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Measuring $^{129}$Xe transfer across the blood-brain barrier using MR spectroscopy

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Purpose: This study develops a tracer kinetic model of xenon uptake in the human brain to determine the transfer rate of inhaled hyperpolarized $^{129}$Xe from cerebral blood to gray matter that accounts for the effects of cerebral physiology, perfusion and magnetization dynamics. The $^{129}$Xe transfer rate is expressed using a tracer transfer coefficient, which estimates the quantity of hyperpolarized $^{129}$Xe dissolved in cerebral blood under exchange with depolarized $^{129}$Xe dissolved in gray matter under equilibrium of concentration.

Theory and Methods: Time-resolved MR spectra of hyperpolarized $^{129}$Xe dissolved in the human brain were acquired from three healthy volunteers. Acquired spectra were numerically fitted with five Lorentzian peaks in accordance with known $^{129}$Xe brain spectral peaks. The signal dynamics of spectral peaks for gray matter and red blood cells were quantified, and correction for the $^{129}$Xe $T_1$ dependence upon blood oxygenation was applied. $^{129}$Xe transfer dynamics determined from the ratio of the peaks for gray matter and red blood cells was numerically fitted with the developed tracer kinetic model.

Results: For all the acquired NMR spectra, the developed tracer kinetic model fitted the data with tracer transfer coefficients between 0.1 and 0.14.

Conclusion: In this study, a tracer kinetic model was developed and validated that estimates the transfer rate of HP $^{129}$Xe from cerebral blood to gray matter in the human brain.

KEYWORDS
blood-brain barrier, gas-exchange, hyperpolarized xenon-129, time-resolved magnetic resonance spectroscopy, tracer kinetic model

1 | INTRODUCTION

The blood-brain barrier (BBB) separates the intravascular space from the brain parenchyma, and is formed by specialized endothelial cells held together by tight junctions, covered by basal lamina and surrounded by pericytes, as shown in Figure 1. It acts as a selectively permeable barrier, which allows molecules essential for brain function through the barrier, while restricting the passage of noxious or neuroactive substances, and is vital for maintaining normal...
neuronal function. The consequence of a ruptured BBB is irregular transportation (and clearance) of gases, nutrients, water and other essential molecules across the barrier. These pathophysiological irregularities of an impaired BBB can be diagnostically assigned to various diseases processes, typically by observing the movement of a tracer across the barrier. Dysfunction of an intact BBB can also occur due to prolonged oxidative stress, causing deposition of plaque (example amyloid β), build-up of lipids, decline of pericytes, cognitive ability and brain function. This can occur even before the barrier becomes leaky or ruptured. For diagnosis, the two most commonly used tracers are iodinated contrast agent for X-ray CT and gadolinium chelated contrast agent for dynamic contrast enhanced MRI, neither of which cross an intact BBB, but are able to when it is leaky or ruptured. The arterial spin labeling (ASL) based MRI technique images magnetically tagged water molecules in the arterial blood delivered to brain tissue. Since the water molecules cross the intact BBB, this technique is being investigated for diagnosis of BBB diseases. Nevertheless, the technique has some limitations due to acquisition strategy (post labeling delay time, labeling plane) competing with physiology (longitudinal relaxation time, arterial transit time) and abundance of water molecules in the brain tissue (background noise, magnetization transfer).

Xenon is an exogenous tracer that passively crosses the intact BBB. Recently, hyperpolarized (HP) xenon-129 has been demonstrated as an agent to image the uptake of inhaled gas into human brain tissue after crossing the intact BBB by MRI, and the method has been shown to be repeatable. Preliminary clinical investigations of HP 129Xe brain MRI have shown novel and complementary image contrast for stroke, Alzheimer’s disease and functional brain imaging. HP 129Xe dissolved in the brain exhibits discrete chemical shifts for various biochemical compartments such as cerebral red blood cells (RBC), cerebrospinal/interstitial fluid, gray matter, white matter and soft muscular fat. The image signal-to-noise ratio (SNR) and contrast is weighted by regional cerebral perfusion, physiology (tissue compartmental volumes, temperature, blood pressure) and gas-transfer from cerebral blood to gray matter across the BBB, while the magnetization history of the HP 129Xe during its journey through these compartments is also factorial.

The transfer dynamics of HP 129Xe, a passive tracer, is not influenced by regional cellular metabolism, oxygen extraction or electrolytic balance. Thus, HP 129Xe MRI potentially holds unique information about the BBB by characterizing the passive transferability across the barrier. Nevertheless, this is influenced by the effects of regional brain physiology and perfusion. The HP aspect of the tracer adds further challenges as the MR detection is limited to the HP pool of 129Xe, but the gas transfer (membrane diffusion) dynamics are influenced by the concentration of all 129Xe atoms in the respective compartments, some of which may not be HP and therefore are undetectable.

This study develops a tracer kinetic model to determine the transfer rate of HP 129Xe from the cerebral blood to gray matter by considering the mass transfer of 129Xe irrespective of its status of hyperpolarization, with the aim of quantitatively measuring the compartmental transfer dynamics in brain tissue.

![Diagram of BBB and xenon transfer](image-url)
order to characterize the BBB function. In contrast to earlier mathematical modeling studies of $^{129}$Xe uptake in brain tissue that arrived at the concentration of $^{129}$Xe over time duration, the model presented here uses the concentrations of $^{129}$Xe in cerebral blood and gray matter compartments measured using NMR spectroscopy to estimate the transfer dynamics between them. The proposed model also considers the variation in longitudinal relaxation of $^{129}$Xe dissolved in the blood by monitoring the variation in oxygenation-dependent chemical shift of RBC spectral peak.

