Diffusion Dispersion Imaging: Mapping OGSE Frequency Dependence in the Human Brain

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Abstract
Purpose: Oscillating gradient spin-echo (OGSE) diffusion MRI provides information about the microstructure of biological tissues via the frequency dependence of the apparent diffusion coefficient (ADC). ADC dependence on OGSE frequency has been explored in numerous rodent studies, but applications in human brain have been limited and have suffered from low resolution, long scan times and a limited exploration of the nature of the ADC dependence on frequency.
Methods: Multiple frequency OGSE acquisitions were acquired in healthy subjects using a head-only 7 T system to explore the frequency dependence of ADC, the “diffusion dispersion”, at a single voxel level. A highly efficient protocol for mapping diffusion dispersion was developed by optimizing the “diffusion dispersion-to-noise ratio”, which quantifies the propagation of signal noise into diffusion dispersion parameter estimates.
Results: For the first time, a linear dependence of ADC on the square root of frequency was demonstrated throughout the brains of multiple healthy humans. High quality, full-brain maps of diffusion dispersion were also demonstrated at an isotropic resolution of 2 mm in a scan time of 6 minute.
Conclusion: This work sheds light on the nature of diffusion dispersion in the healthy human brain and introduces full brain diffusion dispersion mapping at clinically relevant scan times. These advances may lead to new biomarkers of pathology or improved microstructural modelling.
In Introduction
Water diffusion in biological tissues is restricted by microstructure composition. As a result, the apparent diffusion coefficient (ADC) measured with diffusion magnetic resonance imaging (dMRI) generally depends on the effective diffusion time ($\Delta_{eff}$), the time during which water molecules probe their surrounding environment. At short diffusion times, molecules only travel short distances and as such do not interact with barriers like cellular membranes, and estimated ADC will be similar to the intrinsic diffusion coefficient (1). For longer diffusion times, on the other hand, water spins have a higher chance of interacting with obstacles and the observed ADC will be decreased. Thus, measuring $\Delta_{eff}$-dependence of ADC provides an opportunity for additional insight into the microstructure of biological tissues compared to ADC alone.

Traditional dMRI is performed using pulsed gradient spin-echo (PGSE) with $\Delta_{eff}$ typically greater than 30 ms in human applications (2). Oscillating gradient spin-echo (OGSE) encoding is a dMRI method that enables short $\Delta_{eff}$ by using rapidly oscillating diffusion gradients, as $\Delta_{eff}$ scales inversely with oscillating frequency, $f$. OGSE diffusion encoding has been demonstrated to provide unique sensitivity to microstructural changes in pathology for several preclinical studies. Does et al. studied the $f$-dependence of ADC in the gray matter of normal and globally ischemic rat brain with frequencies ranging from 0 ($\Delta_{eff} = 10$ ms) to 1000 Hz, and observed ADC increases as much as 24% in vivo and 50% postmortem (3). Bongers et al. found that OGSE was more effective than PGSE as an early MRI biomarker for radiation therapy response monitoring in glioblastoma mouse models, and that tumor ADC was generally 30-50% higher than in surrounding white matter for a frequency of 200 Hz compared to 0 Hz ($\Delta_{eff} = 18$ ms) (4). They also detected a 15% increase in the tumor ADC in response to radiation, while PGSE showed a lower sensitivity to radiation changes. Gore et al. also showed OGSE is a potentially earlier and more sensitive indicator of tumor treatment response than conventional PGSE (5). Potential benefits of using OGSE encoding in delineating tissue microstructure has also been reported in other studies of animal models of stroke (6), multiple sclerosis (7), and cancer (8).
The successful application of OGSE encoding and the unique insight into pathology it enables in animal models makes its translation into human studies appealing. However, lower gradient strengths on human MR systems significantly reduces the maximum attainable b-value and frequency for a given echo time. Consequently, in vivo human OGSE acquisitions suffer from an inherently low ADC-to-noise ratio (9). Nevertheless, ADC dependence on OGSE frequency has been observed in both grey and white matter regions in the healthy human brain (10), and OGSE can provide complementary microstructural information to PGSE in acute ischemic stroke (11). However, scan times were long (20 minutes for full brain coverage), resolution was low (2 x 2 x 2.5 mm$^3$), no voxel-wise maps of frequency dependence have been depicted, and a parameterization of the dependence of ADC on frequency (i.e., the “diffusion dispersion” (12)) has not been demonstrated in the in vivo human brain. Notably, a $f^9$ dependence of ADC has been predicted by considering long-range structural correlations, where $9$ is a parameter given by the dimension and class of structural disorder (12). Mouse models have demonstrated a $9=\frac{1}{2}$ behaviour in both healthy (13) and globally ischemic (3,12) rodent brains. A trend towards $f^{1/2}$ dependence can be observed from the data presented in the in vivo human brain (10), but this behaviour was not explicitly explored and only 2 non-zero frequencies were acquired.

