 256 echoes are sampled at ~1 ms and then combined in weighted summation to increase fMRI signal contrast. This multi-echo coarse voxel (MECV) pulse sequence is shown experimentally at 1.5 T to provide the same signal contrast to noise ratio as obtained by spiral imaging for a primary motor cortex ROI, but with potential for enhanced temporal resolution. A neurofeedback experiment also illustrates measurement and calculation of fMRI signals within 1 s, emphasizing the future potential of the approach.

Key words: fMRI, neurofeedback, multi-echo T2* measurements, outer volume saturation, real-time.

Introduction

In most functional neuroimaging applications, brain activity is calculated in the hours and days after the imaging session. In "neurofeedback" (NF) applications, however, individuals learn to regulate a signal that is calculated from their brain activity in "real-time" (seconds or less after the imaging data are acquired), for therapeutic purposes. Historically, NF has been developed primarily to assist in seizure control using electroencephalography (EEG) recordings(1-2), with more recent EEG NF including development of brain machine interfaces(3). Real-time fMRI is also starting to be used for NF to record activity not only from the cortex, but also deep within the brain. Several fMRI NF applications include therapeutic suppression of negative emotion(4), improvement of motor performance(5-6) and linguistic processing(7), and suppression of chronic pain(8). In the future, fMRI NF research may play a role in developing new rehabilitation methods for specific patient populations with psychiatric or neurological impairments(9).

Despite the promise of such studies, fMRI NF experiments are challenging to undertake because the underlying blood oxygenation level-dependent (BOLD) signals are intrinsically weak, related to hemodynamics that are very sluggish compared to the millisecond timescales associated with electrophysiological signaling in the brain. Such fMRI studies have mainly involved using multi-slice 2D echo planar imaging (EPI) or spiral imaging, with fast computing and specially-developed algorithms for rapid calculation of brain activity. Additional pulse sequence development would be useful to measure BOLD signals with high contrast-to-noise ratio (CNR) and high temporal sampling, to enhance the ability to regulate brain activity rapidly during fMRI experiments.

Importantly, many fMRI-NF experiments probe the spatial average of brain activity from only one or two small regions of interest (ROIs) - a very small fraction of the total brain voxels. It may be beneficial, therefore, to consider pulse sequences for fMRI NF that trade the time spent on spatial encoding for enhanced temporal information . For example, the single voxel methods originally developed for

magnetic resonance spectroscopy (MRS) enable detailed temporal sampling of the isolated voxel within as little as a single repetition time(10). Such methods were used to probe BOLD signal biophysics in the early development of fMRI(11), although their time efficiency for real-time fMRI NF has not been explored. Intermediate between single voxel and whole-brain coverage, methods have been developed that spatially resolve multiple compartments by limited phase encoding(12), as well as various "line-scan" methods that involve one-dimensional frequency encoding readouts or spatial localization provided by isolating a column of voxels in space(13-16). In particular, line-scan methods provide the sensitivity benefits of single voxel approaches, with improved volume of coverage and computationally efficient spatial reconstruction. Appropriate orientation of the line-scan should enable activity in multiple brain regions to be probed rapidly.

The present work involves preliminary investigation of such a pulse sequence. A column of magnetization is selected in two spatial dimensions using radiofrequency (RF) and gradient pulses to achieve outer volume suppression (OVS)(17-18). Spatial information along the column length is frequency-encoded using flyback gradients(19) providing computationally efficient spatial reconstruction through use of one-dimensional Fourier Transformation. The spatial encoding strategy also enables detailed multi-echo sampling of the T2* decay curve for enhanced BOLD contrast through use of echo-weighted summation(20-22). A prototype version of this multi-echo coarse voxel (MECV) sequence was developed and investigated in pilot experiments involving six young healthy adults on a 1.5 T MRI system. Percent BOLD signal change and contrast-to-noise ratio (CNR) per square root of acquisition time were determined and compared with the capabilities of a representative fMRI sequence involving spiral k-space readout. An example MECV fMRI-NF experiment was also conducted, demonstrating the effectiveness of the technique. The experimental results are subsequently discussed in the context of optimizing the MECV sequence in the future, particularly to increase temporal resolution.

