
Aidin Arbabi
Jason Kai
Ali R Khan
Corey A Baron

Follow this and additional works at: https://ir.lib.uwo.ca/brainpub

Part of the Neurosciences Commons, and the Psychology Commons
Diffusion dispersion imaging: Mapping oscillating gradient spin-echo frequency dependence in the human brain

Aidin Arbabi | Jason Kai | Ali R. Khan | Corey A. Baron

Centre for Functional and Metabolic Mapping, Robarts Research Institute, Schulich School of Medicine & Dentistry, The University of Western Ontario, London, Ontario, Canada

Purpose: Oscillating gradient spin-echo (OGSE) diffusion MRI provides information about the microstructure of biological tissues by means of the frequency dependence of the apparent diffusion coefficient (ADC). ADC dependence on OGSE frequency has been explored in numerous rodent studies, but applications in the human brain have been limited and have suffered from low contrast between different frequencies, long scan times, and a limited exploration of the nature of the ADC dependence on frequency.

Theory and Methods: Multiple frequency OGSE acquisitions were acquired in healthy subjects at 7T to explore the power-law frequency dependence of ADC, the “diffusion dispersion.” Furthermore, a method for optimizing the estimation of the ADC difference between different OGSE frequencies was developed, which enabled the design of a highly efficient protocol for mapping diffusion dispersion.

Results: For the first time, evidence of a linear dependence of ADC on the square root of frequency in healthy human white matter was obtained. Using the optimized protocol, high-quality, full-brain maps of apparent diffusion dispersion rate were also demonstrated at an isotropic resolution of 2 mm in a scan time of 6 min.

Conclusions: 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 modeling.

KEYWORDS
diffusion, diffusion time, disorder, dispersion, microstructure, MRI, OGSE, oscillating gradient

1 INTRODUCTION

Water diffusion in biological tissues is restricted by microstructure composition. As a result, the apparent diffusion coefficient (ADC) measured with diffusion MRI (dMRI) generally depends on the effective diffusion time ($\Delta_{\text{eff}}$), the time during which water molecules probe their surrounding environment. As diffusion times approach zero, molecules only travel short distances and fewer interact with barriers such as cellular membranes, and the estimated ADC approaches the intrinsic diffusion coefficient up to surface-to-volume effects.\textsuperscript{1,2} 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
\( \Delta_{\text{eff}} \) -dependence of ADC provides an opportunity for additional insight into the microstructure of biological tissues compared with ADC alone. Traditional dMRI is performed using pulsed gradient spin-echo (PGSE) with \( \Delta_{\text{eff}} \) typically greater than 30 ms in human applications.\(^3\) In Stepišnik’s groundbreaking work in the 1980s, oscillating gradient spin-echo (OGSE) encoding was introduced as a method that enables short \( \Delta_{\text{eff}} \) by using rapidly oscillating diffusion gradients, as \( \Delta_{\text{eff}} \) scales inversely with oscillating frequency, \( \omega \).\(^4,5\) OGSE diffusion encoding provides an extra dimension for probing axon diameter,\(^5\) surface-to-volume ratios\(^7\) and microstructural disorder,\(^8\) and has been demonstrated to provide unique sensitivity to microstructural changes in pathology for several preclinical studies. For example, Does et al studied the \( \omega \)-dependence of ADC in the gray matter of normal and globally ischemic rat brain with frequencies ranging from 0 (\( \Delta_{\text{eff}} = 10 \) ms) to 1000 Hz, and observed ADC increases as much as 24% in vivo and 50% postmortem.\(^9\) 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 with 0 Hz (\( \Delta_{\text{eff}} = 18 \) ms).\(^10\) They also detected a 15% increase in the tumor ADC in response to radiation, while PGSE showed a lower sensitivity to radiation changes. Colvin et al also showed OGSE is a potentially earlier and more sensitive indicator of tumor treatment response than conventional PGSE.\(^11\) Potential benefits of using OGSE encoding in delineating tissue microstructure has also been reported in other studies of animal models of stroke,\(^12\) multiple sclerosis,\(^13\) and cancer.\(^14\)

High-performance small-bore systems have also recently enabled the combination of OGSE and multiple diffusion encoding, which may provide a new dimension of sensitivity to investigate pathology.\(^15,16\)

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 (TE). Consequently, in vivo human OGSE acquisitions suffer from an inherently low ADC-to-noise ratio.\(^17\) Nevertheless, ADC dependence on OGSE frequency has been observed in both gray and white matter regions in the healthy human brain,\(^18,19\) and OGSE can provide complementary microstructural information to PGSE in acute ischemic stroke.\(^20\) However, scan times were long (20 min for full-brain coverage with 2.5-mm-thick slices), single-voxel maps of ADC differences between PGSE and OGSE have had poor SNR, and a parameterization of the dependence of ADC on frequency (i.e., the “diffusion dispersion”)\(^8\) has not been demonstrated in the in vivo human brain.