In this work, we explored the $f^9$ dependence of ADC in healthy subjects for frequencies in the range of 0 to 60 Hz by performing in vivo PGSE and OGSE ADC mapping at 7 T with $b = 450$ s/mm$^2$. For the first time, a linear dependence of ADC on $f^{1/2}$ was observed at the single-voxel level throughout the brain and in all subjects. Capitalizing on this finding, an optimized protocol was developed to acquire and generate high-resolution (2 mm isotropic) full-brain maps of the diffusion dispersion in a scan time of only 6 minutes.

**Theory**

**Diffusion dispersion**: A parameterization that allows visualization of maps of the frequency dependence of ADC throughout the human brain has thus-far not been demonstrated. To develop images reflecting ADC change with frequency, we define the diffusion dispersion (DD$_9$) as the slope of linear regression of ADC with $f^9$:
\[ ADC(f) = DD_\theta f^\theta + ADC_{f0} \]  

where \( ADC_{f0} \) is the PGSE ADC. It is evident that with an a priori value chosen for \( \theta \), an acquisition at only two frequencies is required to estimate \( DD_\theta \). Accordingly, considering computation of the mean ADC from a uniformly distributed multi-directional acquisition (e.g., tetrahedral encoding (9,14)) for PGSE and OGSE at a single frequency, the expression for \( DD_\theta \) is:

\[
DD_\theta = \frac{1}{N_d f^\theta} \sum_{d=1}^{N_d} \left[ -\frac{\ln(S_{f,d})}{b_{f,d}} + \frac{\ln(S_{f0,d})}{b_{f0,d}} \right] 
\]

where \( N_d \) is the number of diffusion directions, \( S_o \) is the \( b = 0 \) signal, \( S_{f,d} \) and \( S_{f0,d} \) are the direction-dependent diffusion weighted signals (DWIs) at frequencies \( f > 0 \) and \( f = 0 \), respectively, and \( b_{f,d} \) and \( b_{f0,d} \) are the direction-dependent b-values at frequencies \( f > 0 \) and \( f = 0 \), respectively. Note that while the b-values would ideally be identical for all acquisitions, small differences in b will likely occur in practice due to cross terms that arise from the crusher gradients on either side of the refocusing RF pulse. However, assuming these variations in b are small, the expression can be simplified to a format where a \( b = 0 \) acquisition is not required, which is advantageous for scan time reductions that could help facilitate clinical translation:

\[
DD_\theta = \frac{1}{N_d f^\theta} \sum_{d=1}^{N_d} \left[ -\frac{\ln(S_{f,d})}{b_{f,d}} + \frac{\ln(S_{f0,d})}{b_{f0,d}} \right] + \varepsilon 
\]

\[
\varepsilon = \frac{1}{N_d f^\theta} \sum_{d=1}^{N_d} \left[ \frac{\ln(S_o)}{b_{f,d}} - \frac{\ln(S_o)}{b_{f0,d}} \right] 
\]
where $\varepsilon$ is the error incurred by omitting the acquisition of $b = 0$ images. Notably, $\varepsilon = 0$ when identical $b$-values are used for all acquisitions.

