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Interleaved ^{31}P MRS Imaging of Human Frontal and Occipital Lobes using Dual RF Coils Incorporated with Single-Channel Transmitter-Receiver and Dynamic B_0 Shimming

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Abstract

In vivo ^{31}P MRS provides a unique tool for noninvasively studying brain energy metabolism and mitochondrial function. Assessment of bioenergetic impairment in different brain regions is essential to understand the pathophysiology and progression of human brain diseases. This paper presents a simple and effective approach allowing interleaved measurement of ^{31}P spectra and imaging from two distinct human brain regions of interest with dynamic B_0 shimming capability. A transistor-transistor logic controller was employed to actively switch the single-channel X-nuclear RF transmitter-receiver between two ^{31}P RF surface coils enabling to interleaved acquisition of two ^{31}P FIDs from human occipital and frontal lobes within the same repetition time. Linear gradients were incorporated into RF pulse sequence to perform the first-order dynamic shimming to further improve spectral resolution. The overall results demonstrate that the approach provides a cost-effective and time-efficient solution for reliable ^{31}P MRS measurement of cerebral phosphate metabolites and ATP metabolic fluxes from two human brain regions with high detection sensitivity and spectral quality at 7 Tesla. The same design concept can be extended to acquire multiple spectra from more than two brain regions or can be employed for other MR applications beyond the ^{31}P spin.

Graphical abstract

Illustration of dual—coil technique enabling interleaved ^{31}P MRS imaging from human occipital lobe (Coil 1) and frontal lobe (Coil 2) at 7 Tesla with the capability of dynamic B_0 shimming for obtaining high quality 3D CSI data as demonstrated from single voxel spectra as well as the maps of PCr integral measured from the frontal lobe (left panel) and occipital lobe (right panel).

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Disclosure

The authors declare no conflict of interest.

Keywords

*In vivo*³¹P MRS; human brain; high-energy phosphorous metabolism; neuroenergetics; dynamic B₀ shimming

1 | INTRODUCTION

*In vivo*³¹P magnetic resonance (MR) spectroscopy (MRS) provides a unique and non-invasive tool for assessing cerebral high-energy phosphate metabolites, phosphate lipid metabolism, intracellular pH and redox state of NAD (nicotinamide adenine dinucleotide) and neuroenergetics^{1–6}. Moreover, the ³¹P MRS technique incorporated with the magnetization transfer (MT) preparation (³¹P-MT MRS) offers new utility enabling researchers to non-invasively examine the kinetics of key bioenergetic reactions catalyzed by the creatine kinase (CK) and adenosine triphosphate (ATP) synthase (ATP_{ase}) and their metabolic fluxes^{7,8}. In this regard, *in vivo*³¹P or ³¹P-MT MRS studies have shown the bioenergetic impairment specifically in the frontal lobe in psychiatric patients like Schizophrenia⁹ and neurodegenerative diseases, like Alzheimer's disease^{10,11}.

With the increasing recognition of complex neurological disorders involving a behavioral and cognitive impairment commonly linking to dysfunction in specific brain regions^{12–16}, examination of functional and metabolic impairments in multiple brain regions of interest is essential to advance the understanding of underlying pathophysiological mechanisms and to improve diagnosis and treatment of diseases.

To detect *in vivo*³¹P spectra from multiple brain regions, one common approach is to employ a large size ³¹P radiofrequency (RF) coil in combination with three-dimensional (3D) chemical shift imaging (CSI) for measuring the ³¹P MRS signals across the whole brain^{17–19}. However, the presence of static magnetic field (B₀) inhomogeneity in critical human brain regions, particularly the frontal and temporal lobes as a result of the large susceptibility difference between the brain tissue and surrounding air cavity, poses a technical challenge for B₀ field shimming and obtaining high-quality ³¹P MRS data. Another limitation is relatively low detection sensitivity because of the large volume coil size, resulting in a low signal-to-noise ratio (SNR) or spatial resolution of CSI in the cortical regions of the human brain as compared to the use of RF surface coil(s). An alternative approach to overcome the technical limitations is to use multiple surface coils incorporated with multi-channel RF receivers and split RF transmission power from a single channel transmit or use transmitter-receiver (transceiver) arrays or volume coil^{20–23}. Despite the

merits of high detection sensitivity and large imaging coverage, these approaches require advanced hardware equipment such as multi-channel X-nuclear receivers or transceivers, which are not commonly available even for the MR scanners equipped with the X-nucleus MRS capability. Moreover, it is challenging to perform regional dynamic B_0 shimming for those brain regions prone to susceptibility artifact since all ^{31}P signals (or FIDs) from multiple RF receiver channels need to be acquired at the same time. For instance, strong B_0 inhomogeneity in the human frontal lobe causes a magnetic field distortion due to the susceptibility difference between air cavity and brain tissue, consequently a broader resonance linewidth and poor spectral quality²⁴. Therefore, it is a challenge to simultaneously obtain high-quality *in vivo* ^{31}P spectra or CSIs from distinct brain regions of interest for most MR scanners that are not equipped with advanced shimming technology^{25–28}.

To address these technical difficulties faced by most scanners, we herein present a simple and effective design that incorporates the transistor-transistor logic (TTL) controller and modified RF pulse sequence with an existing single-channel X-nuclear RF transceiver for rapid switching the RF transceiver connection and interleaved signal acquisition between two distanced ^{31}P RF surface coils covering the human occipital lobe (OL) and frontal lobe (FL), respectively. This design enables simultaneous assessment of the high-energy phosphorous metabolism from two human brain regions of interest at 7 Tesla (T) and supports the dynamic B_0 shimming utility for further improving the spectral quality of ^{31}P MRS or CSI acquired in the human FL: a difficult brain region to reach an optimal shimming. This method was validated using a phantom and in human brain.