Notably, a \( \omega^\theta \) dependence of ADC has been predicted both in the short (\( \omega \rightarrow \infty \)) and long (\( \omega \rightarrow 0 \)) diffusion time regimes.\(^21\) In the short diffusion time regime, \( \theta = -1/2 \) and ADC differences are directly proportional to surface-to-volume ratios.\(^2,7\) In the long diffusion time regime, coarse graining occurs and the dependence on frequency is related to long-range structural correlations, where \( \theta \) is a parameter given by the effective dimension of diffusion and the class of structural disorder.\(^8\) \( \theta = 1/2 \) has been demonstrated in both healthy\(^22\) and globally ischemic\(^8,9\) rodent brain tissue. A trend toward \( \theta < 1 \) can be observed from the data presented in the in vivo human brain,\(^18\) but this behavior was not explicitly explored and only 2 non-zero frequencies were acquired.

In this work, we explored the \( \omega^\theta \) 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 7T with \( b = 450 \) s/mm\(^2\). For the first time, evidence for \( \theta = 1/2 \) has been obtained in the in vivo human brain. Capitalizing on this finding, an optimized protocol was developed to acquire high SNR, clinical-resolution (2 mm isotropic) full-brain maps of the ADC difference between PGSE and OGSE in a scan time of only 6 min.

## 2 | THEORY

### 2.1 | Mapping ADC differences

Considering a power law relationship between ADC and OGSE frequency,\(^8\) we define the apparent diffusion dispersion rate (\( \Lambda \)) as the slope of linear regression of ADC with \( \omega^\theta \):

\[
D_\omega = \Lambda \omega^\theta + D_{\omega0}
\]

(1)

where \( D_\omega \) is the OGSE ADC at a frequency \( \omega \) and \( D_{\omega0} \) is the ADC at \( \omega = 0 \). Accordingly, the apparent diffusion dispersion rate is directly proportional to the difference in ADC between an OGSE (\( \omega > 0 \)) and PGSE (\( \omega \approx 0 \)) scan, \( \Delta D \):

\[
\Lambda = \frac{\Delta D}{\omega^\theta}.
\]

(2)

Thus, mapping \( \Delta D \) can serve as a surrogate for mapping the apparent diffusion dispersion rate that requires only a single OGSE and PGSE acquisition. Accordingly, considering computation of the mean ADC (MD) from a uniformly distributed multidirectional acquisition (e.g., tetrahedral encoding)\(^17,23\) for PGSE and OGSE at a single frequency, the expression for \( \Delta D \) is:

\[
\Delta D = -\frac{1}{N_\omega} \sum_{i=1}^{N_\omega} \ln \left( \frac{S_{\omega,i}}{S_{\omega0,i}} \right) b_{\omega,i} + \frac{1}{N_{\omega0}} \sum_{i=1}^{N_{\omega0}} \ln \left( \frac{S_{\omega0,i}}{S_{\omega,i}} \right) b_{\omega0,i}
\]

(3)
where \( N_ω \) and \( N_{ω0} \) are the number of OGSE and PGSE acquisitions, respectively, \( S_0 \) is the \( b = 0 \) signal, \( S_{ω,i} \) and \( S_{ω0,i} \) are the direction-dependent diffusion weighted signals at frequencies \( ω > 0 \) and \( ω = 0 \), respectively, and \( b_{ω,i} \) and \( b_{ω0,i} \) are the direction-dependent \( b \)-values at frequencies \( ω > 0 \) and \( ω = 0 \), respectively.

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 radiofrequency (RF) pulse. However, assuming these variations in \( b \) are small, the expression can be simplified to a format where a \( b = 0 \)-value is not acquired is not necessary, which is advantageous for scan time reductions that could help facilitate clinical translation:

\[
\Delta D = \frac{1}{N_ω} \sum_{i=1}^{N_ω} \left[-\ln \left(S_{ω,i}\right)\right] \frac{1}{b_{ω,i}} + \frac{1}{N_{ω0}} \sum_{i=1}^{N_{ω0}} \left[\ln \left(S_{ω0,i}\right)\right] + E \tag{4}
\]

\[
E = \frac{1}{N_ω} \sum_{i=1}^{N_ω} \ln \left(S_{ω,i}\right) \frac{1}{b_{ω,i}} - \frac{1}{N_{ω0}} \sum_{i=1}^{N_{ω0}} \ln \left(S_{ω0,i}\right) \frac{1}{b_{ω0,i}} \tag{5}
\]

where \( E \) is a bias incurred by omitting the acquisition of \( b = 0 \) images. \( E = 0 \) when identical \( b \)-values are used for all acquisitions. Notably, for a priori known \( ω \), the apparent diffusion dispersion rate can be readily determined from \( ΔD \) using Equation 2.

