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PHOSPHORUS-31 MR SPECTROSCOPY OF THE HUMAN BRAIN : TECHNICAL ASPECTS AND BIOMEDICAL APPLICATIONS

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ABSTRACT

Phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) is a non-invasive method that provides useful information about metabolism and phosphoenergetic status in both physiologic and pathologic conditions of the human brain. With the progressive advances in magnetic resonance imaging (MRI) technology, particularly with higher magnetic field strengths, ^{31}P-MRS has been more easily implemented and more readily available in the past few years, which has increasingly extended its access and favored its use in different research fields. However, the current knowledge about this advanced neuroimaging modality is still scarce and fragmented in the literature. Hence, in order to contribute to future researches and to shorten the gap between neuroscientific studies and common clinical routines, we present a comprehensive review about the basic technical aspects and biomedical applications of ^{31}P-MRS.

Keywords: ^{31}P-MRS, MRI, phosphorus spectroscopy, magnetic resonance imaging, neurometabolism, energetics, phospholipids, pH, magnesium, cell membrane

INTRODUCTION

Magnetic resonance spectroscopy (MRS) offers the unique ability to noninvasively measure, in vivo, the chemical composition of biological tissues. This method can be combined to the anatomic information provided by magnetic resonance imaging (MRI), giving functional data that can improve the understanding of the pathophysiological processes at a molecular level [(1,2)].

Most MRS studies have focused in the evaluation of proton (^{1}H) signal, due to the intrinsic physical characteristics of this nucleus and because it is possible to perform the proton spectroscopic acquisition with the same coil used to obtain conventional magnetic resonance (MR) images. However, with the progressive technical improvements in recent years, such as the development of different MRS pulse sequences, improvement of data processing, as well as commercial availability of high and ultra-high magnetic field scanners, phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) has been more easily implemented [(3-5)].

Our purpose is to provide a comprehensive overview about the concepts, technical aspects and implementation of ^{31}P-MRS. Thereafter, we summarize the metabolites identified and their roles in brain physiology and pathology. The aim of this review is not to be an exhaustive compendium, but rather to guide and familiarize researchers and students with the basic principles of ^{31}P-MRS.

TECHNICAL ASPECTS

The nucleus has an intrinsic magnetic spin that is resultant from the uneven number of protons or neutrons. When exposed to a strong magnetic field, there is an alignment of these spins in a parallel or antiparallel direction to the applied field. If a specific radiofrequency pulse is applied for few microseconds (with the Characteristic precession frequency for each nucleus studied), there is a misalignment of the total Magnetization vector.

When the radiofrequency (RF) pulse ceases, there is a realignment of the magnetic field, which generates a small electric signal, known as free induction decay (FID). This signal is detected by a RF coil, and, by means of transformation from time domain to frequency domain through a mathematical equation (Fourier transform), the spectral graph is obtained [6,7].

The precession frequency of the nuclei can be calculated by the Larmor equation, and it is proportional to the intensity of the magnetic field and to the gyromagnetic constant, which is specific to each chemical element or isotope. The nuclei within the molecules, however, suffer from small shifts of the precession frequency due to the magnetic field generated by adjacent electrons, and this phenomenon is called chemical shift. Each molecule has then specific chemical shifts, measured in Hertz (Hz) or parts per million (ppm) [6].

The result of this process is not an anatomical image, but a spectral graph, in which each metabolite has its specific position corresponding to the variation of resonance frequency (chemical shift), expressed in ppm on the horizontal scale (X axis), while the amplitude of each metabolite is represented in the vertical axis (Y axis), which allows their relative quantification [2,7-11].

Albeit not fully explored, ^{31}P-MRS provides unique and relevant information about the bioenergetics state, the composition of the cell membrane, intracellular pH and the concentration of magnesium (Mg^{2+}), which cannot be obtained with other conventional or spectroscopic techniques [12].

However, this method has not been implemented widespread because it is necessary that the MR equipment is prepared to work in the resonance frequency of the phosphorus-31 (^{31}P) nucleus, and it is also required a dedicated brain coil (Fig. 1) to detect the specific signal [12,13].