2 | METHODS

All phantom and human experiments were carried out on a Siemens whole-body/90-cm bore 7T human scanner (MAGNETOM, Erlangen, Germany) equipped with single-channel broadband X-nuclear transceiver. *In vivo* brain ^{31}P MRS-MT experiments were performed on three healthy male volunteers (mean $\pm$ SD = 20 ± 1 years old), and the human study protocol was approved by the Institutional Review Board of the University of Minnesota. Informed consent was obtained from the participants prior to the MR measurement.

2.1 | Dual-coil ^{31}P MRS system

Figure 1 illustrates the configuration of the dual-coil ^{31}P MRS system consisting of two single-loop ^{31}P surface coils for acquiring ^{31}P MRS or chemical shift imaging (CSI) from the human OL (Channel 1) and FL (Channel 2), respectively; two passively decoupled butterfly-shape ^1H coils for anatomic MRI and B_0 shimming; a X-nuclear transmit-receiver (T/R) switch connecting with a single-channel RF power transmitter (Tx) and a single-channel RF receiver (Rx); and a TTL controller. The size of the single-loop ^{31}P surface coils (~ 5 cm diameter) was desired to ensure that the detected ^{31}P signal was dominated from the targeted brain tissue in the OL or FL with an optimized RF pulse flip angle. A home-built TTL controller comprised lumped elements controlled by a digital logic circuitry and a PIN diode. A TTL pulsed signal controlled by the MR console and RF pulse sequence was sent to the TTL controller for toggling the T/R switch (thus, the Tx/Rx connections) between the

two ^{31}P surface coils for interleaved RF transmission and acquisition of two ^{31}P FIDs from the OL and FL, respectively, within the same repetition time (TR). After placing the ^{31}P coils at the target brain regions, each coil resonator was tuned and matched separately with minimal mutual interference due to the small coil size and the large distance between the two coils.

The scheme of RF pulse sequence is designed for the interleaved acquisition of *in vivo* ^{31}P MR spectra from two brain regions with the option for dynamic B_0 shimming (Fig. 2). The sequence enables to collect regional ^{31}P FIDs from the brain regions defined by the RF magnetic field (B_1) profile of the ^{31}P surface coil without additional spatial localization, or to acquire 3D C SI data by adding 3D phase encoding gradients between the RF excitation pulse and analog-to-digital converter (ADC) acquisition. Two short TTL trigger pulses were inserted at the beginning of the first and second half of the TR period, respectively, for toggling the ^{31}P spin excitation and FID detection between the two ^{31}P coils: one (Channel 1) measured the FID from the OL and another (Channel 2) from the FL within the same TR. The acquired ^{31}P FIDs were alternatively saved in the same ADC and separated through the post data processing. The B_1 profiles of the two ^{31}P surface coils were not electronically coupled (the isolation was < -27 dB between the two coils), and the RF pulse delivered by one ^{31}P coil only affected the targeted brain region. Therefore, there was no signal saturation effect from the RF excitation pulse applied to another ^{31}P coil during the magnetization recovery, and the true repetition time for each channel's signal acquisition was the same as TR, thus, to maximize SNR.

The isolation between the two ^1H coils was -25 dB. The ^1H coils were driven as transceivers with adjustable RF amplitude and phase to optimize ^1H B_1 field and MRI signal intensities. Prior to ^{31}P MRS experiments using both ^1H coils, global B_0 shimming covering a rectangular box (with an oblique) including both the FL and OL regions was first carried out with a dual echo in the steady-state MRI pulse sequence incorporated with high-order shimming (up to 3rd order shim). Subsequently, the linear shimming in x, y and z directions was manually adjusted and optimized only for the FL region using the frontal ^1H RF coil to further improve spectral quality. The first-order shimming values were converted to the linear gradient strengths for before (G_x , G_y , G_z) and after ($G_{f,x}$, $G_{f,y}$, and $G_{f,z}$) the manual shimming, and the offset of linear shimming gradients ($\delta G_x = G_x - G_{f,x}$, $\delta G_y = G_y - G_{f,y}$, and $\delta G_z = G_z - G_{f,z}$) were turned on throughout the duration of the 2nd half of TR for dynamic shimming and acquiring optimized ^{31}P FID from the FL (see Fig. 2). The carrier frequencies of RF pulse and receiver were adjusted and optimized for the two ^{31}P coil channels, independently.

2.2 | ^{31}P -MT MRS measurement

A single-pulse-acquire sequence was carried out for studying cerebral high-energy phosphorous metabolisms in the human FL and OL. The ^{31}P -MT MRS technique was implemented using the B_1 insensitive selective train to obliterate signal scheme (BISTRO)²⁹ to selectively saturate the γ -ATP resonance (-2.5 ppm from the phosphocreatine (PCr) resonance); The crusher gradients (isosceles trapezoidal shape, ramp up/down time = 1 ms, top base time = 4 ms, amplitude = 40 mT/m, and a random order of either positive or

negative gradient sign) were inserted between the RF saturation pulses (hyperbolic secant RF pulse waveform, pulse length = 51.2 ms, saturation pulse bandwidth = 160 Hz or 1.3 ppm for ^{31}P MRS at 7T). Each BISTRO pulse train consisted 8 RF pulses with varied voltage amplitude and a scaling factor of 0.02, 0.04, 0.07, 0.14, 0.27, 0.49, 0.82, and 1, respectively; and the same BISTRO pulse train was repeated three times. The RF pulse power of the BISTRO trains was adjusted for optimal saturation of γ -ATP resonance. Total magnetization saturation duration was 1.37 s, and the pre-saturation delay time was 1.63 s for each RF coil channel, which could lengthen the TR time owing to the manner of interleaved acquisition. The control spectrum was also acquired in the absence of γ -ATP saturation.

Using a series of RF pulse input voltages, the reference RF power for nominal 90-degree excitation pulse flip angle (FA) for each ^{31}P coil was determined by the voltage which reaches the maximum signal intensity of PCr measured under full relaxation condition (TR = 20 s, FA = 90°, single average, and 500 μs hard pulse) and then reset to achieve an Ernst flip angle for γ -ATP for the desired TR. The ^{31}P -MT MRS data were acquired alternatively from the OL and FL using the acquisition parameters (TR = 3 s, spectral receiver bandwidth (BW) = 5 kHz, excitation (hard) pulse length = 300 μs , Ernst flip angle = 84.6°, number of complex FID points = 800, and number of signal average = 320).