2 | THEORY

2.1 | Tracer kinetic model for HP $^{129}$Xe uptake in the brain

After inhalation of HP $^{129}$Xe, it crosses the alveolar-capillary barrier and is transported to the brain through the systemic circulation in approximately 4 s. In the brain, $^{129}$Xe crosses the intact BBB passively in to the brain parenchyma, and thereafter is under continuous diffusional exchange across the barrier. The cerebral blood volume of ~4 mL for 100 g of gray matter and cerebral capillary of radius 2.5~4 µm implies that the radius of the gray matter coaxial with the capillary and mean distance between capillaries would be 12.5~20 µm and 25~40 µm respectively, as shown in Figure 1. As the diffusion coefficient of xenon dissolved in the cerebral blood or gray matter has not been characterized, it can be approximated by using the diffusion coefficient dissolved in water of ~1 × 10$^{-5}$ cm$^2$ s$^{-1}$. Under these conditions, a 95% equilibrium of concentration of $^{129}$Xe between cerebral blood and gray matter is reached in 0.2~0.4 seconds. Hence, the NMR spectral peaks in time-resolved spectra that are acquired using a sequence repetition time (TR), that is longer than both the cerebral mean transit time ($\approx$3.3 s) and equilibrium time (0.4 s), are linearly proportional to the concentration in the respective biochemical compartments.

Consider time-resolved NMR spectroscopic acquisitions where each acquisition consists of a RF excitation pulse and subsequent saturation pulses. After every acquisition the bulk magnetization of HP $^{129}$Xe is depolarized (DP) to thermal equilibrium such that the NMR signal from further excitation of this pool of $^{129}$Xe in the brain is too weak to be detectable. Therefore, in each of the acquired time-resolved spectra, the spectral peaks do not represent the total quantity; instead, they represent the quantity of HP $^{129}$Xe accumulated between two consecutive NMR acquisitions. Nevertheless, there is continuous accumulation of DP $^{129}$Xe in the brain. Due to their respective discrete chemical shifts, the change in the relative concentration of HP $^{129}$Xe in cerebral blood and gray matter can be monitored over time, and thus HP $^{129}$Xe can be used as a tracer to examine the transfer dynamics across the shared barrier. Because there is a continuous arterial in-flow of HP $^{129}$Xe to the cerebral vasculature, the forward transfer ($T_F$) of $^{129}$Xe from cerebral blood to gray matter is HP $^{129}$Xe and therefore is detectable, annotated as $T_F$ in Figure 1. We define the $T_F$ rate as the quantity of HP $^{129}$Xe delivered to gray matter in the time duration (TR) between two successive acquisitions, considering both arterial in-flow of HP $^{129}$Xe and diffusional gas-exchange across the BBB. Due to the radiofrequency (RF) saturation pulses used after each acquisition, the backward transfer of $^{129}$Xe from gray matter to cerebral blood is DP $^{129}$Xe and therefore is undetectable, annotated as $T_B$ in Figure 1. NMR detection depends on the magnetization ($M$), which is proportional to the quantity ($Q$) and polarization of $^{129}$Xe, whereas the transfer dynamics depends on concentration ($C$), which is proportional to the quantity irrespective of its status of polarization.

For a given cerebral blood flow for gray matter $F$, partition coefficient of xenon between gray matter and blood $\lambda$, cerebral mean transit time $\psi$, cerebral blood volume $V_{Blood}$ per volume of gray matter $V_{GM}$, concentration of HP $^{129}$Xe in arterial blood $C_A$ and NMR spectral repetition time $t_{TR}$, using Fick’s principle developed for an inert gas tracer by Kety, we can arrive at the concentration of $^{129}$Xe in gray matter $C_{GM}$ for the time instance immediately after the ($n-1$)$^{th}$ RF acquisition as shown in Equation (1); nevertheless, this pool of $^{129}$Xe would be DP $^{129}$Xe.

$$C_{GM,DP} = \lambda C_A \left(1 - e^{-\frac{tTR}{\psi}}\right)$$

where, $F\lambda^{-1}V_{GM}^{-1} = V_{Blood}\lambda^{-1}V_{GM}^{-1}\psi^{-1} = V^{-1}\psi^{-1}$ and $V^{-1} = V_{Blood}\lambda^{-1}V_{GM}^{-1}$. The quantities of HP ($Q_{GM,HP}$) and DP ($Q_{GM,DP}$) $^{129}$Xe in the gray matter at the time instance at the $n^{th}$ RF acquisition are:

$$Q_{GM,HP} = \lambda V_{GM} C_A \left(1 - e^{-\frac{tTR}{\psi}}\right)$$

$$Q_{GM,DP} = \lambda V_{GM} C_A \left(1 - e^{-\frac{tTR}{\psi}}\right)$$

Such that, the total quantity of xenon is $Q_{GM} = Q_{GM,HP} + Q_{GM,DP}$. Between the time instances of the ($n - 1$)$^{th}$ and $n^{th}$ RF acquisition, there is continuous diffusional exchange of $^{129}$Xe between gray matter and cerebral blood. If we let $r$ be the fraction of $^{129}$Xe in gray matter that would exchange with $^{129}$Xe in cerebral blood, we have $Q_{GM} = (1 - r)Q_{GM} + rQ_{GM}$, where $rQ_{GM}$ is the quantity of $^{129}$Xe that would exchange with cerebral blood. Further, because we have two pools of $^{129}$Xe (HP and DP) in both gray matter and cerebral blood, for the fraction of $^{129}$Xe that would exchange with cerebral blood, we have four possibilities of
exchange: (i) HP\textsuperscript{129}Xe being replaced by HP\textsuperscript{129}Xe \( Q_{GM,HP\rightarrow HP} \), (ii) HP\textsuperscript{129}Xe being replaced by DP \( Q_{GM,HP\rightarrow DP} \), (iii) DP \( \text{HP}^{129}\text{Xe} \) being replaced by DP \( Q_{GM,DP\rightarrow DP} \), and (iv) DP \( \text{HP}^{129}\text{Xe} \) being replaced by HP \( Q_{GM,DP\rightarrow HP} \). Letting \( k_1 \) and \( k_2 \) be the factors that determine the fraction of \( 129\text{Xe} \) of a particular pool being replaced by the same pool, we can then derive the six-term expression:

\[
Q_{GM} = (1-r) \left( Q_{GM,HP} + Q_{GM,DP} \right) + r \left( k_1 Q_{GM,HP\rightarrow HP} + (1-k_1) Q_{GM,HP\rightarrow DP} \right) + k_2 Q_{GM,DP\rightarrow DP} + (1-k_2) Q_{GM,DP\rightarrow HP} \tag{3}
\]

The factors \( 1-k_1 \) and \( 1-k_2 \) are the tracer transfer constants that determine the fraction of one pool of \( 129\text{Xe} \) being replaced by the other pool. For simplicity of calculation in the current context, we use \( k = k_1 = k_2 \). In Equation (3), only the first, third, and last term relate to HP \( 129\text{Xe} \) which contributes to the NMR signal, thus rewriting and substituting from Equation (2), we have:

\[
Q_{GM,HP} = \lambda(V_{GM} C_A) \left[ (1-r(1-k)) \left( 1 - e^{-\frac{t_{GM-Blood}^2}{2}} \right) + r(1-k) \left( 1 - e^{-\frac{286}{t_{GM-Blood}}} \right) \right]. \tag{4}
\]

Equation (4) assumes that the gray matter compartment is solely in exchange with the cerebral blood compartment, and vice versa. The factor \( r \) that determines the fraction of \( 129\text{Xe} \) that would exchange with cerebral blood depends on several factors such as the capillary diameter, the mean distance between capillaries and the diffusivity of \( 129\text{Xe} \). Consider the diffusivity of \( 129\text{Xe} \) in water \( D = 1 \times 10^3 \text{ }\mu\text{m}^2\text{s}^{-1} \) and the mean diffusive displacement from gray matter volume to cerebral blood volume \( d_{GM-Blood} \) \( \approx 12.5 \sim 20 \mu\text{m} \) from Figure 1,\textsuperscript{10-45} the time taken \( t_{GM-Blood} \) for diffusion from gray matter to cerebral blood volume is approximately:

\[
t_{GM-Blood} = \frac{1}{2} d_{GM-Blood} D^{-1} \approx 75 \sim 200 \text{ ms}
\]

Thus, the factor \( r \) can be approximated as:

\[
r = \begin{cases} 
1 & \forall \left( t_{TR} - \psi \right) t_{GM-Blood}^{-1} > 1 \\
\frac{1}{t_{GM-Blood}} & \forall 1 > \left( t_{TR} - \psi \right) t_{GM-Blood}^{-1} > 0 \\
0 & \forall 0 > \left( t_{TR} - \psi \right) t_{GM-Blood}^{-1}
\end{cases}
\]

For the quantity of HP \( 129\text{Xe} \) in cerebral blood, \( Q_{Blood,HP} \), we have \( Q_{Blood,HP} = \frac{V_{Blood} C_A}{V_{Blood} C_A} \), where \( C_{Blood,HP} \) is the concentration of HP \( 129\text{Xe} \) in cerebral blood. Rearranging and integrating for the time interval \( t_{TR} \), we have; \( C_{Blood,HP} = \frac{t_{TR}}{V_{Blood} C_A} \), and \( Q_{Blood,HP} \) as:

\[
Q_{Blood,HP} = \frac{t_{TR}}{V_{Blood} C_A} \tag{5}
\]

Similarly, for the quantity of HP \( 129\text{Xe} \) in arterial blood \( Q_{A,HP} \), \( Q_{A,HP} = C_A V_A \), where \( V_A \) is the arterial blood volume between the lungs and the brain.