Just like the ^{1}H nucleus, the ^{31}P nucleus also represents a nuclear spin number of ½, capable to produce an MRI signal (Table 1). However, because of the physical characteristics of ^{31}P (for example, greater mass), its gyromagnetic ratio (that indicates the level of the interaction between the nucleus and the magnetic field of the MRI scanner) is approximately 2.5 times lower than for ^{1}H. This results in a lower resonance frequency - 51.7 MHz as compared to 127.7 MHz in a field of 3.0 T - and in a much lower sensitivity, only 6.6% when compared to ^{1}H signal [14,15].

These factors imply that to obtain a satisfactory ^{31}P spectrum, comparable to ^{1}H spectrum, it is necessary to repeat the same acquisition several times in order to increase the signal-to-noise ratio (SNR) of the spectrum, resulting in a much longer acquisition time [16]. It should also be noted that the concentration of ^{31}P metabolites (1-14 mM) is lower than that of the metabolites detected in the ^{1}H-MRS, which makes it even more difficult to obtain a ^{31}P spectrum with sufficient signal intensity (Table 2) [14, 17-21].

Due to the short transverse relaxation time (T2) of the ^{31}P metabolites, the techniques most commonly used to obtain the ^{1}H spectrum, like stimulated echo acquisition mode (STEAM) and point resolved spectroscopy (PRESS), which are based on the formation of an echo, are not recommended for the acquisition of the ^{31}P spectrum. These techniques require a minimum TE around 8 to 20 ms, which would result in a

large loss of signal due to the transverse relaxation times for most metabolites. For this reason, the most commonly used techniques are the image selected in vivo spectroscopy (ISIS) or the pulse acquire technique (direct acquisition of the FID signal immediately after the RF pulse), which allow to obtain the signal with a minimum TE around 300 μs [22,23].

In the ISIS technique, the localization of a slice is made through the acquisition of two FIDs, one generated after the application of a 180º pulse selective for one dimension, and the other generated without the prior application of this pulse. The subtraction of these two signals corresponds to the signal of one single slice (one-dimensional, 1D ISIS). For the localization of a volume (three-dimensional, 3D ISIS), it is necessary to acquire eight FIDs. The difference is only whether the selective180º pulse is applied or not in a determined direction, resulting in eight different combinations. In practice, instead of working with subsequent subtraction of the signals, they are acquired with alternating phases (phase cycling), and only the signal of interest is recorded [24,25].

On the other hand, the pulse acquire technique allows only the selection of one single slice, but not a volume, the reason why it is not suitable for the study of minute structures. However, when combined with two-dimensional (2D) or three-dimensional (3D) acquisition of the spectrum (acquisition of multiple volumes of interest, or voxels), it can also be used for evaluation of smaller volumes.

The metabolites present in the spectral curve as single, double, triple or multiple peaks. The factor that generates the division of a resonance signal in two or more peaks in the spectrum is the interaction known as J coupling between adjacent nuclei in the same molecule [4]. The *J* coupling effect can be reduced or completely canceled in the spectrum if, during the signal acquisition, the nucleus responsible for this effect is irradiated by a second RF channel. This technique, used to reduce the *J* coupling effect, is known as decoupling [26].

^{31}P-MRS in vivo presents two double peaks and one triple peak of the adenosine triphosphate molecule (ATP) [27]. However, in this case, the cause of the *J* coupling effect is the interaction of a ^{31}P nucleus with another ^{31}P nucleus, what precludes the reduction of this effect by decoupling in the frequency of ^{1}H nucleus. However, it is observed that the interaction between ^{1}H and ^{31}P within the same molecules, or even with the adjacent water, is large enough to cause broadening of the peaks observed in the ^{31}P spectrum. This effect is particularly important for the phosphodiester peak (Fig. 2), but may also have a lesser effect on the intensity of the other peaks [28,29-33].

Through previous irradiation of the ^{1}H nucleus, it is possible to transfer some of the energy absorbed by ^{1}H to ^{31}P, and thus increase the basic signal from the ^{31}P nuclei. This effect is known as nuclear Overhauser enhancement (nOe).

The intensity of the basic signal can be increased depending on the relation between the gyromagnetic constants of the irradiated and the observed nucleus, on the relaxation times of the nuclei, and on the chosen irradiation method. The nOe effect can also be produced when it is used only a decoupling pulse (because the ^{1}H spins absorb energy that can be transferred to the ^{31}P spins), and thus it could become an extra factor of variability that may affect the reproducibility of the method [34-36]. Therefore, it is recommended that, whenever a decoupling technique is applied, the ^{1}H nuclei should be irradiated prior to the acquisition of ^{31}P-MRS, in order to produce a larger and more controlled nOe effect (Fig. 2).