Methods

The prototype MECV pulse sequence (Fig. 1a) consists of: 1) outer volume suppression (OVS) to eliminate transverse magnetization outside the volume of interest (VOI); 2) standard slice-selective 90° RF excitation with the slice thickness chosen to match the thickness of the VOI to enhance spatial localization, and to excite the VOI; and 3) multi-gradient-echo readout to provide detailed sampling of the resulting T2* decay from the column of coarse voxels within the VOI. The OVS scheme was implemented using a train of very selective suppression (VSS) RF pulses(17) which have been validated for use in the brain by numerical simulation and experiments(18). In the present work, each VSS RF pulse was designed to spread the RF energy evenly throughout the entire pulse duration while achieving a high bandwidth of 11 kHz, a reasonable pulse duration of 2 ms, and high selectivity (ratio of passband width to transition band width) of 25. For a single suppression band, a VSS RF pulse and slice-select gradient were used to excite a slab of tissue, followed by crusher gradients to dephase the resultant transverse magnetization. Four thick suppression bands (50 - 170 mm thickness, shown as slabs shaded in a checkerboard pattern in Fig. 1a) were placed orthogonal to the readout (y) direction. To further define the edges of the VOI, four thinner suppression bands (30 mm thickness) were also placed along the edges of the VOI (not shown in Fig.1a, but detailed in the MECV pulse sequence diagram in Fig. 1b). A standard 90° slice-selective apodized sinc pulse was subsequently used to generate transverse magnetization from within the VOI.

Data within the VOI were subsequently acquired with T2*-weighting using asymmetric flyback echo-planar readout gradients(19) (Fig. 1c). Although a symmetric alternating positive and negative echo planar readout could be used, flyback gradients enable computationally efficient data reconstruction with reduced susceptibility to sampling artifacts. Data acquisition occurs only during the constant positive amplitude segment of each gradient waveform, followed by a rewinding lobe that quickly retraces across the desired portion of k-space within gradient slew-rate limits. In contrast, the odd and even echoes in symmetric readouts can be misaligned because of various gradient timing errors(23), potentially requiring complicated post-processing schemes(24) and increased data reconstruction time. In addition, optimizing

flyback gradients for gradient slew rate has previously enabled higher spatial resolutions and larger spectral bandwidth for high-field proton MRSI compared to symmetric EPI readout(19). For the prototype MECV sequence, two flyback gradient trains were implemented at different spatial resolution, with the maximum of the first gradient echo approximately 5 ms from the isocenter of the sinc pulse in each case. The first implementation used a 62.5 kHz readout for 5 mm spatial resolution in the y direction with 32 voxels over a 16 cm field-of-view (FOV), and 256 echoes with 1.024 ms inter-echo spacing at each voxel location. The second implementation used a 22.73 kHz readout for 10 mm spatial resolution with 16 voxels over the FOV, and 356 echoes with 1.012 ms inter-echo spacing at each voxel location.

Experiments

In preliminary work, the OVS portion of the MECV sequence was appended to an axial slice 2DFT spin echo imaging sequence. From the resulting signal intensity profile acquired in a single volunteer, the residual signal contribution (the sum of signal intensities from outside the VOI) was <10 %. This residual signal level was judged sufficiently low to warrant proceeding with fMRI experiments using the MECV prototype. Two sets of experiments were undertaken, involving small cohorts of young adults with no previous history of psychiatric or neurological disease. Experiment A involved 6 right-handed young adult subjects (3 male) and was designed as an initial investigation of MECV signal characteristics. Experiment B involved 4 right-handed young adult subjects (3 male) to demonstrate MECV capabilities in a simple fMRI-NF experiment. All experiments were conducted with informed consent of the subjects and with the approval of the research ethics board at Sunnybrook Health Sciences Centre. Imaging was performed using a research-dedicated1.5T MR scanner (Signa with 8 channel HD Excite; GE Healthcare, Waukesha, WI) with the standard quadrature birdcage head coil. Through an angled mirror, subjects viewed visual stimuli generated by an LCD projector and displayed on a back-projection screen. The MECV data were acquired at both 5 mm and 10 mm resolutions, and TR = 1 s for comparison with spiral fMRI (see below) after manual prescanning to tune MRI system parameters, including adjustment of