To corroborate tracer kinetics with the detected NMR spectroscopy, let \( M_0 \) be the bulk magnetization, such that \( M_0 = QP \Phi \), where \( Q \) is the quantity of \( 129\text{Xe} \) and \( \Phi \) depends on gyromagnetic ratio, reduced Planck’s constant and nuclear spin quantum number.\textsuperscript{48} \( P \) is the polarization of the sample, such that \( P_{HP} \) and \( P_{DP} \) are the polarization of the HP pool of \( 129\text{Xe} \) that is detectable and DP pool of \( 129\text{Xe} \) that is not detectable respectively. The magnetization in transverse plane is proportion to \( M_0 \), weighted by flip angle and transverse relaxation time \( T_2^* \). For a 90° flip angle, the acquired NMR signal is given by \( M_0 e^{2\pi f_0 t} e^{-\frac{t}{T_2^*}} \), where \( f_0 \) is the center frequency of the spectral peak. The corresponding Fourier transform is given by \( M_0 \left( T_2^* \right) e^{2\pi j f_0 t} + \frac{2\pi j f_0}{T_2^*} \right)^{-1} \), which is a Lorentzian function \( L(\delta, f) \) if we let \( T_2^* = (\pi \delta)^{-1} \), where \( \delta \) is the half power peak width. Further, integrating the spectrum, we have \( M_0 \int_0^\infty L(\delta, f) \approx M_0 \), and thus, the magnitude of the spectral peak \( (M_{GM,MBlood}) \) measures the quantity \( (Q_{GM,MBlood}) \) of \( 129\text{Xe} \) for a given polarization. \( P_{DP} \) depends on the strength of the static magnetic field, Boltzmann’s constant, gyromagnetic ratio, reduced Planck’s constant and temperature of \( 129\text{Xe} \).\textsuperscript{48} \( P_{HP} \) depends on the polarization achieved by the spin-exchange optical pumping process and \( P_{HP} \approx P_{DP} \). The polarization \( (P_{HP}) \) decays by longitudinal relaxation in several distinct biochemical compartments on its journey to the brain; in the gas-phase in the lungs \( T_{1GM} \) in the dissolved-phase in the blood \( T_{1Blood-Blood} \) during the lung-to-brain \( (\text{L} \rightarrow \text{B}) \) transit time \( T_{L-B} \) and in the dissolved-phase in the gray matter \( T_{1GM} \) during the TR \( (t_{TR}) \). Considering the decay of polarization, for a detectable NMR spectral peak at the \( n^{th} \) acquisition, we have the longitudinal magnetization as:

\[
M_A = \Phi P_{HP} \Gamma Q_{A,HP} e^{-\frac{t_{TR}}{T_{1GM}}} e^{-\frac{t_{TR}}{T_{Blood-Blood}}}
\]

\[
M_{Blood} = \Phi P_{HP} b_{RBC} Q_{Blood,HP} e^{-\frac{t_{TR}}{T_{Blood-Blood}}}
\]

\[
M_{GM} = \Phi P_{HP} Q_{GM,HP} e^{-\frac{t_{TR}}{T_{1GM}}}
\]

where, \( b_{RBC} \) is a scalar factor determining the quantity of \( 129\text{Xe} \) in the RBCs in the whole of the head when compared to the total quantity of \( 129\text{Xe} \) in cerebral blood that is in exchange with gray matter. \( I \) is a factor defining the dynamics of \( 129\text{Xe} \) signal in the lungs, such as exchange rate across the
alveolar-capillary barrier and the relative volumes/pressure of alveoli and Pulmonary capillaries. Considering the ratio of $M_{GM}$ by $M_{Blood}$ and rearranging the terms, we have:

$$
\frac{M_{GM}}{M_{Blood}} = \frac{Q_{GM,HP}}{e^{-\frac{\tau_{HP}}{\tau_{GM}}} h_{RBC} Q_{Blood,HP}}
$$

Equation (7) is the tracer kinetic model for transfer dynamics of HP $^{129}$Xe in the brain and is the estimate of the forward transfer $T_F$ rate in Figure 1. The transfer dynamic is independent of $Q_{A,NMR}$ and the term in the brackets in Equation (7) is a constant. Although $\frac{\tau_{HP}}{\tau_{Blood}}$ is independent of time, $T_{Blood}$ varies with the oxygenation of cerebral blood. Nevertheless, this dependence of $T_{Blood}$ is well established in the literature and the chemical shift of the RBC spectral peak can be used to monitor variations in blood oxygenation and apply a $T_1$ correction accordingly.\textsuperscript{32,50-52} Table 1 provides a list of the various parameters used in the study.

### 3 | METHODS

In vivo MR brain spectroscopy with $^{129}$Xe was performed with approval from the UK National Research Ethics Committee. Spectroscopic experiments were conducted on three healthy male volunteers aged 25 y, 33 y and 34 y, and repeated three times for each of the volunteers. The heart rate and SO\textsubscript{2} were monitored throughout the breath hold, which lasted no more than 24 s.

Experiments were performed on a GE HDx 1.5 T clinical MRI scanner. $^{129}$Xe gas was HP to $P_{HP} > 30\%$ polarization using a POLARIS (Sheffield, UK) regulatory approved spin exchange optical pumping polarizer.\textsuperscript{53} HP $^{129}$Xe gas of 500 mL was mixed with N\textsubscript{2} for a total inhaled dose of 1 L. An eight-leg band-pass birdcage RF coil was used\textsuperscript{27} for transceiver; with inner diameter of 300 mm and length of 295 mm. The gas mixture was administered by inhalation from a Tedlar bag as described in Rao et al.\textsuperscript{26} Time-resolved whole-brain spectra were acquired during a breath-hold, so that the HP $^{129}$Xe gas mixture was maintained as a reservoir in the lungs supplying the dissolved $^{129}$Xe plasma and RBC signal to the brain through alveolar-capillary gas exchange and onward through the systemic circulation.