**Diffusion dispersion-to-noise ratio optimization:** To optimize a protocol for diffusion dispersion mapping, sequence parameters that maximize the ratio of the mean $DD_\theta$ to its standard deviation can be evaluated, similar to approaches that have been used to determine optimal parameters for the measurement of ADC (15). For these purposes, identical $b$-values for all directions and frequencies and a direction-independent diffusion tensor are assumed in Eq. 3, which leads to an expression for the “diffusion dispersion-to-noise ratio” (DDNR) given by:

$$DDNR = \frac{DD_\theta}{\sigma_{DD}} = SNR_{f0} \cdot \frac{DD_\theta \cdot bf^\theta}{\sqrt{1 + \frac{\exp(2DD_\theta \cdot bf^\theta)}{N_{OP}}}}$$

$$= \exp(-bD_{f0}) \cdot \exp(-TE(b)/T_2) \frac{DD_\theta \cdot bf^\theta}{\sqrt{1 + \frac{\exp(2DD_\theta \cdot bf^\theta)}{N_{OP}}}}$$

[5]

where $DD_\theta$ is the mean diffusion dispersion, $\sigma_{DD}$ is the standard deviation of diffusion dispersion, $SNR_{f0}$ is the signal-to-noise ratio of the PGSE acquisition, $TE(b)$ is the echo-time (which is $b$-value dependent), $D_{f0}$ is the PGSE ADC value, and $N_{OP}$ is the ratio of the number of OGSE to PGSE acquisitions. Accordingly, Eq. 5 can be used to determine the diffusion encoding parameters ($b$-value, frequency, $TE$, and $N_{OP}$) that maximize DDNR for typical $DD_\theta$, $D_{f0}$, and $T_2$.

**Methods**

**DDNR optimization:** $T_2$ values from 40 ms to 80 ms were used in the optimization, which covers the range of expected values for both grey and white matter at 7 T. From preliminary data of one subject (not shown here), $\theta$ was estimated to be $\frac{1}{2}$, and $DD_{1/2}$ and $D_{f0}$ values were estimated
to range from 10 to 30 $\mu m^2/s^{1/2}$, and 0.6 to $0.8 \times 10^{-3}$ mm$^2$/s, respectively. Notably, $DD_{1/2}$ computed from the ADC data displayed in Baron et al. falls within this range used for optimization (10). A maximum gradient amplitude of 68 mT/m and 240 T/m/s slew rate were assumed for simulation, according to limits used experimentally (see below). TE was also calculated from the sequence timings that reflect our experimental usage of a 2 mm isotropic in-plane resolution with a single shot EPI readout trajectory, 75% phase-encode partial Fourier, and 2778 Hz/pixel readout bandwidth. Non-integer values were permitted for the number of periods in the OGSE waveform to avoid the discretization of DDNR curve and improve the ability to observe trends in the results. A minimum of 2 OGSE periods was enforced (one on each side of the refocusing RF pulse), because symmetry on either side of the refocusing pulse is required to avoid errors from concomitant gradient fields (16).

**In vivo experiments:** MRI scans were performed in a water phantom and in the brains of 4 healthy male subjects on a 7 T head-only system (80 mT/m strength and 350 T/m/s slew rate). This study was approved by the Institutional Review Board at Western University, and informed consent was obtained prior to scanning. To mitigate eddy current artefacts and reduce acoustic noise and gradient duty cycle, the maximum gradient was limited to 68 mT/m with 240 T/m/s slew rate for OGSE scans. A multi-frequency dMRI protocol was acquired using standard PGSE ($\Delta_{eff} = 55$ ms, 0 Hz) and cosine-modulated trapezoidal OGSE with frequencies 30 Hz, 45 Hz, and 60 Hz. The remaining parameters were $b = 450$ s/mm$^2$, 4 direction tetrahedral encoding and $b = 0$ acquisitions with 10 averages each, TE/TR = 111/5500 ms, FOV = 200*200 mm$^2$, 2.5 mm isotropic in-plane resolution, 32 slices (3 mm), and scan time 18 min. Signal changes with respect to OGSE frequency are relatively small (9,10) and estimation of $DD_\theta$ may be particularly sensitive to imaging artefacts compared to ADC. Accordingly, in this foundational work parallel imaging was not implemented to mitigate residual aliasing artefacts and to maximize SNR.