linear shim coefficients. In addition to MECV data acquisition, both experiments involved anatomical imaging (axial 3D fast spoiled gradient echo imaging (FSPGR), 22 cm x 16.5 cm FOV, matrix = 256 x 128, TE/TR/flip angle= 6 ms/35 ms/35^{o}, 128 slices 1.4 mm thick; and a more standard fMRI acquisition (axial 2D single shot spiral-in/out k-space trajectory(25)(20 cm x 20 cm FOV, 64 x 64 matrix, TE/TR/flip angle = 40ms/1000ms/60^{o}, 10 contiguous slices 5 mm thick). In the latter case, the TR equaled 1 s to ensure that a substantial number of slices were obtained for spiral fMRI, representative of what would be adopted in fMRI NF experiments using such a protocol.

Experiment A

The first experiment compared MECV signals to those acquired by spiral fMRI, with minimal data processing pipelines for each method. The 3DFSPGR imaging was used to prescribe the VOI with the column of voxels oriented right-to-left through both primary sensorimotor cortices (SMCs) in each subject, based on anatomical landmarks. The subjects were then scanned with MECV and spiral fMRI. Throughout, each subject performed a 5 min. block design motor task run with alternating task and resting conditions, each of 20 s duration. To generate substantial activation of primary motor cortex, the task was performed by the non-dominant (left) hand using a complex sequence of finger movements(26) consisting of 16 flexions of digits 1-4 against the thumb (1-1-2-3-3-3-4-4-4-4-3-3-3-2-1-1). The rest condition consisted of visual fixation on a cursor presented on the display screen, with the thumb and index finger loosely opposed. Visual cues were also provided to indicate the onset and offset of the motor task. Subjects were allowed to practice the movement sequence prior to imaging, to reduce learning and habituation effects. In addition to the motor task run, subjects were also directed to remain relaxed with their eyes open for the entire 5 min. duration of an additional “resting” run of MECV data collection. These resting run data were subsequently used in MECV data processing strategies. The order of spiral and MECV fMRI runs was randomized across subjects.

Spiral fMRI Data Pre-processing

Using Analysis of Functional NeuroImages (AFNI) software(27), the spiral fMRI time series data were corrected for motion, as well as linear and quadratic trends. Activation maps were created for each subject by fits of the data to a general linear model (GLM), including convolution of a boxcar task waveform with a canonical hemodynamic response function with time-to-peak of 6 s (AFNI *waver* program), and statistically thresholded to $p < 0.05$ with a Bonferroni correction for multiple comparisons. These maps first were used qualitatively to confirm activation of the contralateral SMC for each subject. Secondly, the maps were quantified to determine the fraction of activated spiral imaging voxels that were located within each coarse voxel location, for both coarse voxel sizes, to assess the spatial agreement between fMRI methods.

MECV fMRI Data Pre-processing

The MECV data were processed using MATLAB (The MathWorks, Inc. Natick, MA). Each echo train was first apodized in k-space with a Hann filter to reduce Gibbs ringing and then reconstructed by fast Fourier Transformation, resolving a magnitude time series of T2* decay curves for each coarse voxel in the left-right spatial dimension.

To obtain a single time series with BOLD signal contrast at each coarse voxel location, and also to increase the available signal contrast, echo signals from a given T2* decay curve were combined in weighted linear combination. This approach has been shown to be more effective than obtaining fit estimates of the change in relaxation rate to represent BOLD contrast as a function of time (22). Between methods described in the literature, the CNR-weighting method(21) was chosen based on its performance compared to the simpler, T2*-weighting method(20). Briefly, the T2* -weighting strategy advocates weights determined by the T2*-weighted signal difference between active and resting condition as a function of echo time. That is, early echoes and late echoes exhibit little BOLD contrast and consequently should contribute little weight, whereas intermediate echoes with large BOLD contrast should contribute substantially. Accordingly, each weight w is given by (20):