MR spectroscopy parameters were as follows: center frequency = 17660800 Hz (198 ppm downfield from the $^{129}$Xe gas phase resonance), flip angle = 90°, non-selective RF hard-pulse with duration of 500 µs, receiver bandwidth = 1.2 kHz and number of sample points = 128. The acquisition time was ~107 ms, much longer than $T_2^*$ of $^{129}$Xe in RBC (2 ms\textsuperscript{54}) and gray matter (8.8 ms\textsuperscript{27}). TR was set to 4 s, which is longer than the typical cerebral mean transit time ($\Psi$) of 3.3 s\textsuperscript{39,46,47} and the equilibrium time of 0.4 s,\textsuperscript{45} assuming $\Psi$ will not increase by more than 20% during the breath-hold.\textsuperscript{55} Acquisition of time-resolved spectra was initiated immediately after the inhalation of the gas dose with two cycles of non-selective 90° RF pulses to destroy the polarization of the initial unknown quantity of HP $^{129}$Xe in the brain. After each subsequent pulse-acquire NMR spectroscopic acquisition, two non-selective 90° RF pulses were applied to destroy the polarization of the residual HP $^{129}$Xe.

A summation of five complex Lorentzian peaks in accordance with the known five spectral peaks of $^{129}$Xe dissolved in the human head\textsuperscript{27,36} was numerically fitted to the acquired NMR spectra, and each of the spectral peaks were quantified as a product of $\pi$, height and width of the peak. These quantified

### Table 1 | List of key parameters used for the tracer kinetic model and analysis

| Parameter | Symbol | Value | Reference |
|-----------|--------|-------|-----------|
| Cerebral blood volume for 100 g of gray matter $V_{GM}$ | $V_{Blood}$ | ~4 mL | 37-39 |
| Radius of cerebral capillaries | – | 2.5 ~ 4 µm | 40-43 |
| Mean distance between capillaries | – | 25 ~ 40 µm | 40-43 |
| Diffusion coefficient of $^{129}$Xe dissolved in water | $D$ | $1 \times 10^3$µm$^2$ s$^{-1}$ | 44 |
| Time to reach 95% equilibrium in concentration | – | 0.2 ~ 0.4 s | 45 |
| $^{129}$Xe Partition coefficient gray matter/blood | $\lambda$ | 0.88 | 56 |
| Cerebral mean transit time | $\psi$ | 3.3 s | 39,46,47 |
| Longitudinal relaxation of $^{129}$Xe in blood | $T_{1,\text{Blood}}$ | 4.5 s | 32,50-52 |
| Transverse relaxation of $^{129}$Xe in blood | – | 2 ms | 54 |
| Transverse relaxation of $^{129}$Xe in gray matter | – | 8.8 ms | 27 |
| Factor $r$ | $r$ | 1 | This study |
| $^{129}$Xe displacement time | $\tau_{GM-Blood}$ | 75 ~ 200 ms | This study |
| Repetition Time (TR) | $t_{TR}$ | 4 s | This study |
spectral peaks represent the bulk magnetization of HP $^{129}$Xe in corresponding compartments, namely $M_{GM}$ and $M_{Blood}$ for gray matter and cerebral RBC compartments, respectively.

The transfer dynamics of HP $^{129}$Xe between gray matter and cerebral blood was determined by evaluating the ratio of the time course of the spectral peaks of $^{129}$Xe in gray matter and cerebral RBC ($M_{GM}M_{Blood}^{-1}$). Using typical physiological values; cerebral blood volume for gray matter of 4 mL per 100 g of tissue, $^{37-39}$ cerebral mean transit time of 3.3 s $^{39,46,47}$ and the partition coefficient for xenon dissolved in gray matter to blood as $0.88^{56}$ (see Table 1); the tracer kinetic model in Equation (7) was rescaled and numerically fitted to the acquired transfer dynamics using a range of tracer transfer constants $(1 - k) = 0$ to $1$. The error in the numerical fit was calculated as the standard deviation of the difference between the tracer kinetic model from Equation (7) and the acquired transfer dynamic ratio, expressed as a percentage by normalizing by the mean value of the acquired transfer dynamic ratio.

4 | RESULTS

A typical series of time-resolved spectra acquired from the head of the 34-y-old male volunteer is shown in Figure 2A. Summation of five complex Lorentzian peaks fitted to the acquired spectrum in Figure 2A is shown in Figure 2B. The time course of the individual spectral peaks of HP $^{129}$Xe dissolved in cerebral RBC and gray matter is shown in Figure 2C and D, respectively.

Quantification of the spectral peaks for cerebral blood and gray matter is shown in Figure 3A along with the time course of the individual quantified spectral peaks. The chemical shifts of both individual spectral peaks over the time-course of the acquisition are shown in Figure 3B. Variation in chemical shift can be observed for the cerebral RBC peak. This indicates underlying variations in the oxygenation of cerebral blood and is used to determine the variation in $T_1$ associated with it. The time courses of both quantified individual spectral peaks are shown in Figure 3C. Figure 3C also shows the correction to the quantification of the cerebral RBC peak for variation in $T_1$ of $^{129}$Xe in the RBCs derived using the variation in chemical shift from Figure 3B.

The transfer dynamics of HP $^{129}$Xe between gray matter and cerebral blood is shown in Figure 4A, both with and without the correction for cerebral blood oxygenation applied to the RBC peak, along with the rescaled and fitted tracer kinetic model from Equation (7) for the tracer transfer constant $(1 - k) = 0.12$ . Extrapolation of the model to the case of steady-state xenon tissue saturation is shown in Figure 4B, and indicates that the forward transfer ($T_F$) rate of HP $^{129}$Xe reaches 95% saturation after approximately 200 s. The transfer dynamics of HP $^{129}$Xe

FIGURE 2  A, Acquired spectra for volunteer 34 y old, male. B, Artificially generated spectra comprising five complex Lorentzian peaks to numerically fit the acquired spectra in (A). Artificially generated complex Lorentzian peak for cerebral red blood cells (C) and gray matter (D).
between gray matter and cerebral blood for all the three volunteers for all the three repeats are shown in Figure 5.