The spectroscopic examinations benefit from the use of higher magnetic field strengths that increase the sensitivity of the study and the spectral resolution, with at least linear increases in

SNR. On the other hand, there is also an increase in distortions of the field related to the effects of magnetic susceptibility, which can be minimized with a procedure known as "shimming", held in the preparation phase of the exam with the aim to increase the homogeneity of the magnetic field within the region of interest [37-39].

In order to achieve a spatial resolution that allows assessment of multiple regions of the brain and still offers sufficient SNR, the ideal strategy is to acquire 3D volumes, with a non-selective and adiabatic radiofrequency pulse, where the spatial localization is done with application of phase encoding gradients[16,40-42]. Figure 3 shows the planning of a ^{31}P-MRS acquired with a three-dimensional chemical shift imaging (3D-CSI) sequence with a multivoxel matrix that had total exam duration of 36 minutes.

However, despite the need for adjustments of multiple parameters and the technical challenges for the acquisition of ^{31}P-MRS, there are also some advantages of this modality of spectroscopy. A convenience of the ^{31}P-MRS, as compared to ^{1}H-MRS, is that, because it does not present signals from the water molecules, it is not necessary to apply saturation methods [6].

Another convenience in favor of ^{31}P-MRS is that it presents a large range of dispersion of the chemical shift, around 30 ppm (parts per million) or 2000 Hz (at 3.0 T) [43]. This contributes to a good spectral resolution, with a satisfactory differentiation between the different resonances in the spectrum and an easy identification of the various metabolites, explained in detail in the next section.

METABOLITES

The great interest in ^{31}P-MRS relies on the role that the phosphorylated molecules play in brain biochemistry, energy metabolism, and composition of cell membranes. Three main types of information can be obtained with this examination. The first one is related to the energy pool itself, with the resonances of phosphocreatine (PCr), inorganic phosphate (Pi) and the three isotopomers of adenosine triphosphate (α-, β-, and γ-ATP). Second, the phospholipids, represented by phosphomonoesters (PME) and phosphodiesters (PDE), inform about the synthesis and degradation of the cell membrane, respectively. Finally, it is possible to obtain the value of intracellular pH and the concentration of magnesium (Mg^{2+}) [11]. Figure 4 shows a typical ^{31}P spectrum of the brain with identification of the main metabolites.

Adenosine Triphosphate and Phosphocreatine

^{31}P-MRS is able to distinguish ATP isotopomers in the form of three distinct peaks, from left to right in the curve: a doublet γ-ATP, a doublet α-ATP and a triplet β-ATP[43].The ATP is mainly synthesized in the mitochondria (Fig. 5) from the oxidative phosphorylation of ADP (adenosine diphosphate) catalyzed by the enzyme ATP-synthase, and to a lesser extent by mechanisms of glycolysis, besides the synthesis from the creatinekinase reaction [44-46].

The PCr peak is the most prominent of the ^{31}P spectrum of the brain, resonates at zero ppm, and, therefore, it is the reference to the localization of the other metabolites. PCr is a high-energy molecule, very abundant in the neural tissues, serving as a buffer to maintain a constant level of ATP and to support the demand of energy through the reaction catalyzed by creatinekinase [47], as illustrated in Figure 5.

Membrane Phospholipids

The phosphomonoesters (PME) represent the anabolic activity of cell membranes and their main constituents are the phosphoethanolamine (PE) and phosphocholine (PC), precursors of membrane synthesis. The phosphodiesters (PDE) indicate, in turn, the catabolism of cell membranes, and are constituted by their degradation products, the glycerophosphoethanolamine (GPE) and glycerophosphocholine (GPC). The PDE are products of

the phospholipase enzyme activity and are converted into PME by the activity of the enzyme phosphodiesterase. The ratio PME / PDE is an indicator of the turnover of cell membranes, and it is representative of changes in the phospholipids double-layer [48,49].

The functioning and the plasticity of the brain are dramatically influenced by the physical and chemical properties of the neuronal membrane. This membrane is formed by a double layer of phospholipids, with immersed receptors, ion channels and other proteins involved in signal transduction and maintenance of cellular homeostasis [50]. The structure of the cell membrane determines its fluidity, as well as the number, density and affinity of receptors that modulate the signaling mechanisms. In addition, phospholipids serve as a substrate for the synthesis of intra and intercellular mediators, which indicates their relevance in the mechanisms of neurotransmission [51-54].