$$w(TE_n) = \frac{TE_n \cdot e^{-\frac{TE_n}{T2^*_{est}}}}{\sum_{n=1}^{N} TE_n \cdot e^{-\frac{TE_n}{T2^*_{est}}}}, \quad [1]$$

where TE_n is the TE value at echo number n, and N is total number of echoes. The value $T2^*_{est}$ is an estimate of T2*, obtained either from literature values for gray matter or by fitting the T2* decay data. The denominator of Eq. [1] provides normalization such that all w are less than unity. Alternatively, the CNR-weighting method advocates that echoes should be weighted not only by considering the available BOLD signal contrast at each TE_n, but also the subject-specific noise. In this case, the derived expression (28) is

$$w(TE_n) = \frac{SNR(TE_n) \cdot TE_n}{\sum_{n=1}^{N} SNR(TE_n) \cdot TE_n}, \quad [2]$$

where $SNR(TE_n)$ is the temporal SNR measured at each TE value for the resting run data for each subject, taken as the mean signal amplitude, S_n, divided by the sample standard deviation σ_n, taken over all TR time points. Once calculated, the CNR-weights were then separately multiplied with the T2* decay curves as a function of TE for each coarse voxel and summed. Data from one out of six subjects were discarded due to error in experimental setup for the resting run.

Comparing MECV and Spiral fMRI Signal Characteristics

The signal characteristics of spiral and MECV pulse sequences were subsequently compared at the voxel locations with respective BOLD signal maxima. The MECV location in question was identified as the "sensorimotor cortex coarse voxel" (SMC CV), whereas the analogous location for spiral fMRI was identified as the "SMC region of interest" (SMC ROI) and obtained by spatially averaging all time series from 1mm x 1 mm x 1 mm resampled voxel data contained within this location. The two time series were then processed with a second order Butterworth digital low-pass filter (0.10 Hz cut-off frequency) for all TE values to suppress fluctuations due to the respiratory cycle. Such filtration is easily adopted in real-time processing, compared to more retrospective methods, such as RETROICOR(29). The time

series for both the SMC CV and the SMC ROI were then fitted using the same GLM procedure described above. Activation was compared in terms of %BOLD, the percent signal change according to:

$$\%BOLD = \frac{\beta}{b_0} \cdot 100\%, \qquad [3]$$

where β is the fit coefficient of the boxcar task waveform and b_0 is the fit coefficient of the constant baseline component to the time series data. Data from the SMC CV and SMC ROI were also compared in terms of CNR per square root of acquisition time, T_{acq}, with CNR taken as

$$CNR = \frac{\beta}{\sigma_{ts}}, \qquad [4]$$

where σ_{ts} is the temporal standard deviation of the time series, calculated over the resting periods in the block design motor task. For MECV acquisitions, only data sampled during the constant amplitude portion of the flyback gradient echo train were used in the analysis, corresponding to T_{acq} values of 131 and 251 ms for 5 mm and 10 mm spatial resolution, respectively. For spiral in/out acquisitions, the k-space readouts of interest were taken over 4 slices encompassing the SMC ROI, corresponding to T_{acq} = 341 ms.

Experiment B

The second experiment utilized the 5mm, 32-voxel MECV fMRI sequence in a simple NF experiment. During scanning, subjects were asked to determine a hidden task condition corresponding either to right or left hand clenching. By performing the task with the hand of their choice, the subject received visual NF derived from activation in SMC voxels reflecting whether their choice was "correct", allowing them to modify their behavior appropriately.

For this experiment, the left and right SMC locations (single CVs) were chosen based on FSPGR MRI, a spiral fMRI "localizer" run consisting of bilateral hand clenching (20 s clenching, 20 s rest, 5 repetitions), and an analogous MECV fMRI localizer run. The rest condition was implemented as in Experiment A.