All ^{31}P -MT spectra were processed using non-linear least squares fitting algorithm of the AMARES ³⁰ using jMRUI 5.2 software program ^{30,31} with the prior knowledge and fitting constraints including Lorentzian fitting, linewidth (Hz) and chemical shift ranges. Post-processing of the ^{31}P MR spectra included zero-filling of FIDs to 2048 data points. A spectral linewidth reported herein was measured in the phase mode after spectral phase correction, and determined by the full-width at half-maximum (FWHM) of the resonance peak without the use of line broadening.

The concentrations of ATP, PCr, and inorganic phosphate (Pi) metabolites in the human brain were determined from the control ^{31}P spectra (in the absence of γ -ATP saturation) after correcting a partial saturation factor due to the use of a short TR. Absolute concentrations of PCr and Pi were then calibrated using the cerebral ATP concentration of 2.8 mM as an internal reference ⁵. The forward reaction rate constants (k_f) under partially relaxed acquisition condition were calculated according to the following equation:

$$M_c/M_s \approx 1 + k_f \cdot T_1^{\text{nom}} \quad [1]$$

where M_c and M_s are control and γ -ATP saturated magnetization signal; T_1^{nom} is the nominal longitudinal relaxation time (T_1) that depends on the intrinsic T_1 values of ATP, PCr and Pi at a given magnetic field strength, TR and FA parameters ^{7,32}, and it was simulated and determined in this study. The forward reaction fluxes can be calculated by $F_{f,ATPase} = k_{f,ATPase} [\text{Pi}]_{\text{intra}}$ for the ATP_{ase} reaction and $F_{f,CK} = k_{f,CK} [\text{PCr}]$ for the CK reaction ^{6,32}, where $[\text{Pi}]_{\text{intra}}$ is the intracellular Pi concentration.

2.3 | pH Measurement

The intracellular and extracellular pH values were determined from the chemical shift difference of Pi (δ_{Pi}) relative to PCr based on the following equation using intracellular Pi ($\text{P}_{\text{i}}^{\text{in}}$) and extracellular Pi ($\text{P}_{\text{i}}^{\text{ex}}$) resonance signals, respectively ^{33,34}:

$$\text{pH} = 6.77 + \log_{10} [(\delta_{\text{Pi}} - 3.29) / (5.68 - \delta_{\text{Pi}})]. \quad [2]$$

2.4 | ^{31}P CSI measurement

With the application of 3D phase encoding gradients as shown in Fig. 2, 3D ^{31}P CSI was performed to explore the sensitivity for assessing the brain high-energy phosphate metabolites and to access the signal profile and coverage of the single-loop ^{31}P coils in the FL or OL. The ^{31}P MRS imaging was realized using the 3D Fourier series window (FSW) CSI technique; in which weighted k-space filtering was applied according to the Fourier coefficients for a predetermined voxel shape following an optimum determination of the Fourier series ³⁵. All ^{31}P FSW-CSI data for both RF coil channels were acquired using the same acquisition parameters: TR = 1.2 s, spectral BW = 5 kHz, excitation RF (hard) pulse length = 300 μs , Ernst flip angle ($\gamma\text{-ATP}$) = 67.1° , field of view = $120 \times 120 \times 90 \text{ mm}^3$, 3D phase encoding step = $7 \times 7 \times 5$, total k-space scan number = 112 per CSI volume, number of complex FID points = 800, number of signal average = 8. The nominal CSI voxel (3D cylindrical shape, and circular shape on the CSI plane) size was 5.3 ml, and the total CSI acquisition time was 18 minutes. Post-processing of the ^{31}P MRS or FSW-CSI voxel spectral data included zero-filling of FIDs to 2048 data points with a line broadening of 10 Hz for enhancing SNR.

The PCr and $\gamma\text{-ATP}$ resonance integral images were generated from the 3D FSW-CSI dataset using a home-built program coded in Matlab v14.0 (MathWorks, Natick, MA). After phase correction of the ^{31}P FSW-CSI voxel spectra in the frequency domain, the integrals of PCr and $\gamma\text{-ATP}$ resonance peaks were estimated and employed to reconstruct high-resolution images and spatial profiles using the established interpolation algorithm as well as the ratio maps between the PCr and $\gamma\text{-ATP}$ resonance integrals.

3 | RESULTS

Figure 3 shows the comparison results of *in vivo* ^{31}P spectral data from the human OL and FL acquired with and without the use of first-order dynamic B_0 shimming at 7T. In the absence of the dynamic B_0 shimming, the ^{31}P MR spectrum of the FL showed a broader linewidth and asymmetric shape of PCr resonance (Fig. 3B and 3D), resulting in a relatively low resonance intensity, thus, low SNR (=100). In contrast, the application of the calibrated offset linear gradients ($G = \pm 10 \mu\text{T/m}$) for optimal B_0 shimming of the FL region significantly improved the line shape and narrowed the linewidth (Fig. 3C, spectral linewidth or FWHM of PCr = 11.3 Hz or 0.09 ppm at 7T; SNR=130), reaching comparable quality of the ^{31}P spectra as in the OL (Fig. 3A, FWHM of PCr = 10.1 Hz, SNR = 140) for this representative subject.

We also compared the spectral linewidths of ^{31}P spectra acquired from the FL and OL regions from the same subject as shown in Fig. 3 under two acquisition conditions: dual-coil configuration with dynamic shimming (11.3 Hz in FL and 10.1 Hz in OL) versus regional shimming within the lobe of interest using a traditional single ^{31}P coil approach (10.3 Hz in FL and 9.0 Hz in OL). Therefore, the difference was small (about 1 Hz) between the two-coil (global plus dynamic shimming) and single-coil (optimal shimming focused on a single lobe of interest) configuration. The proposed method provides an effective approach for interleaved acquisition of ^{31}P spectra from two brain regions with high spectral resolution and quality.