Intracellular pH and Magnesium

The peak of inorganic phosphate (Pi) is localized between the PME and PDE peaks. It is directly involved in the synthesis of ATP (Fig. 5), and its chemical shift relative to PCr peak (δ_1) is used to calculate the intracellular pH, according to the formula [55-58]:

$$pH = 6{,}77 + \log_{10}\frac{\delta_1 - 3{,}29}{5{,}68 - \delta_1} \qquad [1]$$

Modulation of pH in the human brain is a puzzling combination of countless osmotic and metabolic mechanisms that are primarily related to the transport and diffusion of ions, buffer systems, activity of carbonic anhydrase and energy consumption [59-63].

Free cytosolic Mg^{2+} (pMg) can be estimated by in vivo ^{31}P-MRS from the β-ATP chemical shift (δ_β), which in turn depends on the fraction of total ATP linked to Mg^{2+}, according to the equation below [55,64]:

$$pMg = 4{,}24 - \log_{10}\frac{(\delta_\beta + 18{,}58)^{0{,}420}}{(-15{,}74 - \delta_\beta)^{0{,}840}} \qquad [2]$$

Table 3 summarizes the main metabolites obtained with ^{31}P-MRS, indicating their position in the spectral curve and their roles in brain metabolism.

BIOMEDICAL APPLICATIONS

^{31}P-MRS has been used in metabolic evaluation of the heart [65,66], liver [67-69], skeletal muscle [70-72], and brain [73-75] in humans and animal models.

In the investigation of the human brain, in particular, this method has shown some peculiarities in the pattern of physiological distribution of the phosphate metabolites. It was identified higher levels of PCr and PCr/ATP in gray matter compared to the white matter [76,77]. Another study found significant differences in the values of PME and PDE, which were higher in white matter compared to gray matter [78]. On the other hand, it does not seem to exist significant differences in the levels of Pi, intracellular pH or the concentration of Mg^{2+} between the white and gray matters [18,76]. Most authors assume that the tissue specificity (gray matter versus white matter) is more important than the topography of the tissue (for example, occipital lobe versus frontal lobe). There is also no evidence of variations between the cortical or deep gray matters [77-79].

Evidence from studies in animals and humans suggest that the mitochondria undergo progressive morphological and functional changes with aging [80-82]. The most consistent findings of studies that evaluated the effects of aging on the quantification of metabolites with ^{31}P-MRS were increased levels of PCr and decreased intracellular pH. These investigations have also reported a reduction in PME and an increase in PDE, probably reflecting reduced synthesis and increased degradation of cell membranes [83-87].

In a study of 34 healthy volunteers, there were no significant differences between males and females

for any of the brain metabolites quantified with ^{31}P-MRS [85].

Because human brain is highly dependent on energy production in comparison to other organs, it is not surprising that energetic abnormalities are related to various brain disorders. ^{31}P-MRS has been used in the investigation of a variety of neurological disorders: multiple sclerosis [88,89], cerebral ischemia [90-92], migraine [93-95], and various neurodegenerative disorders [96-100].

^{31}P-MRS was also used in various studies to determine the metabolic profile of brain tumors. The results demonstrated trends to alkalinization in different histologic types, such as meningiomas, pituitary adenomas and glial tumors [101-105].

However, it is in the field of neuropsychiatric research that ^{31}P-MRS has played a greater role. Indeed, it is believed that the phospholipid membrane plays a major role in some deterministic hypotheses of these diseases [52, 106, 107]. Some studies have shown a variety of abnormalities, mainly related to the membrane phospholipids and to measurements of intracellular pH in various diseases, such as schizophrenia [48, 108, 109], attention-deficit/ hyperactivity disorder [110, 111], depression [107, 112], and bipolar disorder [113].

Most studies of ^{31}P-MRS in epilepsy were directed to the evaluation of mesial temporal sclerosis (MTS) [114- 118]. Despite some controversial findings and methodological differences in previous studies, it is believed that ^{31}P-MRS will become a potential tool to aid in the lateralization of the epileptogenic focus, in the monitoring of clinical treatments, in defining the extent of surgical resection, and to predict the postoperative result [118-121]. Our group has recently demonstrated several abnormalities in patients with epilepsy secondary to cortical malformations detected with ^{31}P-MRS at 3.0 T [122].