Precise SMC locations were determined based on neuroanatomy as well as the spatial agreement between spiral fMRI results, and MECV T2* decay, time series, and spectral analysis of the VOI. During NF runs, raw MECV data were transferred from the scanner using an established real-time interface(30) and subsequently processed on a laptop (Toshiba Portege M400) using custom MATLAB processing scripts. The MATLAB psychophysics toolbox(31) was used to generate visual stimuli for NF dynamically. After low-pass filtration, the multi-echo data were combined using the T2*-weighting approach to generate time series data with BOLD contrast, without collecting resting run data. The neurofeedback signal, F, was a laterality metric calculated according to

$$F = P \cdot (\%L - \%R), \qquad [5]$$

where %L and %R represent %BOLD changes in the left and right SMC CVs, respectively. The value for P was ±1, depending on whether right or left hand clenching was the hidden task. In the 20 s rest block occurring before each task block, the F value was presented as a vertical scale with units ranging from -2.5% to +2.5% with positive values indicating that the hidden task was chosen correctly. Five runs were acquired per subject, each consisting of 5 alternating task and rest blocks (20 s per condition). The hidden task was held fixed during each run and was manipulated pseudo-randomly across runs with P = (-1, 1, 1, -1, -1). Motor performance was visually monitored at the MRI console (by M.C.) during each run for each subject. The resulting data were analyzed to determine how many runs each subject correctly determined the hidden task; the block when each subject started to perform the hidden task correctly; and the frequency with which the NF metric correctly reflected motor behavior.

Results

Experiment A

Figure 2 illustrates the fraction of active spiral imaging voxels that shared the same anatomical location as the coarse voxels. Bar heights and error bars indicate the mean fraction and standard error of the mean, respectively. The average size of the head from right to left was 134 ± 3 mm. The overall pattern of

activation within the VOI was characteristic of a complex motor task; as anticipated, high fractions occurred in the contralateral (right) primary SMC, located nominally 2.5 cm from the right edge of the brain, with approximately 5% BOLD signal variation at both coarse voxel resolutions. Small fractions were also observed in ipsilateral SMC (peak fractions of 20 %), and in midbrain locations (fractions of <10%). Spatial dependence of the activated fraction of voxels obtained by spiral fMRI was consistent for both coarse voxel resolutions across the VOI. All subsequently chosen SMC ROIs for both spatial resolutions exhibited at least 75 % overlap in activation volume for all subjects.

Figure 3 shows MECV T2* decay curves and temporal noise levels from the selected SMC coarse voxels as acquired during the resting run, averaged over all subjects and TR time points. Error bars shaded in gray indicate the standard error of the mean. In Fig. 3a, the maximum signal at the shortest echo time (TE = 6 ms) from the larger coarse voxel (10 mm x 20 mm x 20 mm) was 1.84 ± 0.08 times that from the coarse voxel with half the volume (5 mm x 20 mm x 20 mm). The average T2* values were 49 ± 5 ms and 60 ± 4 ms and for the larger and smaller SMC coarse voxel, respectively, based on two-parameter mono-exponential fits (amplitude and relaxation time) to the data. The average temporal noise levels (standard deviation of the signal at each echo time across all the time points in the time series during resting runs) are shown in Fig. 3b. Noise levels from a background (BG) coarse voxel outside the brain (rightmost coarse voxel) were independent of TE and were comparable between the smaller and larger coarse voxels. Temporal noise levels for large and small SMC coarse voxels showed substantial TE dependence, similar in shape to the T2* decay curves in Fig.3a, with a trend toward lower noise at longer TE values. The maximum temporal noise at the shortest echo time from the larger coarse voxel was 2.19 ± 1.07 times that from the smaller coarse voxel with half the volume. The average temporal noise from the larger coarse voxel remained greater than that of the smaller coarse voxel for TE<85 ms. At larger TE values, temporal noise for both coarse voxel sizes was similar.

The average CNR-weights versus TE value are shown in Fig. 4 across all the subjects for large and small SMC CVs, with the shaded areas representing ±1 sample standard deviation. The weights show

substantial TE dependence, with early and late echoes weighted much less than intermediate TE values ranging from approximately 50 - 150 ms. The large SMC CV exhibits weights emphasizing slightly lower TE values than exhibited by the small SMC CV. In both cases, the TE value with maximum CNR-weighting is significantly longer than the estimated T2* value for the coarse voxel. The large error bars indicate that the CNR-weights were also quite variable across the group. Inspection of data for individual subjects revealed cases where the weights were similar to the theoretical BOLD contrast based on T2 -weighting, as well as others where CNR-weights showed appreciable deviation from this model.