### 2.2 ADC difference map optimization

To optimize a protocol for ADC differences, sequence parameters that maximize the ratio of the mean \( ΔD \) to its standard deviation can be evaluated, similar to approaches that have been used to determine optimal parameters for the measurement of ADC.\(^{24}\) For these purposes, identical \( b \)-values for all directions and frequencies (i.e., \( E = 0 \)) and a direction-independent diffusion tensor are assumed in Equation 4, which leads to the expression (Appendix):

\[
\frac{ΔD}{σ_{ΔD}} = SNR_0 \sqrt{N_{ω0}} \cdot b Δω^θ \left(1 + \frac{2 b Δω^θ}{R_{op}}\right)^{-\frac{1}{2}} e^{-b Δω e^{-TE(b)/T_z}} \tag{6}
\]

where \( σ_{ΔD} \) is the SD of estimated ADC difference between OGSE and PGSE, \( SNR_0 \) is the signal-to-noise ratio of a proton density scan with \( TE = 0 \) and \( b = 0 \), \( TE(b) \) is the \( b \)-value dependent echo-time, \( D_{ω0} \) is the PGSE ADC value, \( N_ω \) is the number of PGSE acquisitions, and \( R_{op} \) is the ratio of the number of OGSE to PGSE acquisitions. It can be shown that \( ΔD/σ_{ΔD} \) is maximized when \( R_{op} = e^{b Δω} \) (Appendix), which together with Equation 6 can be used to determine the diffusion encoding parameters \((b, f, TE, R_{op})\) that maximize \( ΔD/σ_{ΔD} \) for typical \( θ \), \( ω \), \( D_{ω0} \), and \( T_z \).

### 3 METHODS

#### 3.1 Multiple frequency OGSE

MRI scans were performed in a water phantom and 6 healthy male subjects on a 7T 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 before scanning. To mitigate eddy current artifacts 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. Multiple frequency dMRI data were acquired in a single scan that used standard PGSE (\( Δ_{eff} = 41 \) ms, 0 Hz) and cosine-modulated trapezoidal OGSE with frequencies 30 Hz,

![FIGURE 1 Gradient waveforms and frequency spectra](Equation 8) for the multifrequency scan, which used nominal frequencies of 0 Hz (A,B), 30 Hz (C,D), 45 Hz (E,F), and 60 Hz (G,H).

For all frequencies, \( b = 450 \) s/mm\(^2\). Implicit gradient reversal due to the 180° RF pulse has been applied, and the shown gradient amplitudes were applied simultaneously on all 3 gradient channels in a tetrahedral scheme.
45 Hz, and 60 Hz (Figure 1). The remaining parameters were $b = 450 \text{ s/mm}^2$, 4 direction tetrahedral encoding and $b = 0$ acquisitions with 10 averages each, TE/repetition time = $111/5500 \text{ ms}$, field of view = $200 \times 200 \text{ mm}^2$, 2.5 mm isotropic in-plane resolution, 32 slices (3 mm), and scan time 18 min. The image volume was interpolated to 1.25 mm $\times$ 1.25 mm $\times$ 1.50 mm resolution before analysis. Signal changes with respect to OGSE frequency are relatively small, and estimation of $\Lambda$ and $\theta$ may be particularly sensitive to imaging artifacts compared with ADC. Accordingly, in this initial work parallel imaging was not implemented to mitigate residual aliasing artifacts and to maximize SNR. Registration between diffusion directions and frequencies was performed using FSL.

For anatomical reference, $b = 1000 \text{ s/mm}^2$ standard PGSE diffusion tensor imaging (DTI) was acquired with 30 directions and 6 $b = 0$ acquisitions (TE/repetition time $= 53/8200 \text{ ms}$, field of view $= 200 \times 200 \text{ mm}^2$, 2 mm isotropic resolution, scan time 5 min). The DTI scan was registered to the OGSE scan, which was followed by probabilistic whole-brain tractography using MRTrax.26,27 Tract bundles were extracted using an in-house automated tract clustering pipeline28,29 (Supporting Information Video S1, which is available online).