CONCLUSIONS

In conclusion, phosphorus metabolites play an important role in brain metabolism. However, the exact mechanisms in which they are involved in different neurological disorders remain to be determined. In the future, ^{31}P-MRS may be a useful diagnostic tool, and may also help in the follow-up of patients and on the decision-making process. New studies are needed to better evaluate this method, and to ultimately shorten the distances between neuroscience and routine clinical practices. We believe that a better understanding of the ^{31}P-MRS methodology and its applications is critical in the development of upcoming researches.

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REFERENCES

1. Viondury J, Meyerhoff DJ, Cozzone PJ, Weiner MW. 1994 What might be the impact on neurology of the analysis of brain metabolism by in vivo magnetic resonance spectroscopy? J Neurol;241(6):354-371.
2. Xu V, Chan H, Lin AP, Sailasuta N, Valencerina S, Tran T, Hovener J, Ross BD. 2008 MR Spectroscopy in Diagnosis and Neurological Decision-Making. Semin Neurol;28(4):407-422.
3. Lei H, Zhu XH, Zhang XL, Qiao HY, Ugurbil K, Chen W. 2003 P-31-P-31 coupling and ATP T-2 measurement in human brain at 7T. Magn Reson Med;50(3):656-658.
4. Jensen JE, Drost DJ, Menon RS, Williamson PC. 2002 In vivo brain P-31-MRS: measuring

the phospholipid resonances at 4 Tesla from small voxels. NMR Biomed;15(5):338-347.

5. Qiao HY, Zhang XL, Zhu XH, Du F, Chen W. 2006 In vivo P-31 MRS of human brain at high/ultrahigh fields: a quantitative comparison of NMR detection sensitivity and spectral resolution between 4 T and 7 T. Magn Reson Imaging;24(10):1281-1286.
6. Castillo M, Kwock L, Mukherji SK. 1996 Clinical applications of proton MR spectroscopy. AJNR Am J Neuroradiol;17(1):1-15.
7. Kwock L. 1998 Localized MR spectroscopy - Basic principles. Neuroimaging Clin N Am;8(4):713-+.
8. Christensen JD, Yurgelun-Todd DA, Babb SM, Gruber SA, Cohen BM, Renshaw PF. 1999 Measurement of human brain dexfenfluramine concentration by 19F magnetic resonance spectroscopy. Brain Res;834(1-2):1-5.
9. Ross B, Lin A, Harris K, Bhattacharya P, Schweinsburg B. 2003 Clinical experience with C-13 MRS in vivo. NMR Biomed;16(6-7):358-369.
10. Forester BP, Streeter CC, Berlow YA, Tian H, Wardrop M, Finn CT, Harper D, Renshaw PF, Moore CM. 2009 Brain Lithium Levels and Effects on Cognition and Mood in Geriatric Bipolar Disorder: A Lithium-7 Magnetic Resonance Spectroscopy Study. Am J Geriatr Psychiatry;17(1):13-23.
11. Kuzniecky RI. 2004 Clinical applications of MR spectroscopy in epilepsy. Neuroimag Clin N Am;14:507-516.
12. Menuel C, Guillevin R, Costalat R, Perrin M, Sahli-Amor M, Martin-Duverneuil N, Chiras J. 2010 Phosphorus magnetic resonance spectroscopy: Brain pathologies applications. J Neuroradiol;37(2):73-82.
13. Avdievich NT, Hetherington HP. 2007 4 T Actively detuneable double-tuned H-1/P-31 head volume coil and four-channel P-31 phased array for human brain spectroscopy. J Magn Reson;186(2):341-346.
14. de Graaf R. In vivo NMR spectroscopy – Principles and Techniques. In: Sons JW, editor. Chichester, England; 1998. p 64.
15. Mandal PK. 2007 Magnetic resonance spectroscopy (MRS) and its application in Alzheimer's disease.30A(1):40-64.
16. Blenman RAM, Port JD, Felmlee JP. 2007 Selective maximization of P-31 MR spectroscopic signals of in vivo human brain metabolites at 3T. J Magn Reson Imaging;25(3):628-634.
17. Lara RS, Matson GB, Hugg JW, Maudsley AA, Weiner MW. 1993 Quantitation of in vivo phosphorus metabolites in human brain with magnetic-resonance spectroscopic imaging (MRSI). Magn Reson Imaging;11(2):273-278.
18. Buchli R, Duc CO, Martin E, Boesiger P. 1994 Assessment of absolute metabolite concentrations in human tissue by P-31 MRS in-vivo .1. Cerebrum, cerebellum, cerebral gray and white-matter. Magn Reson Med;32(4):447-452.
19. Merboldt KD, Chien D, Hanicke W, Gyngell ML, Bruhn H, Frahm J. 1990 Localized P-31 NMR-spectroscopy of the adult human brain in vivo using stimulated-echo (STEAM) sequences. J Magn Reson;89(2):343-361.
20. Goo HW. 2010 High field strength magnetic resonance imaging in children. Journal of the Korean Medical Association;53(12):1093-1102.
21. Goodwill PW, Conolly SM. 2010 The X-Space Formulation of the Magnetic Particle Imaging Process: 1-D Signal, Resolution, Bandwidth, SNR, SAR, and Magnetostimulation. IEEE Trans Med Imaging;29(11):1851-1859.
22. Ordidge RJ, Connelly A, Lohman JAB. 1986 Image-selected in vivo spectroscopy (ISIS) - a new technique for spatially selective NMR-spectroscopy. J Magn Reson;66(2):283-294.