Comparing signal characteristics across pulse sequences, Fig. 5 shows representative MECV time series data and analogous data obtained from the SMC ROI by spiral fMRI. Except for a single subject, BOLD contrast was observed to be larger using the MECV sequence. Over the group of subjects, however, the results were statistically similar for the two pulse sequences and the experimental parameters investigated. Figure 6 shows mean %BOLD and CNR per square root acquisition time values for the MECV and spiral fMRI data. Error bars indicate the standard error of the mean. Given that initial statistical tests showed no effect of coarse voxel size on %BOLD contrast, Fig. 6 only compares signal characteristics at 5 mm coarse voxel resolution. Within experimental error, both pulse sequences exhibited equal signal characteristics (non-parametric Wilcoxon sign-rank test: %BOLD, p = 0.1875; $CNR/\sqrt{T_{acq}}$, p = 0.44), although trends were observed that the MECV sequence provided larger values for both metrics.

Experiment B

Representative feedback signals, hand choice, and time series data from a single subject are shown in Fig. 7 for one run of the NF experiment. For this run, the hidden task involved activation of the left SMC, which the subject realized after the first block of feedback. The MECV fMRI signals show the appropriate modulations, and the visual feedback corresponded very well to the motor behavior in previous blocks. The mean latency of the real-time system was substantially less than TR = 1 s and was

measured as 717 ± 118ms, timed from the start of T2* decay data acquisition to the final output of the real-time calculations.

Table 1 summarizes the results of Experiment B over the 4 subjects and 18 data runs. There was 100% success in matching the target SMC, which occurred rapidly in each run. In 16/18 runs only 1 feedback cycle was required for successful matching. Partly this was due to the robustness of the feedback signal, F, which correctly identified the laterality of brain activity 92 % of the time.

Discussion

In the past, studies have explored spectroscopic, T2, and T2* measurements from a column of voxels(13-16). The most pertinent(14) describes a method for multi-echo T2*-weighted measurements of the primary motor cortex. However, this previous work provided reduced multi-echo imaging capability (32 echoes), did not provide signal sensitivity comparisons with more conventional fMRI pulses sequences, and was not designed with real-time fMRI NF in mind. The present work shows that by using the appropriate calibration procedures and simple data processing techniques, the data obtainable from the prototype MECV pulse sequence provides %BOLD and $CNR/\sqrt{T_{acq}}$ values well-localized in the SMC comparable to conventional single-echo acquisition achieved by multi-slice spiral fMRI, as would typically be used in a real-time fMRI NF experiment. Furthermore, fMRI signals are computed easily and rapidly, well within TR = 1 s without placing heavy demands on computer hardware and software. In what follows, the significance of these findings is discussed.

The T2* decay data acquired using the MECV sequence (Fig. 3) displayed several interesting characteristics. In particular, the average baseline T2* value (60 ±4 ms) at 1.5 T for the SMC coarse voxel of smaller size (5 mm x 20 mm x 20 mm) agrees with results from a previous study using similar voxel size (T2*= 58 ms(11)) and is slightly smaller than the reported results at higher spatial resolution

for cortical gray matter (T2* = 69.4 ms(32); 65 ms(33); 78 ms(34); and 73.2 ms(35)). As expected, the baseline T2* value for the larger coarse voxel (10 mm x 20 mm x 20 mm) is reduced compared to that of the smaller coarse voxel due to more pronounced magnetic field inhomogeneity and intra-voxel dephasing. However, the effects of magnetic field inhomogeneity in the larger coarse voxel were not overly problematic, given that the echo weighting strategies enhanced the overall BOLD contrast sensitivity from each T2* decay curve and provided comparable CNR and % BOLD signal change between the two spatial resolutions within experimental error(data not shown).