MD values from each frequency of the multifrequency scan were obtained in each of the tracts. To mitigate partial volume errors from cerebrospinal fluid (CSF) that can concomitant gradient fields.30

Accordingly, the acquired signal is related to $F(\omega)$ and the frequency dependent ADC by Does et al.9:

$$S = S_0 \exp \left( -\frac{1}{\pi} \int_{0}^{\infty} F(\omega)D(\omega)F^*(\omega)d\omega \right)$$

(9)

3.2 | Sequence optimization

$T_2$ values from 40 ms to 80 ms were used in the optimization, which covers the range of expected values for both gray and white matter at 7 T. The multiple frequency scans implicated $\theta \approx 1/2$ and $\Lambda \approx 10 \mu\text{m}^2/\text{s}^{1/2}$ (see the Results section); accordingly, $\theta$ and $\Lambda$ values were estimated to range from 0.4 to 0.6 and 6 to 14 $\mu\text{m}^2/\text{s}^{1/2}$, respectively. $D_{ac0}$ values were estimated to be between 0.6 and 0.8 $\times 10^{-3} \text{ mm}^2/\text{s}$. A maximum gradient amplitude of 68 mT/m and 240 T/m/s slew rate were assumed for simulation, according to limits used experimentally. TE was also calculated from the sequence timings that reflect 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 on our 7T system. Noninteger values were permitted for the number of periods in the OGSE waveform to avoid discretization of the $\Delta/\sigma\Delta_D$ surface and improve the ability to observe trends in the results. A minimum of 2 OGSE periods was enforced (1 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.

3.3 | Optimized ADC difference mapping acquisition

A dMRI protocol was specified to maximize $\Delta D/\sigma_{\Delta D}$ based on our findings from Equation 6 (see the Results section), and was acquired in the same subjects. This scan consisted of 2 frequencies acquired with $b = 720 \text{ s/mm}^2$: standard PGSE ($\Delta_{e_{ff}} = 32 \text{ ms}$, 0 Hz), and cosine-modulated trapezoidal OGSE with frequency 38 Hz. The other parameters were 4 direction tetrahedral encoding with 6 averages each, $TE/TR = 82/8200 \text{ ms}$, $FOV = 200 \times 200 \text{ mm}^2$, 2 mm isotropic in-plane resolution, 48 slices (2 mm), and scan time 6 min. Acquisitions with $b = 0$ were not acquired.

All image reconstructions used an order 2 Kaiser-Bessel k-space filter to suppress Gibbs ringing (an order 3 filter was used for the multiple frequency scan, which had brighter CSF), PCA denoising before receiver combination, and SENSE-1 coil combination using a direct method that outputs real-valued signal.32
4 | RESULTS

4.1 | Multiple frequency OGSE

In the water phantom, ADC values were within 1% of the PGSE value at all OGSE frequencies (Supporting Information Figure S1). MD maps computed from the multiple-frequency scan were of comparable quality over all frequencies (Figure 2) and subjects (Supporting Information Figure S2). Over all subjects, the maximum likelihood estimation of $\theta$ was $0.47 \pm 0.05$, and $\Lambda$ ranged from $8 \pm 4 \mu m^2/s^{0.53}$ to $13 \pm 2 \mu m^2/s^{0.53}$, depending on the tract (Figure 3). Over all tracts, the mean apparent diffusion dispersion rate was $\Lambda=11\pm1 \mu m^2/s^{0.53}$. The mean SNR over all subjects and tracts was $20\pm5$ in the $b=450 \text{s/mm}^2$, 60 Hz raw images.

4.2 | Sequence optimization

Figure 4A shows $\Delta D/\sigma_{\Delta D}$ variation with $b$-value and $\omega$ for $T_2=60 \text{ ms}, D_{060}=0.7 \times 10^{-3} \text{ mm}^2/\text{s}, \omega=1/2$, and $\Lambda=10 \mu m^2/s^{1/2}$. The minimum required $TE$ for $\Delta D/\sigma_{\Delta D}$ values in Figure 4A are depicted in Figure 4B. Table 1 depicts the optimal acquisition parameters for a range of plausible $T_2$, $D_{060}, \theta$, and $\Lambda$ values. Notably, for all combinations of input parameters, the optimal $\Delta D/\sigma_{\Delta D}$ occurred when only the minimum of 2 OGSE periods were used. Accordingly, Figure 4C depicts the $\Delta D/\sigma_{\Delta D}$ with respect to $\omega$ and $b$ for 2 periods and the same $T_2, D_{060}, \theta$, and $\Lambda$ as in Figure 4A, assuming the gradients are used at the hardware maximum. Also visible from Table 1 is that the optimal choice of $\omega$ and $R_{op}$ only weakly depend on the input parameters and are near 40 Hz and 1 for all cases, respectively. Accordingly, a frequency of 38 Hz with 2 OGSE periods (corresponding to $b=720 \text{ s/mm}^2, TE=82 \text{ ms}$, and $R_{op}=1$) were chosen as parameters for the optimized 6-min in vivo diffusion dispersion scan.