Figure 4 displays typical *in vivo* ^{31}P -MT spectra in the absence (control) and the presence of γ -ATP saturation (i.e., MT) preparation (pointed by red arrows) acquired from the human OL (Fig. 4A and 4C) and FL (Fig. 4B and 4D) from two representative subjects. Overall, *in vivo* ^{31}P control spectra showed excellent quality and high sensitivity allowing for the reliable detection and quantification of the PCr, ATP, Pi and other phosphorus metabolite signals in healthy human brains. The ^{31}P -MT spectra with γ -ATP saturation indicated sufficient saturation efficiency at given MT preparation duration with optimal RF saturation powers for each ^{31}P RF coil channels.

The PCr concentrations measured in the OL and FL were 4.12 ± 0.11 mM and 4.08 ± 0.21 mM, respectively. The intracellular P_i^{in} concentrations for the OL and FL were 1.05 ± 0.04 mM and 0.94 ± 0.05 mM and corresponding extracellular P_i^{ex} concentrations were 0.34 ± 0.01 mM and 0.40 ± 0.03 mM, respectively, after the correction of the T_1 saturation effect for PCr (apparent $T_1 = 3.37$ s) and Pi (apparent $T_1 = 3.19$ s) ³⁶.

Under partially relaxed acquisition condition at given nominal excitation RF pulse flip angle and TR, estimated T_1^{nom} values for PCr and P_i^{in} were 1.91 s and 1.55 s, which were determined by the slopes of the solid lines in Fig. 5. The forward rate constants of $k_{f,\text{CK}}$ (for PCr $\rightarrow$ ATP reaction) were 0.389 ± 0.002 s⁻¹ and 0.32 ± 0.01 s⁻¹ for the OL and the FL, respectively, which are in good agreement with previously reported values ³². The forward rate constants of $k_{f,\text{ATP}}$ (for Pi $\rightarrow$ ATP reaction) were 0.14 ± 0.06 s⁻¹ for the OL, and 0.18 ± 0.02 s⁻¹ for the FL. Accordingly, the forward CK reaction fluxes were 87.5 ± 1.7 $\mu\text{mol/g/min}$ and 71.9 ± 1.6 $\mu\text{mol/g/min}$, and the forward ATP_{ase} reaction fluxes were 8.1 ± 3.7 $\mu\text{mol/g/min}$ and 9.4 ± 1.3 $\mu\text{mol/g/min}$ for the OL and FL, respectively, after the unit conversion using the brain tissue density of 1.1 g/ml ⁶.

The measured intracellular pH was 7.03 ± 0.01 identically for the OL and FL, and the pH result is consistent with the value of 7.03 in the human gray matter dominated brain regions ¹⁹. The extracellular pH was 7.45 ± 0.04 and 7.47 ± 0.01 for the OL and FL, respectively.

Figures 6 displays *in vivo* 3D ^{31}P CSI results from three representative image slices (Figs. 6B–6D; in coronal orientation) detected in the OL from one subject and corresponding maps of PCr (Figs. 6F–6H) and γ -ATP resonance integrals (Figs. 6I–6K), respectively. The large integral variation reflects the inhomogeneous B_1 and signal intensity profiles of the ^{31}P surface coil. In contrast, the ratio map between the PCr and γ -ATP integrals shows relatively

uniform distribution in the central brain region covered by the surface coil even without the correction of relaxation saturation effect because of the lack of information regarding the spatial distribution of RF pulse flip angle in this study. Figure 7 shows the similar results detected in the FL from the same subject. Given the proximity of the ^{31}P RF coils, each ^{31}P CSI showed a sufficient signal coverage and excellent detection sensitivity for the desired cortical lobes without signal overlapping between the two ^{31}P coils. In conjunction with the linear dynamic B_0 shimming, *in vivo* ^{31}P spectra taken from representative CSI voxels indicate comparable spectral quality with narrow resonance linewidth and excellent SNR for both the OL (Fig. 6E, SNR=60) and FL (Fig. 7E, SNR=45) regions.

Although two ^{31}P coils as employed in this study had the same coil design and size, the coil planes to conform the human head shape were different between the frontal and occipital lobes. The occipital-lobe ^{31}P coil plane was approximately parallel to the B_0 direction (or z axis, see Fig. 6) and it produced an optimal distribution of B_1 field (i.e., the transverse magnetic field component B_{xy}) for covering the occipital lobe. In contrast, the frontal-lobe ^{31}P coil plane was slightly tilted from the z axis for most subjects in order to conform the front head shape (see Fig. 7), resulting in a reduction in B_{xy} (accompanying by an increase in B_z), thus, reducing the detection sensitivity and ^{31}P signal in the frontal lobe. The degree of signal reduction varied between inter subjects depending on the front head shape and RF coil setup.

4 | DISCUSSION

We demonstrate a novel design of dual-coil ^{31}P MRS system for interleaved measurement and imaging of the regional high-energy phosphorous metabolism in two human brain regions of interest. Using an existing single channel X-nuclear RF transmit amplifier and receiver, ^{31}P MRS data were successfully collected from the frontal and occipital lobes within the same TR, providing a time-efficient way to reduce total acquisition time to half compared to the single acquisition approach for two brain regions, thus, for improving SNR by the square root of 2. Notably, with further adjustment of the linear gradients for dynamic shimming, the *in vivo* ^{31}P spectrum of the frontal brain region showed high-quality with better spectral line-shape compared to that without adjustment. This merit enables reliable assessment and quantification of the cerebral phosphorus metabolites in the frontal lobe which plays an essential role in high cognitive brain function. In addition, the 3D ^{31}P CSI results demonstrate sufficient signal coverage and good B_0 homogeneity achieved with the dual-coil ^{31}P MRS system, resulting in excellent spectral quality and phosphate metabolite images in distinct two brain regions.