Figures 3 and 4 provide useful information about the noise, and CNR characteristics of T2* decay as measured using the prototype MECV sequence. In Fig. 3b, the noise properties of the T2* decay from sensorimotor cortex have marked TE dependence. This is consistent with a previously developed model of BOLD noise characteristics(36), where three noise contributions are anticipated: "non-BOLD" noise proportional to signal intensity as a function of TE, arising from sources such as respiratory fluctuations and scanner imperfections; "physiological" noise proportional to BOLD contrast as a function of TE, produced by the same mechanisms that lead to activation induced changes on T2*-weighted signals, such as fluctuations in cerebral blood and metabolism; and thermal noise independent of TE, arising from the subject and the MRI system electronics. Of these components, the non-BOLD noise contribution associated with T2*-decay from SMC CVs is largest, suggesting that refinements of the MECV sequence should focus on reducing potential noise sources in this category (eg. improved correction for respiratory fluctuations, cardiac fluctuations, as well as effects arising from RF amplifier stability, and eddy currents generated by flyback gradients). It would be desirable to ensure that the value of TE most heavily CNR-weighted approaches the average T2* estimate for a given coarse voxel. Nevertheless, Fig. 4 indicates that there is substantial CNR available over the range of TE values from approximately 50-150 ms, and that use of CNR-weighting of densely sampled T2* decay is sufficient to provide an overall time series with good %BOLD signal characteristics from coarse voxels.

Indeed, the MECV method and spiral imaging provide comparable % BOLD and $CNR/\sqrt{T_{acq}}$ values over equivalent volumes. However, this observation should be considered in the context of a previous study(21), which reported that CNR-weighting of multi-echo EPI yielded CNR improvement over single-echo EPI by as much as 25% ± 13%. The improvement was probably due in part to the spatial resolution employed (3.5 mm isotropic voxels) at higher field (3T). However, another possibility is that experimental confounds reduced the quality of the MECV results in Experiment A. For example, no independent measure of motor performance was included in Experiment A to confirm that subjects performed equivalently during MECV and spiral acquisitions. Although runs were randomized to control for systematic effects such as learning and habituation, other cognitive effects (such as failure to maintain attention to the task) remain potential confounds. There is also a slight, systematic confound in using the CNR-weights for the long echo trains collected in the present work, because the CNR at late echoes is erroneously elevated due to collecting magnitude, rather than complex data. More effective OVS, either through improved RF pulse design (see below) or improved receive coil geometry would also slightly improve %BOLD and CNR values. Lastly, it is worth noting that prior to the present fMRI work, echo-weighting summation strategies have been employed only in the context of multi-echo EPI. For much more densely sampled T2*-decay curves, such as those provided by the MECV sequence, there may be intrinsic limits to the contrast gain afforded by echo summation, due to noise correlations between echoes(37). Future theoretical and experimental investigations of this possibility would be useful.

Nevertheless, the comparison to spiral imaging made in the present work is useful within the NF context, given that spiral imaging has been implemented in fMRI NF studies using delineated ROIs of similar size(6). The comparable results observed between the two protocols at TR = 1 s in this study are sufficient to conclude that the ME approach may be useful for real-time NF. This is reinforced by the simplicity with which Experiment B was implemented, and the rapidity with which subjects learned the hidden task condition. Furthermore, Figs. 4-7 also indicate that there is scope to perform NF at TR values substantially below 1 s. Implementing such enhanced temporal resolution can be readily achieved. For

the current prototype, OVS and flyback gradients were approximately 30 ms and 300 ms in duration, respectively. The OVS component can be performed more rapidly and efficiently (*eg.* using BASSI pulses(38), or by using multidimensionally-selective RF pulses combined with parallel transmission schemes(39)), feasibly in half the time or less. Figure 4 suggests that a substantial portion of the available BOLD contrast can be obtained by CNR-weighting of echoes up to 150 ms, with later echoes providing little contribution. There is also considerable scope to minimize data processing time. In the prototype implementation, neither MATLAB software nor the real-time data server (used to access raw data stored in scanner memory)(30), provide optimal processing speed. Recently, work has started in the laboratory to develop a more refined version of the MECV sequence on a 3T TIM Trio MRI system (software version B15, Siemens, Erlangen, Germany). Utilizing the system "image construction engine" computing, network transfer to a computer running "real-time" AFNI and subsequently to an additional computer for stimulus display, the current latency between data acquisition and display of laterality metrics is 180 ± 30 ms, without writing data to disk. This pipeline enables NF at approximately 300 ms temporal resolution and still can be substantially improved.