4.3 | Optimized ADC difference mapping acquisition

Example $\Delta D$ maps computed from the optimized acquisition and corresponding DTI fractional anisotropy (FA) and MD maps are depicted in Figure 5. Example $\Delta D$ maps from multiple slices in all the subjects are shown in Supporting Information Figure S3. Notably, with the assumption of a

![FIGURE 2](image)

**FIGURE 2** Example MD maps in 1 subject where comparable image quality is observed across OGSE frequencies
consistent $\theta$ at all voxels, a $\Lambda$ map can be readily obtained by a simple global scaling of the $\Delta D$ map (Equation 2); accordingly, a scale bar for $\Lambda$ assuming $\theta = 1/2$ is also shown in Figure 5. Example sagittal images of $\Delta D$ and FA are shown in Figure 6, along with histograms over all subjects of $\Delta D$ (from the optimized scan) and the parallel eigenvalues, perpendicular eigenvalues, and FA (from the DTI scan) in regions of interest in the genu, body, and splenium. The mean values from the histograms are plotted in Supporting Information Figure S4. A trend toward increasing $\Delta D$ from the genu to splenium is observed, in contrast to a U-shaped variation of the diffusion parameters.

5 | DISCUSSION

In this work, evidence for a $\omega^{1/2}$ dependence of MD 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 and globally ischemic rodent brains. In addition, our finding of $\Lambda$ values $\sim 10 \mu m^2/s^{1/2}$ (Figure 3) agrees with ADC results reported at a field strength of 4.7T; for example, $\Lambda$ computed from the corticospinal tract using their reported ADC’s is approximately $10 \mu m^2/s^{1/2}$ when $\theta = 1/2$. Furthermore, optimal methods to acquire maps of the ADC difference between PGSE and OGSE without requiring $b = 0$ images were reported here, which enabled full-brain, clinical resolution maps of the MD difference in a scan time of 6 min. The PGSE/OGSE MD difference may be applicable as a new biomarker for pathology and, furthermore, may improve microstructural modeling approaches, as diffusion time dependencies can help resolve model fitting degeneracies. While the proposed optimized protocol does not provide an estimation of MD, the novel information that is available from OGSE is primarily $\Delta D$ and the acquisition of MD may be better served by a standard DTI acquired with a shorter TE and the same imaging parameters (field of view, resolution, resolution,
By including \( \omega = 0 \) in the fitting model, there is an implicit assumption that these experiments were in the long diffusion time regime (\( \omega \rightarrow 0 \)), similar to the analysis of rodent data by Novikov et al.\(^8\) In this regime, the observation of \( \theta = 1/2 \) in white matter is consistent with either highly correlated structural disorder or short-range disorder along 1 dimension.\(^8\)

**TABLE 1** \( \Delta D/\sigma_{\Delta D} \) optimization

<table>
<thead>
<tr>
<th>Tissue properties</th>
<th>Optimal diffusion encoding parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>( T_2 [\text{ms}] )</td>
<td>( \Lambda [\mu \text{m}^2/\text{s}^{1.8}] )</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>60</td>
<td>14</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
</tr>
</tbody>
</table>

Optimal diffusion encoding parameters (\( \omega, b\)-value, TE, and \( R_{op} \)) vary with \( T_2, D_{sat}, \theta, \) and \( \Lambda \). The optimal parameters for the nominal expected parameters are shown in the top row, while the other rows show the result of varying the highlighted cells with respect to the top row values. Notably, \( \omega \) and \( R_{op} \) are almost independent on the input parameters.

**FIGURE 5** Example MD, color-coded FA, and optimized \( \Delta D \) maps from multiple slices in 1 subject. MD and FA maps were computed from the standard DTI scan, and \( \Delta D \) maps were calculated from the optimized acquisition. A scale bar for \( \Lambda \) is also shown for the case when \( \theta = 1/2 \). Voxels with negative \( \Lambda \) are set to zero in the \( \Delta D \) maps, which generally occurs in the CSF.
Given that the permeability of myelinated axons is expected to be negligible at these diffusion times,21 and that the intracellular signal is expected to dominate the frequency dependence over extracellular, the latter explanation is favored. The assumption of a long diffusion time regime is likely appropriate given that preclinical studies have estimated that frequencies larger than 90 Hz are required to enter the short diffusion times even higher.