For each of the acquisitions, the transfer dynamics with and without the correction for blood oxygenation, along with the variation in chemical shift of $^{129}$Xe in RBCs and the numerical fit of the tracer kinetic model in Equation (7) are shown. The developed tracer kinetic model returned values for the tracer transfer constant between 0.1 and 0.14 over the three volunteers. The error in the numerical fit was between 2.3% and 4.2% as indicated in Figure 5.
The unique aspects of the proposed MR spectroscopy technique based on a tracer kinetic model are as follows; First, the dynamics of the relative quantity of $^{129}$Xe is quantified using spectral peaks separated by their distinct chemical shifts, avoiding potential uncertainties related to non-specific binding and partial volume estimates for gray matter and blood which appear to vary with disease progression and aging in the brain.\(^{13,57-60}\) Second, the NMR signal from the tracer ($\text{HP}^{129}$Xe) once detected after RF excitation becomes NMR invisible ($\text{DP}^{129}$Xe), enabling the observation of the physiological dynamics of cerebral uptake and diffusional exchange.

An interesting observation of the model is that it predicts that the forward transfer ($T_F$) rate ($M_{\text{GM}}M_{\text{Blood}}^{-1}$ from Equation 7) increases until saturation. This is because, over time, $\text{DP}^{129}$Xe accumulates in the gray matter that will diffuse back ($\text{backward transfer}T_B$) in to cerebral blood and displace an equal amount of $\text{HP}^{129}$Xe ($\text{forward transfer}T_F$) from cerebral blood to gray matter. This exchange occurs without disrupting the equilibrium in concentration of overall $^{129}$Xe (irrespective of its status of polarization) between the two compartments. In addition, due to continuous arterial blood flow carrying fresh $\text{HP}^{129}$Xe to the head, the concentration of $\text{DP}^{129}$Xe in cerebral blood is much lower than that of gray matter increasing the likelihood of $\text{DP}^{129}$Xe in gray matter being replaced by $\text{HP}^{129}$Xe. Extrapolation of the model to 200 s and beyond indicates that the model ($M_{\text{GM}}M_{\text{Blood}}^{-1}$) quickly saturates and is $AV_{\text{GM}}C_A\beta_{\text{RBC}}^{-1}Q_{\text{Blood},\text{HH}}^{-1}e^{-\frac{7\phi}{1-V_{\text{GM}}V_{\text{Blood}}}}\left(1 - ke^{-2\phi}\right)$ at acquisition $n = \infty$. Nevertheless, this saturation time does not have physiological interpretation in the current context.

The factors $k_1$ and $k_2$ may not be equal, and estimating these factors individually and their inter-relationship is the scope of future study. The key limitations of the model are that the spectral measurements are performed over the whole brain, and thus average values are considered for cerebral blood flow, cerebral blood volume, mean transit time and gray matter volume. Using spatially resolved spectroscopy and for a known regional mean transit time and cerebral blood volume for gray matter, that can be estimated from $^1\text{H}$ MRI for example,\(^{61}\) the proposed tracer kinetic model estimates the regional efficacy of $^{129}$Xe transfer or uptake across the intact BBB. This might provide additional useful insight in to the underlying regional pathophysiology, such as BBB surface area and intact-barrier permeability/transferability changes. An in depth clinical investigation of the method in this aspect is the scope of future work. Also, if the mean transit time is known a priori, the NMR pulse repetition time can be optimized. Uncertainty in the estimation can be attributed to errors in the numerical fit of the spectra, which in turn can be attributed to the achieved SNR. Future studies will be aided by increases in the signal-to-noise ratio of the spectra, for example by using high-sensitivity radio frequency coils\(^{26}\) and improved polarization of $^{129}$Xe gas,\(^{53}\) and these improvements will hopefully facilitate a time-resolved spectroscopic imaging implementation of the global spectroscopy concept proposed here.

**FIGURE 4** A, Transfer dynamics of $^{129}$Xe between cerebral blood and gray matter, with and without correction of the RBC peak (see Figure 3C), along with a rescaled and fitted tracer kinetic model (from Equation 7) with a tracer transfer constant ($1-k$) = 0.12. Error bars calculated considering three repetitions. B, Extrapolation of the tracer kinetic model to illustrate that the forward transfer ($T_F$) rate of HP$^{129}$Xe reaches 95% saturation at approximately 200 s.
6 | CONCLUSIONS

In this study, we developed a tracer kinetic model for time-resolved NMR spectra of HP $^{129}$Xe in the human brain to estimate the transfer rate of HP $^{129}$Xe from cerebral blood to gray matter that depends on a tracer transfer constant for a known mean transit time and cerebral blood volume for gray matter. We believe this model will enable further studies to determine regional $^{129}$Xe tracer transfer constants with a focus of gaining insight into the pathophysiology of the BBB in diseases such as intact-barrier edema, arterial plaque, inflammation, infarct following stroke and to aid the assessment of drug delivery to the brain. In addition, in light of the passive nature of the xenon tracer, it could serve as a cross-reference for studies involving oxygen, water or glucose uptake, which are driven by metabolism and/or electrolytic balance.

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REFERENCES

1. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood–brain barrier. *Neurobiol Dis*. 2010;37:13-25.

2. Wintermark M, Sesay M, Barbier E, et al. Comparative overview of brain perfusion imaging techniques. *Stroke*. 2005;36:e83-e99.