Another dMRI protocol was specified to maximize DDNR based on our findings from Eq. 5 (the full optimization results are reported below). This scan consisted of two frequencies: standard
PGSE (\(\Delta_{\text{eff}} = 55 \text{ ms, 0 Hz}\)), and cosine-modulated trapezoidal OGSE with frequency 38 Hz (\(b = 720 \text{ s/mm}^2\)). The other parameters were 4 direction tetrahedral encoding with 6 averages each, TE/TR = 82/8200 ms, FOV = 200*200 mm\(^2\), 2 mm isotropic in-plane resolution, 48 slices (2 mm), and scan time 6 min. For anatomical reference, \(b = 1000 \text{ s/mm}^2\) standard PGSE diffusion tensor imaging (DTI) was acquired with matched spatial resolution and slice prescription with 30 directions and 6 \(b = 0\) acquisitions (TE/TR = 53/8200 ms, scan time 5 min).

For all scans, registration between diffusion directions and frequencies was performed using FSL (17). For the multiple-frequency scan, \(DD_\theta\) maps were calculated using voxel-wise linear regression via Eq. 1, while the optimized scan applied Eq. 3 (ignoring \(\varepsilon\)). Negative \(DD_\theta\) values are not physiologically plausible (18), and were masked. MD and FA maps were computed from the standard DTI scan using MRtrix 3.0. To obtain histograms of \(DD_{1/2}\) in grey and white matter, brain tissue was segmented using a semi-automated in-house algorithm that selects voxels with mean PGSE ADC between 0.5 and 0.9 * 10\(^{-3}\) mm\(^2\)/s and manually excludes non-brain-tissue signal (e.g., near skull).

Results

**DDNR optimization:** Figure 1a shows DDNR variation with b-value and \(f\) for \(T_2 = 60 \text{ ms, } D_{f0} = 0.7 * 10^{-3} \text{ mm}^2/\text{s}, \) and \(DD_{1/2} = 20 \mu\text{m}^2/\text{s}^{1/2}\). The minimum required TE for DDNR values in Figure 1a are depicted in Figure 1b. Notably, for all combinations of input parameters, the optimal DDNR occurred when only the minimum of 2 OGSE periods were used. Figure 1c depicts the DDNR with respect to \(f\) and \(b\) for two periods and the same \(T_2, D_{f0}, \) and \(DD_{1/2}\) as in Figure 1a, assuming the gradients are employed at the hardware maximum. Table 1 depicts the optimal acquisition parameters for a range of plausible \(T_2, D_{f0}, \) and \(DD_{1/2}\) values. Notably, the optimal choice of \(f\) and \(N_{\text{op}}\) only weakly depend on the input parameters, and are near 40 Hz and 1 for all cases, respectively. Accordingly, \(f = 38 \text{ Hz with 2 OGSE periods (corresponding to } b = 720 \text{ s/mm}^2, \text{ TE = 82 ms, and } N_{\text{op}} = 1)\) were chosen as parameters for the optimized 6-minute in vivo diffusion dispersion scan.
**Experiments:** In the water phantom, ADC values were within 1.5% of the PGSE value at all OGSE frequencies (Supporting Information Figure S1). DD$_{1/2}$ maps computed from the multiple-frequency scan were of comparable quality for all subjects (Figure 2a). Likewise, similar quality was observed between subjects for individual mean ADC maps at each frequency (Supporting Information Figure S2). ADC and DD$_{1/2}$ maps at a range of slices throughout the brain in one subject are depicted in Supporting Information Figure S3. DD$_{1/2}$ histograms of all subjects have considerable overlap, with the majority of voxels indicating DD$_{1/2}$ ~ 20 to 25 μm$^2$/s$^{1/2}$ (Figure 2c), which is within the range of the DD$_{1/2}$ values used for DDNR optimization. Overall, R$^2$~0.99 throughout the brain tissue of all subjects, which suggests $\delta = \frac{1}{2}$ in healthy human brain tissue (Figure 2b,d). The frequency dependence of ADC is further demonstrated in Figure 3a-c within example regions-of-interest (ROIs). ADC increased with $f$ (Figure 3b), and linearly increased with $f^{1/2}$ (Figure 3c) in the chosen ROIs in all subjects. Example DD$_{1/2}$ maps computed from the optimized acquisition and corresponding DTI FA and MD maps are depicted in Figure 4. Example optimized DD$_{1/2}$ maps from multiple slices in all the subjects are shown in Supporting Information Figure S4.