The above hypothesis that the frequency dependence is described by short-range disorder along the axons results in the interpretation that differences in $\Lambda$ (and $\Delta D$ for unchanged $\theta$) describe differences in the amount of disorder along the axons, which may include local variations of thickness or directionality along the axon. This assertion is supported by increases in $\Delta D$ observed acutely after stroke,35 where neurite beading increases disorder along the axons. Likewise, the observation in Figure 6 of decreased $\Delta D$ in the genu compared with the splenium is suggestive of less disorder along fibres, which may indicate more consistent axon or other fibre (e.g., astrocyte processes) directionality and/or thickness, or differing volume fractions of axons to support cell processes. Similar large differences of the DTI eigenvalues or FA between the genu and splenium were not observed, which suggests that $\Delta D$ provides complementary microstructural information to DTI.

The primary limitation of this study is that only 4 frequencies is not sufficient for a robust fit of $\theta$. Acquiring data at more frequencies is particularly difficult on human systems due to scan time constraints and because high frequencies drastically reduce the $b$-value, which in turn reduces the absolute signal differences between different frequencies (because $S_\omega = S_\omega e^{-\Delta D};$ see the Appendix). Low non-zero frequencies are also challenging because they require long TE to accommodate a full cosine period on each side of the 180° RF pulse. For example, including a frequency of 15 Hz in the multiple frequency scan would have required a prohibitively long TE of 178 ms. High-performance gradient systems with high slew rates and maximum gradient strengths would enable more robust estimation of $\theta$ and $\Lambda$ as they would allow access to higher OGSE frequencies. That said, the findings for optimizing a pulse sequence for measuring the ADC difference between PGSE and OGSE were only weakly dependent on $\theta$.

Our acquisition in a water phantom revealed biases of ADC $\sim 0.5\%$ compared with the mean over all frequencies. This may have been caused by eddy current artifacts or slightly nonlinear gradient amplifier gain at very high gradient amplitudes. Nevertheless, these deviations are small compared with the change in ADC of approximately 25% observed in human brain tissue between OGSE at 60 Hz and PGSE. Another potential source of bias for the optimized approach is the omission of $E$ (Equation 4), which was required to skip $b = 0$ acquisitions. However, for the optimized protocol implemented in this work, this would result in $E \sim 10^{-19}$ mm$^2$/s for $\theta = 1/2$, $\Lambda = 10$ mm$^2$/s$^{1/2}$ and $D_{\omega 0} = 0.7 \times 10^{-3}$ mm$^2$/s; accordingly, $E$ can likely be ignored in practice. Finally, it may also be tempting to further simplify Equation 4 to use the nominal $b$-value without any consideration of cross-terms; however, this would lead to an error in $\Delta D$ of approximately 7% and is accordingly not recommended.

The $\Delta D/\sigma_{\Delta D}$ computations suggested that an OGSE frequency $\sim 40$ Hz is optimal for a broad range of physiologically feasible values of $T_2$, $D_{\omega 0}$ and the diffusion dispersion power law scaling ($\theta$) and rate ($\Lambda$). However, the optimal values strongly depend on 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, in this case the optimal parameters are still obtained with only 2 OGSE periods, similar to the results here. 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 $\Delta D/\sigma_{\Delta D}$ achievable on human systems, remedying this spectral blurring may not be worth the $\Delta D/\sigma_{\Delta D}$ cost.

The noise propagation analysis did not consider Rician noise because real-valued images with Gaussian noise were used in this work. However, the results likely approximately apply to absolute value images with Rician noise because achieving $\Delta D$ maps with reasonable SNR requires the raw signal level for both OGSE and PGSE to be much higher than the noise floor (e.g., the optimal $\Delta D/\sigma_{\Delta D} < 5\%$ of the PGSE signal; Figure 4).