What could be achieved with this type of temporal resolution? Previous fMRI NF studies with TR values in the 1 – 2 s range have demonstrated regulation of brain activity(4-7,9,40-41), either in terms of the amplitude or extent of BOLD signals. However, higher temporal resolution, in addition to removing potential aliasing artifacts associated with cardiac pulsatility, enables the onset of BOLD hemodynamic responses to be captured much more precisely. For example, previous high temporal resolution fMRI at 4.0 T recorded the sequence of neural information processing at the 100 ms time scale(42). In addition, differences in the power spectrum of resting state fMRI data before and after long-term motor training have recently been observed(43). Given the high temporal resolution and real-time capability of the MECV sequence, it is of interest to explore whether these or other fMRI signal properties can be used as feedback metrics to modulate behavioral performance, as well as the relationship between fMRI NF

signals and their electrophysiological counterparts. Work is ongoing in the laboratory to explore such issues.

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Figure Captions

Fig. 1 Pulse sequence diagram of the multi-echo coarse voxel (MECV) pulse sequence. a) Conceptual diagram indicating the components of outer volume saturation (OVS) in three spatial dimensions, slice-selective excitation to improve spatial localization, and subsequent readout providing a column of coarse voxels. b) Outer volume and 90° slice selection radiofrequency (RF) and gradient waveforms in the G_x, G_y, and G_z directions. VSS= very selective saturation pulses (see text for details). c) Excitation and data acquisition portion of the pulse sequence, showing flyback gradient echo train.

Fig. 2 Bar plots illustrating the mean fraction of spiral voxels active within coarse voxel locations as a function of position (right to left), across subjects performing a complex unilateral motor task with their left hand (see text for details). Plots are shown both for smaller (5 mm by 20 mm by 20 mm) and larger (10 mm by 20 mm by 20 mm) coarse voxels, respectively. Error bars denote the standard error of the mean.

Fig. 3 Plots of a) mean T2* decay and b) mean temporal noise as a function of echo time for various coarse voxel locations, obtained from the resting run data across subjects. Temporal noise was calculated as the sample standard deviation for all points in each time series. Areas shaded in gray represent the standard error of the mean. SMC=sensorimotor cortex, BG=background.

Fig. 4 Plots of contrast-to-noise ratio (CNR) weights versus echo time for smaller and larger coarse voxels centered on primary sensorimotor cortex. Areas shaded in gray represent ±1 sample standard deviation.

Fig. 5 Representative time series data for the multi-echo coarse voxel (MECV) sequence (solid line) compared to data obtained with two dimensional multi-slice spiral fMRI readout (dashed line). The spiral data were spatially averaged to match the 5 mm by 20 mm by 20 mm coarse voxel volume and location.

Fig. 6 Mean %BOLD and $CNR/\sqrt{T_{acq}}$ values for MECV and multi-slice spiral fMRI data. MECV fMRI results are shown for a 5 mm by 20 mm by 20 mm coarse voxel, and spiral fMRI results are for the spatial average of region of interest of equivalent size, each optimally placed in sensorimotor cortex. Error bars denote the standard error of the mean.

Fig. 7 Representative results obtained using the MECV pulse sequence in a simple neurofeedback experiment. Feedback signal (F metric, see text for details), hand choice, and activation from coarse voxels corresponding to primary sensorimotor cortex (SMC) for the left and right hand are plotted as a function of time. The subject was able to determine the correct hand to move (left) after observing a single block of their brain activity.

Table 1. Summary of Results for Experiment B

Subject	Match Target	First Feedback Cycle	Metric Accuracy
1	5/5	5/5	24/25
2	5/5	4/5	22/25
3	5/5	5/5	25/25
4	3/3	2/3	12/15
Summary	18/18 (100 %)	16/18 (90%)	83/90 (92 %)