**Discussion**

In this work, a $f^{1/2}$ dependence of ADC on OGSE frequency was reported for the first time in the human brain in vivo. This trend is similar to recent reports in both healthy (13) and globally ischemic (3,12) rodent brains. In addition, our finding of DD$_{1/2}$ values ~ 20 to 25 μm$^2$/s$^{1/2}$ (Figure 2) agrees with ADC results reported at a field strength of 4.7 T (10); for example, DD$_{1/2}$ computed from the corticospinal tract using their reported ADC’s is approximately 24 μm$^2$/s$^{1/2}$. Further, methods to compute diffusion dispersion maps without requiring b=0 images and while optimizing the “diffusion dispersion-to-noise ratio” were reported, which enabled full-brain, high resolution maps of the diffusion dispersion in a scan time of 6 minutes. Diffusion dispersion may be applicable as a new biomarker for pathology and, further, the ability to map diffusion dispersion in vivo may improve microstructural modelling approaches, as diffusion time dependencies can help resolve model fitting degeneracies (18). While the proposed optimized protocol does not provide estimations of ADC or the diffusion tensor, these parameters may be
more robustly estimated from a standard DTI acquired with a shorter TE and the same imaging parameters (FOV, resolution, bandwidth), as was done here (Figure 4).

The DDNR simulations had the surprising result that an OGSE frequency ~ 40 Hz is optimal for a broad range of physiologically feasible values of $T_2$, ADC, and diffusion dispersion. However, the optimal values may change for different gradient hardware limits or direction schemes. For example, the optimal frequency for tetrahedral encoding with 300 mT/m gradients is ~100 Hz (all other parameters, including slew rate, kept the same as those used for Table 1). Notably, for this case, the optimal parameters are still obtained with only 2 OGSE periods, similar to the results in Figure 1. This general finding suggests that increasing the b-value by increasing the number of OGSE periods is not worth the SNR losses incurred by the greatly increased TE. This conclusion does not consider the narrowing of OGSE spectra that occurs with an increased number of periods; however, given the generally low DDNR achievable on human systems, remedying this spectral blurring may not be worth the DDNR cost.

The optimized acquisition did not acquire any imaging volumes with $b = 0$, and the DWIs at the various frequencies are compared directly using Eq. 3. Notably, $b = 0$ images have extremely bright cerebrospinal fluid (CSF), particularly at the long TE required for OGSE, which results in severe Gibb’s ringing. When an ADC is computed, the different Gibbs ringing profiles for $b = 0$ and diffusion weighted acquisitions causes amplified ringing in ADC maps (19). Because the computation of $DD_{1/2}$ compares only diffusion weighted signals with the same diffusion weighting, the CSF signal is fairly consistent, and this type of Gibbs ringing amplification is mitigated (Figure 5). That said, the CSF signal for PGSE is slightly lower than for OGSE because of signal losses from incoherent flow (OGSE is inherently flow-compensated) (10), which results in negative $DD_{1/2}$ values in the fluid. Negative $DD_{1/2}$ is not expected in brain tissue, where diffusion is restricted/hindered and flow is absent; accordingly, voxels with negative $DD_{1/2}$ were masked in all displayed images.
OGSE acquisitions on human systems utilize relatively low b-values, which may make estimations of diffusion dispersion sensitive to perfusion. For estimations of DD$_{1/2}$ to be insensitive to perfusion, the perfusion signal must be much less than the tissue signal at all frequencies used in Eq. 3. In mice, no dependence on perfusion was observed for frequencies up to 200 Hz for b > 300 s/mm$^2$ (13); accordingly, this assumption was likely satisfied here, where b-values of at least 450 s/mm$^2$ and a maximum frequency of only 60 Hz were utilized. Also, considering that all images used to compute DD$_{1/2}$ in this work were diffusion weighted, DD$_{1/2}$ may be less sensitive to perfusion than ADC at the low b-values typically used for OGSE.

While $\vartheta = \frac{1}{2}$ was implicated here in the healthy human brain, this may not be the case in neurological disorders. Accordingly, care should be taken in the application of optimized protocols that compute DD$_{1/2}$ from only a single OGSE frequency in pathologies where the nature of $\vartheta$ has not been explored. In fact, the value of $\vartheta$, if observed to change with pathology, could be an informative biomarker itself and/or enhance microstructural modelling.