As aforementioned, the putative presence of complex neurological symptoms commonly linked to neurodegenerative diseases have prompted the need for re-evaluating classic diagnostic/treatment approaches to the neurodegenerative disease. For instance, there has been a high association between clinical manifestations of motor restlessness in the upper motor system and cognitive impairments in the frontal areas in amyotrophic lateral sclerosis^{12,13}. In addition, the central viewpoint of upper motor dysfunction in Parkinson's disease has been revised due to frequent reports of non-motor symptoms encompassing cognitive dysfunction in the frontal lobe^{14,16} and visual dysfunction in the occipital

lobe^{37,38}. In this regard, the proposed method in this work capable of simultaneous assessment of the bioenergetic abnormalities in the target brain regions of interest could provide insights into the pathophysiology underlying neurodegenerative diseases.

Detection sensitivity or SNR is essential for *in vivo* MRS measurement as it significantly influences the accuracy and precision for assessing and quantifying cerebral metabolites not only for X-nuclei but also ¹H MRS^{39–42}. Moreover, low concentrations (a few millimolar) of the phosphate metabolites in the human brains become a daunting challenge for achieving high spatial or temporal resolution of ³¹P MRS imaging. Given the known lower sensitivity of RF volume coil, *in vivo* ³¹P MRS with application of two single-loop ³¹P surface coils in the present work shows higher detection sensitivity and excellent SNR in the desired cortical regions of interest in the human brain at 7T; thus, it could provide a valuable solution for addressing scientific questions demanding high SNR or imaging spatial resolution in the cortical regions of interest. The lack of physical proximity between the two RF surface coils inherently minimized unwanted interactions between the brain regions and allowed for discrete acquisition of *in vivo* ³¹P MRS data with comparable spectral quality within the same sampling time. Accordingly, the combination of the dual ³¹P surface coils with CSI method as demonstrated in this work bears considerable potential for further investigation of the correlation of high-energy phosphorous metabolism between different human brain regions or for functional imaging of neuroenergetic changes between rest and activated brain states with rich matrices of physiological measures including the high-energy phosphorous metabolites of ATP and PCr, $F_{i,ATPase}$ and $F_{i,CK}$, intra- and extra-cellular pH, intracellular free $[Mg^{+2}]$, metabolic precursors for phosphorous lipid metabolisms.

To homogenizing the B₀ field is an essential prerequisite to enhance spectral quality and resolution for all *in vivo* MRS applications. For this reason, several advanced B₀ shimming techniques have been proposed^{25–28}. Despite the substantial improvement of B₀ homogeneity, the availability of those methods is still limited to most conventional MR scanners. In addition, the current-state-of-the-art technology employing either multiple-channel receivers or transceivers acquires the FIDs from the multiple RF receiver coils at the same time, thus, is difficult to perform alternative and dynamic B₀ shimming for individual RF coils at a different time within a single TR period. Most of conventional MR systems including the scanner employed in the present study do not allow real-time updating of high-order shim currents owing to the eddy currents induced by fast switching shim currents and slow decays, leading to the degradation of spectral quality. The present study was limited to the first-order dynamic shimming using the linear gradients. Nevertheless, the concept of the alternative B₀ shimming among multiple RF coils within the same repetition time is not limited to the first-order shim, and it can be incorporated with other advanced dynamic shimming techniques enabling first- and higher-order dynamic shimming.

Early attempts at dynamic shimming showed the improved image quality by updating the linear shim terms dynamically in multi-slice imaging acquisition^{43,44} as well as in single-voxel ¹H MRS⁴⁵. We implemented this approach by adjusting linear gradients for first-order shimming of the FL region, providing the perceptible improved quality of *in vivo* ³¹P spectra in the FL comparable to that of the OL that is less problematic for achieving satisfactory B₀ shimming. On the other hand, two different shimming offsets could be readily incorporated

into the pulse sequence (Fig. 2) and employed alternatively to the two ^{31}P coils for further improving the spectral resolution in both brain regions.

In principle, *in vivo* MR spectra from multiple voxels could be acquired using a large (or volume) RF coil incorporated with one of single-voxel localization MRS methods (e.g., ISIS: Image Selected In Vivo Spectroscopy ⁴⁶, PRESS: Point Resolved Spectroscopy ⁴⁷; or STEM: Stimulated Echo Acquisition Mode ⁴⁸) and the option of dynamic shimming *if* the selected voxels are not spatially overlapped in a Cartesian coordinate system. Therefore, this approach is limited only to the oblique arrangement of multiple voxels and not suitable for the case if one is interested (for instance as investigated in the present study) in the human frontal and occipital lobes, which are aligned on the same sagittal plane. Although the voxel localization using multiple frequency-selective RF pulses could be not spatially overlapped between multiple voxels, the RF power delivered from all RF pulses employed to acquire multiple voxels will be absorbed by all brain regions covered by the RF coil. The average specific absorption rate (SAR) of the brain tissue approximately equals to the multiply of voxel numbers and the SAR required to collect a single voxel MRS. This could pose a safety concern especially at ultrahigh fields.

5 | CONCLUSION

We demonstrate that the new dual-coil ^{31}P MRS approach as described in this work could offer a cost-effective and time-efficient solution for interleaved *in vivo* ^{31}P MRS measurements and imaging from multiple desired brain regions based on an existing single-channel transmitter-receiver configuration with optimal SNR and spectral resolution. It could provide a valuable metabolic imaging tool for examining the cerebral energy metabolisms in healthy subjects and impairments in patients in desired and multiple brain regions. Moreover, the same approach and design can be: 1) extended to more than two RF coil channels, thus, covering more brain regions; 2) adapted to other X-nuclei or ^1H MRS; and 3) potentially used for functional MRI studies from multiple brain regions of interest with higher sensitivity and spatiotemporal resolution.