The optimized acquisition did not acquire any imaging volumes with $b = 0$, and the diffusion-weighted images (DWI) at the various frequencies were compared directly using Equation 4 with $E$ ignored. Notably, $b = 0$ images have extremely bright CSF, particularly at the long TE required for OGSE, which results in severe Gibbs ringing. When an MD is computed, the different Gibbs ringing profiles for $b = 0$ and diffusion-weighted acquisitions cause amplified ringing in MD maps.36 Because the computation of $\Delta D$ in Equation 4 compares only diffusion weighted signals with the same diffusion weighting, the CSF signal is fairly consistent, and this type of Gibbs ringing amplification is partially mitigated (Figure 7). That said, the CSF signal for PGSE is lower than for OGSE because of signal losses from incoherent flow (OGSE is inherently flow-compensated), which results in negative $\Delta D$ values in the fluid.9,18 Negative $\Delta D$ is not physiologically plausible in brain tissue, where diffusion is restricted/hindered and flow is absent31; accordingly, voxels with negative $\Delta D$ were masked in displayed images.

OGSE acquisitions on human systems use relatively low $b$-values, which may make estimations of diffusion dispersion sensitive to perfusion. For the acquisitions and fitted parameters to be insensitive to perfusion, the perfusion signal must be much less than the tissue signal at all frequencies used. In mice, no dependence on perfusion was observed for frequencies up to 200 Hz for $b > 300 \text{s/mm}^2$ (see Wu and Zhang22); accordingly, this assumption was likely satisfied here, where $b$-values of at least 450 s/mm² and a maximum frequency of only 60 Hz were used. On the other hand, at high $b$-values, higher order terms in the cumulant expansion of $D(\omega)$16 and rotational variance37,38 may need to be considered for accurate estimation of $\theta$ and $\Lambda$. However, at the $b$-values used here ($\leq 700 \text{s/mm}^2$), it is not expected that higher order terms or rotational variance affected our results.39

While $\theta = 1/2$ was implicated here in healthy human white matter, this may not be the case in other tissue types or in neurological disorders. Accordingly, care should be taken in the interpretation of changes in $\Delta D$ in pathology, which could result from a combination of $\theta$ and $\Lambda$ changes.

6 | CONCLUSIONS

In conclusion, we have provided evidence for a $\omega^{1/2}$ dependence of ADC in the in vivo human brain using OGSE diffusion MRI and developed an optimized acquisition
protocol that enabled full-brain mapping of ADC differences between PGSE and OGSE in a clinically relevant 6 min. The ability to rapidly probe diffusion dispersion in vivo opens the door for the exploration of new biomarkers and more sophisticated microstructural models.

**REFERENCES**


Neglecting the signal bias from omitting the \( b = 0 \) scan, the difference in mean ADC between OGSE and PGSE is, from Equation 4:

\[
\Delta D = \frac{-\ln (S_{o\alpha})}{b} + \frac{\ln (S_{o\beta})}{b},
\]

where \( S_{o\alpha} \) and \( S_{o\beta} \) are the OGSE and PGSE signals along the different encoding directions \( i \), respectively, \( b \) is the diffusion weighting, \( \omega^b \) is the frequency, \( N_o \) is the number of OGSE acquisitions, and \( N_{\alpha} \) is the number of PGSE acquisitions. To simplify variance propagation with a modest loss of generality, we will assume equal signal levels and \( b \)-values along all directions (i.e., isotropic diffusion and negligible gradient cross terms) and the same noise variance, \( \sigma \), for both PGSE and OGSE, which yields:

\[
\sigma^2_{\Delta D} = \frac{1}{N_o} \left( \frac{\partial \Delta D}{\partial S_o} \right)^2 \sigma^2 + \frac{1}{N_{\alpha}} \left( \frac{\partial \Delta D}{\partial S_{\alpha}} \right)^2 \sigma^2
\]

\[
= \sigma^2 \left( \frac{1}{N_o} \sigma^2_{S_o} + \frac{1}{N_{\alpha}} \sigma^2_{S_{\alpha}} \right)
\]

APPENDIX: Signal to noise ratio of \( \Delta D \) estimation

Neglecting the signal bias from omitting the \( b = 0 \) scan, the difference in mean ADC between OGSE and PGSE is, from Equation 4:

\[
\Delta D = \frac{-\ln (S_{o\alpha})}{b} + \frac{\ln (S_{o\beta})}{b},
\]

where \( S_{o\alpha} \) and \( S_{o\beta} \) are the OGSE and PGSE signals along the different encoding directions \( i \), respectively, \( b \) is the diffusion weighting, \( \omega^b \) is the frequency, \( N_o \) is the number of OGSE acquisitions, and \( N_{\alpha} \) is the number of PGSE acquisitions. To simplify variance propagation with a modest loss of generality, we will assume equal signal levels and \( b \)-values along all directions (i.e., isotropic diffusion and negligible gradient cross terms) and the same noise variance, \( \sigma \), for both PGSE and OGSE, which yields:

\[
\sigma^2_{\Delta D} = \frac{1}{N_o} \left( \frac{\partial \Delta D}{\partial S_o} \right)^2 \sigma^2 + \frac{1}{N_{\alpha}} \left( \frac{\partial \Delta D}{\partial S_{\alpha}} \right)^2 \sigma^2
\]

\[
= \sigma^2 \left( \frac{1}{N_o} \sigma^2_{S_o} + \frac{1}{N_{\alpha}} \sigma^2_{S_{\alpha}} \right)
\]