Our acquisition in a water phantom revealed a maximum -1.5% bias in ADC at a frequency of 60 Hz. This may have been caused by eddy current artefacts or slightly non-linear gradient amplifier gain at very high gradient amplitudes. Nevertheless, this bias is small compared to the change in ADC of approximately +25% observed in human brain tissue. Another potential source of error is $\varepsilon$ (Eq. 4), which stems from omitting the b = 0 acquisition in the optimized scan. However, for the optimized protocol implemented in this work, this would result in $\varepsilon \sim 10^{-14}$ mm$^2$/s$^{3/2}$ for a true DD$_{1/2}$ of 25 mm$^2$/s$^{3/2}$ and $D_{f0} = 0.7 \times 10^{-3}$ mm$^2$/s; accordingly, $\varepsilon$ can likely be ignored in practice. Finally, it may also be tempting to further simplify Eq. 3 to use the nominal b-value without any consideration of cross-terms; however, for our scan parameters and the same example DD$_{1/2}$ and $D_{f0}$, this would lead to an error in DD$_{1/2}$ of approximately 6% and is accordingly not recommended.

**Conclusion**
In conclusion, we have demonstrated a $f^{1/2}$ dependence of ADC in the in vivo human brain using oscillating gradient spin-echo diffusion MRI, and developed an optimized acquisition protocol that enabled full brain mapping of the diffusion dispersion in a clinically relevant 6 minutes. The ability to rapidly characterize diffusion dispersion in vivo opens the door for the exploration of new biomarkers and more sophisticated microstructural models.

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### Tables

**Table 1: DDNR optimization.**

| Tissue Properties | Optimal Diffusion Encoding Parameters |
|-------------------|---------------------------------------|
|                  | $T_2$ [ms] | $DD_{1/2}$ [µm$^2$/s$^{1/2}$] | $D_{f0} \times 10^3$ [mm$^2$/s] | $f$ [Hz] | $b$-value [s/mm$^2$] | Min TE [ms] | $N_{op}$ |
|-------------------|------------|-------------------------------|---------------------------------|---------|--------------------|-------------|---------|
|                   | 60         | 20                            | 0.7                             | 39      | 700                | 81          | 1.09    |
|                   | 40         | 20                            | 0.7                             | 43      | 520                | 76          | 1.07    |
|                   | 80         | 20                            | 0.7                             | 38      | 755                | 82          | 1.1     |
|                   | 60         | 10                            | 0.7                             | 38      | 755                | 82          | 1.05    |
|                   | 60         | 30                            | 0.7                             | 39      | 700                | 81          | 1.14    |
|                   | 60         | 20                            | 0.6                             | 38      | 755                | 82          | 1.1     |
|                   | 60         | 20                            | 0.8                             | 41      | 600                | 78          | 1.08    |

Optimal diffusion encoding parameters ($f$, $b$-value, TE, and $N_{op}$) vary with $T_2$, $D_{f0}$, and $DD_{1/2}$. The simulated optimal parameters for the average parameters, $T_2 = 60$ ms, $D_{f0} = 0.7 \times 10^3$ mm$^2$/s, and $DD_{1/2} = 20$ µm$^2$/s$^{1/2}$, are shown in the top row. Notably, $f$ and $N_{op}$ are almost independent on the input parameters.
Figures