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ABBREVIATIONS

3D	three-dimensional
ADC	analog-to-digital converter
ATP	adenosine triphosphate
ATP_{ase}	ATP synthase
B₀	static magnetic field

CK	creatine kinase
CSI	chemical shift imaging
FA	flip angle
FID	free induction decay
FL	frontal lobe
FSW	Fourier series window
MR	magnetic resonance
MRS	MR spectroscopy
MT	magnetization transfer
NAD	nicotinamide adenine dinucleotide
OL	occipital lobe
PCr	phosphocreatine
Piⁱⁿ	intracellular inorganic phosphate
Pi^{ex}	extracellular inorganic phosphate
GPC	glycerophosphocreatine
GPE	glycerophosphoethanolamine
PC	phosphocholine
PE	phosphoethanolamine
RF	radiofrequency
SNR	signal-to-noise ratio
T	Tesla
TR	repetition time
TTL	transistor-transistor logic

References

1. Ackerman JJ, Grove TH, Wong GG, Gadian DG, Radda GK. Mapping of metabolites in whole animals by ³¹P NMR using surface coils. *Nature*. 1980; 283(5743):167–170. [PubMed: 7350541]
2. Bottomley PA, Charles HC, Roemer PB, et al. Human in vivo phosphate metabolite imaging with ³¹P NMR. *Magn Reson Med*. 1988; 7(3):319–336. [PubMed: 3205148]
3. Bottomley PA, Hardy CJ. Rapid, reliable in vivo assays of human phosphate metabolites by nuclear magnetic resonance. *Clin Chem*. 1989; 35(3):392–395. [PubMed: 2920404]

4. Du F, Cooper A, Lukas SE, Cohen BM, Ongur D. Creatine kinase and ATP synthase reaction rates in human frontal lobe measured by ^{31}P magnetization transfer spectroscopy at 4T. *Magn Reson Imaging*. 2013; 31(1):102–108. [PubMed: 22898695]
5. Zhu XH, Lu M, Lee BY, Ugurbil K, Chen W. In vivo NAD assay reveals the intracellular NAD contents and redox state in healthy human brain and their age dependences. *Proc Natl Acad Sci U S A*. 2015; 112(9):2876–2881. [PubMed: 25730862]
6. Lei H, Ugurbil K, Chen W. Measurement of unidirectional Pi to ATP flux in human visual cortex at 7 T by using in vivo ^{31}P magnetic resonance spectroscopy. *Proc Natl Acad Sci U S A*. 2003; 100(24):14409–14414. [PubMed: 14612566]
7. Xiong Q, Du F, Zhu X, et al. ATP production rate via creatine kinase or ATP synthase in vivo: a novel superfast magnetization saturation transfer method. *Circ Res*. 2011; 108(6):653–663. [PubMed: 21293002]
8. Du F, Zhu XH, Zhang Y, et al. Tightly coupled brain activity and cerebral ATP metabolic rate. *Proc Natl Acad Sci U S A*. 2008; 105(17):6409–6414. [PubMed: 18443293]
9. Du F, Cooper AJ, Thida T, et al. In vivo evidence for cerebral bioenergetic abnormalities in schizophrenia measured using ^{31}P magnetization transfer spectroscopy. *JAMA Psychiatry*. 2014; 71(1):19–27. [PubMed: 24196348]
10. Bottomley PA, Cousins JP, Pendrey DL, et al. Alzheimer dementia: quantification of energy metabolism and mobile phosphoesters with P-31 NMR spectroscopy. *Radiology*. 1992; 183(3):695–699. [PubMed: 1584923]
11. Smith CD, Pettigrew LC, Avison MJ, et al. Frontal lobe phosphorus metabolism and neuropsychological function in aging and in Alzheimer's disease. *Ann Neurol*. 1995; 38(2):194–201. [PubMed: 7654066]
12. Ferrari R, Kapogiannis D, Huey ED, Momeni P. FTD and ALS: a tale of two diseases. *Curr Alzheimer Res*. 2011; 8(3):273–294. [PubMed: 21222600]
13. Phukan J, Elamin M, Bede P, et al. The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. *J Neurol Neurosurg Psychiatry*. 2012; 83(1):102–108. [PubMed: 21836033]
14. Taylor AE, Saint-Cyr JA, Lang AE. Frontal lobe dysfunction in Parkinson's disease. The cortical focus of neostriatal outflow. *Brain*. 1986; 109(Pt 5):845–883. [PubMed: 3779372]
15. Weil RS, Schrag AE, Warren JD, Crutch SJ, Lees AJ, Morris HR. Visual dysfunction in Parkinson's disease. *Brain*. 2016; 139(11):2827–2843. [PubMed: 27412389]
16. Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM. Cognitive impairments in early Parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. *J Neurosci*. 2003; 23(15):6351–6356. [PubMed: 12867520]
17. Zhang, XL., Zhu, XH., Qiao, HY., et al. A circular-polarized double-tuned (^{31}P and ^1H) TEM coil for human head MRI/MRS at 7T. Paper presented at: Proceeding of Annual Meeting of International Society for Magnetic Resonance in Medicine (ISMRM); 2003; Toronto, Canada.
18. Avdievich NI, Hetherington HP. 4 T Actively-Detuneable Double-Tuned $^1\text{H}/^{31}\text{P}$ Head Volume Coil and Four-Channel ^{31}P Phased Array for Human Brain Spectroscopy. *Journal of magnetic resonance*. 2007; 186(2):341–346. [PubMed: 17379554]
19. Zhu XH, Qiao H, Du F, et al. Quantitative imaging of energy expenditure in human brain. *Neuroimage*. 2012; 60(4):2107–2117. [PubMed: 22487547]
20. Lee RF, Giaquinto R, Constantinides C, Souza S, Weiss RG, Bottomley PA. A broadband phased-array system for direct phosphorus and sodium metabolic MRI on a clinical scanner. *Magn Reson Med*. 2000; 43(2):269–277. [PubMed: 10680691]
21. Hardy CJ, Bottomley PA, Rohling KW, Roemer PB. An NMR phased array for human cardiac ^{31}P spectroscopy. *Magn Reson Med*. 1992; 28(1):54–64. [PubMed: 1435221]
22. Avdievich NI. Transceiver-Phased Arrays for Human Brain Studies at 7 T. *Appl Magn Reson*. 2011; 41(2–4):483–506. [PubMed: 23516332]
23. Mirkes C, Shajan G, Chadzynski G, Buckenmaier K, Bender B, Scheffler K. ^{31}P CSI of the human brain in healthy subjects and tumor patients at 9.4 T with a three-layered multi-nuclear coil: initial results. *MAGMA*. 2016; 29(3):579–589. [PubMed: 26811174]