3. Albers GW. Diffusion-weighted MRI for evaluation of acute stroke. *Neurology*. 1998;51(Suppl 3):S47-S49.

4. Brindle KM, Izquierdo-Garcia JL, Lewis DY, Mair RJ, Wright AJ. Brain Tumor Imaging. *J Clin Oncol*. 2017;35:2432-2438.

5. Burghart G, Finn CA. *Handbook of MRI scanning* - E-Book. Amsterdam, Netherlands: Elsevier Health Science; 2012.

6. Jack CR Jr, Bernstein MA, Fox NC, et al. The Alzheimer’s disease neuroimaging initiative (ADNI): MRI methods. *J Magn Reson Imaging*. 2008;27:685-691.

7. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer’s disease. *Alzheimers Dement*. 2018;14:535-562.

8. Pham-Huy LA, He H, Pham-Huy C. Free radicals, antioxidants in disease and health. *Int J Biomed Sci*. 2008;4:89-96.

9. Huang W-J, Zhang X, Chen W-W. Role of oxidative stress in aging using arterial spin labeling. *Proc Natl Acad Sci USA*. 2004;51:843-847.

10. Bell RD, Winkler EA, Sagare AP, et al. Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. *Neuron*. 2010;68:409-427.

11. Poon HF, Calabrese V, Scapagnini G, Butterfield DA. Free radicals and brain aging. *Clin Geriatr Med*. 2004;20:329-359.

12. Bell RD, Winkler EA, Sagare AP, et al. Pericytes control key neurovascular functions and neuronal phenotype in the adult brain and during brain aging. *Neuron*. 2010;68:409-427.

13. Heye AK, Culling RD, Valdés Hernández MDC, Thrippleton MJ, Wardlaw JM. Assessment of blood-brain barrier disruption using dynamic contrast-enhanced MRI. A systematic review. *Neuroimage Clin*. 2014;6:262-274.

14. Koenig M, Klotz E, Luka B, Venderink DJ, Spittler JF, Heuser L. Perfusion CT: a worthwhile enhancement of early CT findings before thrombolytic therapy. *Br J Radiol*. 2003;76:220-231.

15. von Kummer R, Allen KL, Holle R, et al. Acute stroke: usefulness of early CT findings before thrombolytic therapy. *Radiology*. 1997;205(2):327-333.

16. Gillard JH, Waldman AD, Barker PB. *Clinical MR Neuroimaging: Physiological and Functional Techniques*. Cambridge, UK: Cambridge University Press; 2009.

17. Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic resonance imaging of perfusion using spin inversion of arterial water. *Proc Natl Acad Sci USA*. 1992;89:212-216.

18. Detre JA, Zhang W, Roberts DA, et al. Tissue specific perfusion imaging using arterial spin labeling. *NMR Biomed*. 1994;7(2):75-82.

19. Alsop DC, Detre JA, Golay X, et al. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magn Reson Med*. 2015;73:102-116.

20. Wang DJJ, Alger JR, Qiao JX, et al. Multi-delay multi-parametric arterial spin-labeled perfusion MRI in acute ischemic stroke - comparison with dynamic susceptibility contrast enhanced perfusion imaging. *Neuroimage Clin*. 2013;3:1-7.

21. Ohene Y, Harrison IF, Nahavandi P, et al. Non-invasive MRI of brain clearance pathways using multiple echo time arterial spin labelling: an aquaporin-4 study. *NeuroImage*. 2019;188:515-523.

22. Shao X, Ma SJ, Casey M, D’Orazio L, Ringman JM, Wang DJJ. Mapping water exchange across the blood–brain barrier using 3D diffusion-prepared arterial spin labeled perfusion MRI. *Magn Reson Med*. 2019;81:3065-3079.

23. Schindlowski M, Boland M, Rüter T, Stücker T. Blood-brain barrier permeability measurement by biexponentially modeling whole-brain arterial spin labeling data with multiple T2-weightings. *NMR Biomed*. 2020;33:e4374.

24. Niibo T, Ohta H, Miyata S, Ikushima I, Yonenaga K, Takeda H. Prediction of blood-brain barrier disruption and intracerebral hemorrhagic infarction using arterial spin-labeling magnetic resonance imaging. *Stroke*. 2017;48:117-122.

25. Buxton RB, Frank LR, Wong EC, Siewert B, Warach S, Edelman RR. A general kinetic model for quantitative perfusion imaging with arterial spin labeling. *Magn Reson Med*. 1998;40:383-396.

26. Rao MR, Stewart NJ, Griffiths PD, Norquay G, Wild JM. Imaging human brain perfusion with inhaled hyperpolarized (129)Xe MRI imaging. *Radiology*. 2018;286:659-665.

27. Rao M, Norquay G, Wild JM. Assessment of repeatability of imaging inhaled hyperpolarized xenon-129 in the human brain. *Proc Int Soc Mag Reson Med*. 2019;27:3319.

28. Rao MR, Norquay G, Griffiths PD, Wild JM. High-resolution spectroscopy and chemical shift imaging of hyperpolarized (129) Xe dissolved in the human brain in vivo at 1.5 tesla. *Magn Reson Med*. 2016;75(6):2227-2234.

29. Hane FT, Li T, Plata J-A, Hassan A, Granberg K, Albert MS. Inhaled xenon washout as a biomarker of Alzheimer’s disease. *Diagnositics*. 2018;8:41.