Figure 1: DDNR optimization: (a) DDNR variation with $f$ and b-value for $T_2 = 60$ ms, $D_{i0} = 0.7*10^{-3}$ mm$^2$/s, and $DD_{1/2} = 20$ $\mu m^2$/s$^{1/2}$, (b) required minimum TE for DDNR values in (a), and (c) DDNR variation with $f$ and b-value with the total number of OGSE periods fixed at 2 (one on each side of the refocusing RF pulse). In (c), DDNR was maximized at $f = 39$ Hz and $b = 700$ s/mm$^2$ with minimum required TE = 81 ms. The lower-left dark blue region (i.e. DDNR=0) in (a) and (b) corresponded to experimentally impossible diffusion encoding states requiring a total number of OGSE periods < 2.
Figure 2: Distribution of DD$_{1/2}$ values and goodness-of-fit ($R^2$). (a) Example DD$_{1/2}$ maps from an individual slice in 4 subjects computed from the multiple-frequency scan, (b) $R^2$ maps that correspond to the images in (a), (c) Distribution of DD$_{1/2}$ values in the entire brain volume of each subject, and (d) $R^2$ distribution in the entire brain volume of each subject (only $R^2>$0.7 are shown). DD$_{1/2}$ histograms overlap with the majority of voxels showing DD$_{1/2}$~20 to 25 $\mu$m$^2$/s$^{1/2}$. Notably, a high $R^2$ is observed throughout the brain for all subjects. A lower $R^2$ is observed in the cerebrospinal fluid, where incoherent flow creates artifactual signal loss for PGSE. Subjects are identified with different colors in (c-d).
Figure 3: ADC frequency dependence in 4 subjects within example ROIs on 2 slices. (a) ROI placements on reference DD_{1/2} maps (red boxes) in one subject (similar locations were manually prescribed for the other subjects), (b) mean ADC change with respect to $f$, and (c) mean ADC change with respect to $f^{1/2}$, with solid lines indicating linear regression. ADC increased with $f$, and linearly increased with $f^{1/2}$ within the chosen ROIs in all subjects. Error bars indicate the standard deviation of voxel values within each ROI. The different subjects are indicated using different colors.
Figure 4: Example MD, color-coded FA, and optimized DD\textsubscript{1/2} maps from multiple slices in one subject, from top to bottom. MD and FA maps were computed from the standard DTI scan, and DD\textsubscript{1/2} maps were calculated from the optimized acquisition. Voxels with negative diffusion dispersion are set to zero in the DD\textsubscript{1/2} maps, which generally occurs in the cerebrospinal fluid.
**Figure 5:** (Top row) Raw data, from left to right: non-diffusion weighted image, PGSE DWI, and 60 Hz OGSE DWI. The CSF signal is greatly reduced in the DWIs compared to the non-diffusion weighted image. The lower CSF signal for 0 Hz DWI compared to 60 Hz is due to incoherent flow, which is mitigated for OGSE because cosine OGSE waveforms are inherently flow-compensated. (Bottom row) ADC and DD$_{1/2}$ maps, from left to right: PGSE ADC, 60 Hz OGSE ADC, and DD$_{1/2}$ maps. Red boxes depict the regions on the ADC maps affected by Gibbs ringing. Notably, the same regions on the DD$_{1/2}$ map are less affected. Images are shown from an individual slice of the multiple-frequency scan in one subject, but similar trends were generally observed in all subjects.
Supporting Figures

**Supporting Information Figure S1**: Frequency dependence of ADC in a water phantom without diffusion restriction: (a) Mean ADC at 0 Hz (PGSE), 30 Hz, 45 Hz, and 60 Hz (OGSE), (b) Percent change in ADC across the chosen encoding frequencies with respect to the reference PGSE ADC. Mean ADC for each frequency was calculated within a multi-slice ROI covering a 24 mm thick slab (12 slices). Error bars in (a) indicate the standard deviation of voxel values within the selected ROI. The maximum variation in ADC was observed for frequency 60 Hz, with the ADC value about 1.5% less than the reference ADC.
Supporting Information Figure S2: Example ADC maps from an individual slice of the multiple-frequency scan in 4 subjects, from top to bottom: PGSE ADC ($\Delta_{eff} = 55$ ms, 0 Hz), 30 Hz OGSE ADC, 45 Hz OSGE ADC, and 60 Hz OGSE ADC.
Supporting Information Figure S3: Example ADC and DD$_{1/2}$ maps from the multiple-frequency scan at a range of slices throughout the brain in one subject, from left to right: PGSE ADC ($\Delta_{eff} = 55$ ms, 0 Hz), 30 Hz OGSE ADC, 45 Hz OSGE ADC, 60 Hz OGSE ADC, and DD$_{1/2}$. Voxels with negative diffusion dispersion are set to zero in the DD$_{1/2}$ maps, which generally occurs in the cerebrospinal fluid.
Supporting Information Figure S4: Example DD_{1/2} maps from multiple slices of the optimized acquisition in 4 subjects. Voxels with negative diffusion dispersion are set to zero in the DD_{1/2} maps, which generally occurs in the cerebrospinal fluid.