The relationship between \( S_{o\alpha} \) and the sequence parameters \( b \) and \( TE \), can be represented by \( S_{o\alpha} = C e^{-\omega^b T_E(b) T_z} \), where \( C \) is a constant related to receiver sensitivities and proton density and \( D_{o\alpha} \) is the ADC measured using PGSE. The function \( TE \) (in) depends on \( b \) and also implicitly depends on the gradient hardware limits and EPI timings. For OGSE, the \( b \)-value is increased by adding more periods on each side of the 180° RF pulse, which in turn lengthens the TE. Substituting this expression for \( S_{o\alpha} \) into Equation A4 and taking the square root yields:

\[
\sigma_{\Delta D} = C \sigma \left( \frac{1}{N_{o\alpha}} + \frac{e^{2bD_{o\alpha}} e^{2bT_E(b) T_z}}{N - N_{o\alpha}} \right)^{1/2} e^{2bD_{o\alpha} e^{2bT_E(b) T_z}}.
\]
\[ \frac{\Delta D}{\sigma_{\Delta D}} = SNR_0 \cdot b \Delta D \left( \frac{1}{N_{\omega_0}} + \frac{e^{2b\Delta D}}{N-N_{\omega_0}} \right)^{-\frac{1}{2}} e^{-bD_{\omega_0} e^{-TE(b)/T_2}}. \quad (A6) \]

Determination of the optimal OGSE frequency based on maximizing \( \Delta D/\sigma_{\Delta D} \) requires knowledge of the dependence of \( \Delta D \) on \( \omega \). Assuming a power law relationship, \( \Delta D = \Lambda \omega^{\theta} \), yields:

\[ \frac{\Delta D}{\sigma_{\Delta D}} = SNR_0 \cdot b \Lambda \omega^{\theta} \left( \frac{1}{N_{\omega_0}} + \frac{e^{2b\Lambda \omega^{\theta}}}{N-N_{\omega_0}} \right)^{-\frac{1}{2}} e^{-bD_{\omega_0} e^{-TE(b)/T_2}}. \quad (A7) \]

The optimal choices of \( b, \omega, \) and \( N_{\omega_0} \) can be straightforwardly determined numerically by performing an exhaustive search to find the combination that maximizes \( \Delta D/\sigma_{\Delta D} \). However, more insight into the optimal \( N_{\omega_0} \) can be obtained by taking the partial derivative with respect to \( N_{\omega_0} \) and setting the result to zero:

\[ -\frac{1}{2} \left( \frac{1}{N_{\omega_0}} + \frac{e^{2b\Lambda \omega^{\theta}}}{N-N_{\omega_0}} \right)^{-\frac{1}{2}} \left( -\frac{1}{N_{\omega_0}^2} + \frac{e^{2b\Lambda \omega^{\theta}}}{(N-N_{\omega_0})^2} \right) = 0. \quad (A8) \]

Recognizing that the ratio of OGSE acquisitions to PGSE acquisitions is \( R_{op} = (N-N_{\omega_0})/N_{\omega_0} \), Equation A8 simplifies to

\[ R_{op} = e^{b\Lambda \omega^{\theta}}. \quad (A9) \]

This motivates rearranging Equation A7 to include \( R_{op} \):

\[ \frac{\Delta D}{\sigma_{\Delta D}} = SNR_0 \sqrt{N_{\omega_0}} \cdot b \Lambda \omega^{\theta} \left( 1 + \frac{e^{2b\Lambda \omega^{\theta}}}{R_{op}} \right)^{-\frac{1}{2}} e^{-bD_{\omega_0} e^{-TE(b)/T_2}}. \quad (A10) \]

It is worth noting that, because the rate of diffusion dispersion \( \Lambda \) is directly proportional to \( \Delta D \), the SNR of an estimation of \( \Lambda \) is equivalent to the expression given in Equation A10 for an a priori known \( \theta \) (i.e., \( \Delta D/\sigma_{\Delta D} = \Lambda/\sigma_{\Lambda} \)).