30. Shepelytskyi Y, Hane FT, Grynkov V, Li T, Hassan A, Albert MS. Hyperpolarized 129Xe time-of-flight MR imaging of perfusion and brain function. *Diagnosis*. 2020;10:630.

31. Norquay G, Leung G, Stewart NJ, Tozer GM, Wolber J, Wild JM. Relaxation and exchange dynamics of hyperpolarized (129) Xe in human blood. *Magn Reson Med*. 2015;74:303-311.

32. Walker TG, Happer W. Spin-exchange optical pumping of noble-gas nuclei. *Rev Mod Phys*. 1997;69:629-642.

33. Peled S, Jolesz FA, Tseng CH, Nascimben L, Albert MS, Walsworth RL. Determinants of tissue delivery for Xe-129 magnetic resonance in humans. *Magn Reson Med*. 1996;36:340-344.

34. Martin CC, Williams RF, Gao JH, Nickerson LDH, Xiong JH, Fox PT. The pharmacokinetics of hyperpolarized xenon: Implications for cerebral MRI. *JMRI-J Magn Reson Imaging*. 1997;7:848–854.

35. Kilian W, Seifert F, Rinneberg H. Dynamic NMR spectroscopy of hyperpolarized 129Xe in human brain analyzed by an uptake model. *Magn Reson Med*. 2004;51:843-847.

36. Kandel E, Schwartz JH, Jessell T. *Principles of Neural Science*. New York City, USA: McGraw-Hill Medical; 2000.

37. Schidlowski M, Boland M, Rüter T, Stücker T. Blood-brain barrier permeability measurement by biexponentially modeling whole-brain arterial spin labeling data with multiple T2-weightings. *NMR Biomed*. 2020;33:e4374.

38. Kandel E, Schwartz JH, Jessell T. *Principles of Neural Science*. New York City, USA: McGraw-Hill Medical; 2000.

39. Leenders KL, Perani D, Lammertse MA, et al. Cerebral blood flow, blood volume and oxygen utilization: normal values and effect of age. *Brain*. 1990;113:27-47.

40. Rengachary SS, Ellenbogen RG. *Principles of Neurosurgery*. Maryland Heights, USA: Elsevier Mosby; 2005.
40. Duelli R, Kuschinsky W. Changes in brain capillary diameter during hypocapnia and hypercapnia. *J Cereb Blood Flow Metab.* 1993;13:1025-1028.

41. Duvernoy H, Delon S, Vannson JL. The vascularization of the human cerebellar cortex. *Brain Res Bull.* 1983;11:419-480.

42. Nicholson CP. Diffusion and related transport mechanisms in brain tissue. *Rep Prog Phys.* 2001;64:815-884.

43. Wong AD, Ye M, Levy AF, Rothstein JD, Bergles DE, Searson PC. The blood-brain barrier: an engineering perspective. *Front Neuroeng.* 2013;6:7.

44. Wise DL, Houghton G. Diffusion coefficients of neon, krypton, xenon, carbon monoxide and nitric oxide in water at 10-60°C. *Chem Eng Sci.* 1968;23:1211-1216.

45. Kety SS. The theory and applications of the exchange of inert gas at the lungs and tissues. *Pharmacol Rev.* 1951;3:1-41.

46. Ibaraki M, Ito H, Shimosegawa E, et al. Cerebral vascular mean transit time in healthy humans: a comparative study with PET and dynamic susceptibility contrast-enhanced MRI. *J Cereb Blood Flow Metab.* 2007;27:404-413.

47. Blinkov SM. *The Human Brain in Figures and Tables: A Quantitative Handbook.* Basic Books; 1968.

48. Haacke EM, Brown RW, Thompson MR, Venkatesan R. *Magnetic Resonance Imaging: Physical Principles and Sequence Design.* Wiley; 1999.

49. De Graaf RA. *In Vivo NMR Spectroscopy: Principles and Techniques.* Chichester, UK: John Wiley & Sons; 2019.

50. Norquay G, Collier GJ, Rao M, Stewart NJ, Wild JM. 129Xe-Rb spin-exchange optical pumping with high photon efficiency. *Phys Rev Lett.* 2018;121:153201.

51. Qing K, Ruppert K, Jiang Y, et al. Regional mapping of gas uptake by blood and tissue in the human lung using hyperpolarized xenon-129 MRI. *J Magn Reson Imaging: JMRI.* 2014;39:346-359.

52. Laitio RM, Kaisti KK, Langsjo JW, et al. Effects of xenon anesthesia on cerebral blood flow in humans - a positron emission tomography study. *Anesthesiology.* 2007;106:1128-1133.

53. Meyer JS, Hayman LA, Amano T, et al. Mapping local blood-flow of human-brain by CT scanning during stable xenon inhalation. *Stroke.* 1981;12:426-436.

54. González Ballester MÁ, Zisserman AP, Brady M. Estimation of the partial volume effect in MRI. *Med Image Anal.* 2002;6:389-405.

55. Tang C, Blatter DD, Parker DL. Accuracy of phase-contrast flow measurements in the presence of partial-volume effects. *J Magn Reson Imaging.* 1993;3:377-385.

56. Matsuda H, Ohsishi T, Asada T, et al. Correction for partial-volume effects on brain perfusion SPECT in healthy men. *J Nucl Med.* 2003;44:1243-1252.

57. Rao M, Norquay G, Wild JM. Investigating gas-exchange and tissue perfusion in the human brain using a combination of proton and hyperpolarized xenon-129 MRI. *Proc Intl Soc Mag Reson Med.* 2019;27:3095.

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