24. Juchem C, de Graaf RA. B₀ magnetic field homogeneity and shimming for in vivo magnetic resonance spectroscopy. *Anal Biochem.* 2017; 529:17–29. [PubMed: 27293215]
25. Juchem C, Nixon TW, McIntyre S, Boer VO, Rothman DL, de Graaf RA. Dynamic multi-coil shimming of the human brain at 7 T. *J Magn Reson.* 2011; 212(2):280–288. [PubMed: 21824794]
26. Stockmann JP, Witzel T, Keil B, et al. A 32-channel combined RF and B₀ shim array for 3T brain imaging. *Magn Reson Med.* 2016; 75(1):441–451. [PubMed: 25689977]
27. Darnell D, Truong TK, Song AW. Integrated parallel reception, excitation, and shimming (iPRES) with multiple shim loops per radio-frequency coil element for improved B₀ shimming. *Magn Reson Med.* 2017; 77(5):2077–2086. [PubMed: 27174387]
28. Pan JW, Lo KM, Hetherington HP. Role of very high order and degree B₀ shimming for spectroscopic imaging of the human brain at 7 tesla. *Magn Reson Med.* 2012; 68(4):1007–1017. [PubMed: 22213108]
29. de Graaf RA, Luo Y, Garwood M, Nicolay K. B₁-insensitive, single-shot localization and water suppression. *J Magn Reson B.* 1996; 113(1):35–45. [PubMed: 8888589]
30. Vanhamme L, van den Boogaart A, Van Huffel S. Improved method for accurate and efficient quantification of MRS data with use of prior knowledge. *J Magn Reson.* 1997; 129(1):35–43. [PubMed: 9405214]
31. Naressi A, Couturier C, Castang I, de Beer R, Graveron-Demilly D. Java-based graphical user interface for MRUI, a software package for quantitation of in vivo/medical magnetic resonance spectroscopy signals. *Comput Biol Med.* 2001; 31(4):269–286. [PubMed: 11334636]
32. Du F, Zhu XH, Qiao H, Zhang X, Chen W. Efficient in vivo ³¹P magnetization transfer approach for noninvasively determining multiple kinetic parameters and metabolic fluxes of ATP metabolism in the human brain. *Magn Reson Med.* 2007; 57(1):103–114. [PubMed: 17191226]
33. Petroff OA, Prichard JW, Behar KL, Alger JR, den Hollander JA, Shulman RG. Cerebral intracellular pH by ³¹P nuclear magnetic resonance spectroscopy. *Neurology.* 1985; 35(6):781–788. [PubMed: 4000479]
34. Patel N, Forton DM, Coutts GA, Thomas HC, Taylor-Robinson SD. Intracellular pH measurements of the whole head and the basal ganglia in chronic liver disease: a phosphorus-31 MR spectroscopy study. *Metab Brain Dis.* 2000; 15(3):223–240. [PubMed: 11206591]
35. Hendrich K, Hu X, Menon RS, et al. Spectroscopic imaging of circular voxels with a two-dimensional Fourier-series window technique. *J Magn Reson B.* 1994; 105(3):225–232. [PubMed: 7850168]
36. Lei H, Zhu XH, Zhang XL, Ugurbil K, Chen W. In vivo ³¹P magnetic resonance spectroscopy of human brain at 7 T: an initial experience. *Magn Reson Med.* 2003; 49(2):199–205. [PubMed: 12541238]
37. Davidsdottir S, Cronin-Golomb A, Lee A. Visual and spatial symptoms in Parkinson's disease. *Vision Res.* 2005; 45(10):1285–1296. [PubMed: 15733961]
38. Uc EY, Rizzo M, Anderson SW, Qian S, Rodnitzky RL, Dawson JD. Visual dysfunction in Parkinson disease without dementia. *Neurology.* 2005; 65(12):1907–1913. [PubMed: 16282276]
39. Gruber S, Mlynarik V, Moser E. High-resolution 3D proton spectroscopic imaging of the human brain at 3 T: SNR issues and application for anatomy-matched voxel sizes. *Magn Reson Med.* 2003; 49(2):299–306. [PubMed: 12541250]
40. Bartha R. Effect of signal-to-noise ratio and spectral linewidth on metabolite quantification at 4 T. *NMR Biomed.* 2007; 20(5):512–521. [PubMed: 17205487]
41. Macri MA, Garreffa G, Giove F, et al. In vivo quantitative ¹H MRS of cerebellum and evaluation of quantitation reproducibility by simulation of different levels of noise and spectral resolution. *Magn Reson Imaging.* 2004; 22(10):1385–1393. [PubMed: 15707788]
42. Kreis R. Issues of spectral quality in clinical ¹H-magnetic resonance spectroscopy and a gallery of artifacts. *NMR Biomed.* 2004; 17(6):361–381. [PubMed: 15468083]
43. Blamire AM, Rothman DL, Nixon T. Dynamic shim updating: a new approach towards optimized whole brain shimming. *Magn Reson Med.* 1996; 36(1):159–165. [PubMed: 8795035]
44. Morrell G, Spielman D. Dynamic shimming for multi-slice magnetic resonance imaging. *Magn Reson Med.* 1997; 38(3):477–483. [PubMed: 9339449]

45. Keating B, Ernst T. Real-time dynamic frequency and shim correction for single-voxel magnetic resonance spectroscopy. *Magn Reson Med*. 2012; 68(5):1339–1345. [PubMed: 22851160]
46. Ordidge RJ, Connelly A, Lohman JAB. Image-selected in vivo spectroscopy (ISIS). A new technique for spatially selective NMR spectroscopy. *J Magn Reson*. 1986; 66:283–294.
47. Bottomley PA. Spatial localization in NMR spectroscopy in vivo. *Ann N Y Acad Sci*. 1987; 508:333–348. [PubMed: 3326459]
48. Frahm J, Merboldt KD, Hancic W. Localized proton spectroscopy using stimulated echoes. *J Magn Reson*. 1987; 72:502–508.

Figure 1. Schematic illustration of the dual-coil ^{31}P MRS system for simultaneous measurement or imaging of ^{31}P -containing metabolites from two brain regions of interest. (A) The system consists of a ^{31}P T/R switch with single-channel RF transmitter and receiver, two butterfly-shape ^1H RF coils, two single-loop ^{31}P RF surface coils and TTL controller between the T/R switch and the ^{31}P coils. With the existing single-channel RF transmitter-receiver configuration for X-nuclear application, the TTL switcher toggles the RF transmit power and signal reception between the two ^{31}P coil channels: Channel (or Coil) 1 for detecting ^{31}P signals from the OL, and Channel (or Coil) 2 for detecting ^{31}P signals from the FL in human brain. (B) The size and geometry of each coil were determined based on the signal coverage and location of the targeted brain regions. D is the diameter of single-loop ^{31}P surface coils, whereas H, W, and L represent the size of the butterfly-shape ^1H coils.

Figure 2.

Schematic illustration of the dual-coil ^{31}P -MT pulse sequence with 3D-CSI capability. This sequence is designed for acquiring either non-localized MRS FIDs or 3D chemical shift imaging data in the absence or presence of 3D phase encoding gradients, respectively. ^{31}P spectra from two channels are acquired alternatively by switching each RF coil channel at the time of $\text{TR}/2$ by sending the TTL pulse from the MR scanner. For further improving B_0 field homogeneity and ^{31}P spectral quality, the adjusted linear gradients are applied to the 2^{nd} TR to perform dynamic B_0 shimming and optimize the ^{31}P spectral quality for the FL. The BISTRO pulse train can be turned on prior to the RF excitation pulse for selectively saturating the γ -ATP resonance and performing the ^{31}P -MT MRS study.

Figure 3.

Comparison of *in vivo* ^{31}P spectra (TR = 3 s, 320 signal averages, 16 minutes of acquisition time per spectrum) in the healthy human brain. *In vivo* ^{31}P spectra were acquired in the OL (A, the PCr resonance outlined by the black dotted line) and in the FL with (C, blue dotted line) and without adjustment of the 1st order gradients (B, red dotted line). (D) Comparison of PCr resonance spectral quality shows a significant improvement in the FL using the dynamic B_0 shimming approach. Pi^{in} : intracellular inorganic phosphate; Pi^{ex} : extracellular inorganic phosphate; GPC: glycerophosphocreatine; GPE: glycerophosphoethanolamine; PC: phosphocholine; PE: phosphoethanolamine.

Figure 4.

Representative *in vivo* ^{31}P -MT spectra simultaneously detected from the OL and FL from healthy human subjects. Top panels (A and C) show the respective ^{31}P control spectra and ^{31}P -MT spectra (with γ -ATP saturation pointed by the red arrows) acquired from the OL, while the bottom panels (B and D) show the control and ^{31}P -MT spectra from the FL. Overall, the ^{31}P MR spectra from the two brain regions show excellent spectral quality and adequate MT saturation efficiency in two representative subjects (TR = 3 s, 320 signal averages, 16 minutes of acquisition time per spectrum).

Figure 5.

Simulated results of M_C/M_S versus forward reaction rate constant (k_f) plot for CK (A) and ATP_{ase} (B) reactions of the human brain at 7T under partial relaxation condition ($TR = 3$ s, $FA = 84.6^\circ$, pre-saturation time delay ($d1$) = 1.63 s). Intrinsic T_1 s for PCr, γ -ATP, and Pi are 4.86, 1.35, and 3.77 s³². Estimated nominal T_1 values (T_1^{norm} , the slope for each solid line plot) for PCr and Pi were 1.91 and 1.55 s, respectively. The simulated T_1^{norm} values were employed to calculate the k_f values for CK and ATP_{ase} reactions according to Equation [1].

Figure 6.

Representative *in vivo* ^{31}P 3D CSI data, PCr and γ -ATP maps, and their ratio map from the human occipital lobe overlaid on the coronal anatomical images. Panel A displays the location of a single-loop ^{31}P coil (Channel 1, blue bar) placed near the OL, the field of view, and slice positions of the 3D ^{31}P -CSI; (B–D) displays the ^{31}P MRS profiles from three selected CSI slices; (E) A single-voxel ^{31}P spectrum denoted in yellow circle in (C) shows excellent detection sensitivity at the given spatial- and temporal-resolution; (F–H) shows the corresponding normalized PCr maps (by setting the maximum peak integral of PCr to 1); (I–K) shows the corresponding normalized γ -ATP maps; (L) shows the ratio map between the PCr and γ -ATP in the region of interest (ROI) as indicated by the white box in (C). ^{31}P CSI data acquired with a single-loop coil clearly demonstrate a sufficient signal coverage (reaching ~ 5.4 cm depth).

Figure 7.

Representative *in vivo* ^{31}P 3D CSI data, PCr and γ -ATP maps, and their ratio map from the human frontal lobe overlaid on the coronal anatomical images. Panel A displays the location of a single-loop ^{31}P coil (Channel 2, blue bar) placed near the FL, the field of view, and slice positions of the 3D ^{31}P -CSI; (B–D) displays the ^{31}P MRS profiles from three selected CSI slices; (E) With dynamic B_0 shimming, the single-voxel ^{31}P MR spectrum (the yellow circle in (C)) shows excellent spectral quality and detection sensitivity; (F–H) shows the corresponding normalized PCr maps; (I–K) shows the corresponding normalized γ -ATP maps; (L) shows the ratio map between the PCr and γ -ATP in the ROI as indicated by the white box in (C). 3D ^{31}P CSI data demonstrate the brain regions with the highest signal detected by the ^{31}P coil was approximately 2.5 cm from the surface of the frontal lobe (Slice 2), which covers critical brain regions including medial frontal gyrus and cingulate gyrus.