23. Kegeles LS, Humaran TJ, Mann JJ. 1998 In vivo neurochemistry of the brain in schizophrenia as revealed by magnetic resonance spectroscopy. Biol Psychiatry;44(6):382-398.
24. Lawry TJ, Karczmar GS, Weiner MW, Matson GB. 1989 Computer-simulation of MRS localization techniques - an analysis of ISIS. Magnetic Resonance in Medicine;9(3):299-314.
25. Burger C, Buchli R, McKinnon G, Meier D, Boesiger P. 1992 The impact of the ISIS experiment order on spatial contamination. Magn Reson Med;26(2):218-230.
26. Gonen O, Mohebbi A, Stoyanova R, Brown TR. 1997 In vivo phosphorus polarization transfer and decoupling from protons in three-dimensional localized nuclear magnetic resonance spectroscopy of human brain. Magn Reson Med;37(2):301-306.
27. Jung WI, Staubert A, Widmaier S, Hoess T, Bunse M, vanErckelens F, Dietze G, Lutz O. 1997 Phosphorus J-coupling constants of ATP in human brain. Magn Reson Med;37(5):802-804.
28. Arias-Mendoza F, Javaid T, Stoyanova R, Brown TR, Gonen O. 1996 Heteronuclear multivoxel spectroscopy of in vivo human brain: Two-dimensional proton interleaved with three-dimensional H-1-decoupled phosphorus chemical shift imaging. NMR Biomed;9(3):105-113.
29. Potwarka JJ, Drost DJ, Williamson PC, Carr T, Canaran G, Rylett WJ, Neufeld RWJ. 1999 A H-1-decoupled P-31 chemical shift imaging study of medicated schizophrenic patients and healthy controls. Biol Psychiatry;45(6):687-693.
30. Govindaraju V, Young K, Maudsley AA. 2000 Proton NMR chemical shifts and coupling constants for brain metabolites. NMR Biomed;13(3):129-153.
31. Barker PB, Golay X, Artemov D, Ouwerkerk R, Smith MA, Shaka AJ. 2001 Broadband proton decoupling for in vivo brain spectroscopy in humans. Magn Reson Med;45(2):226-232.
32. Wang ZW, Lin JC, Mao WH, Liu WZ, Smith MB, Collins CM. 2007 SAR and temperature: Simulations and comparison to regulatory limits for MRI. J Magn Reson Imaging;26(2):437-441.
33. Collins CM. 2009 Numerical field calculations considering the human subject for engineering and safety assurance in MRI. NMR Biomed;22(9):919-926.
34. Beierbeck H, Martino R, Saunders JK, Benezra C. 1976 Nuclear overhauser effect between phosphorus and hydrogen in selected organo phosphorus-compounds. Can J Chem;54(12):1918-1922.
35. Li CW, Negendank WG, MurphyBoesch J, PadavicShaller K, Brown TR. 1996 Molar quantitation of hepatic metabolites in vivo in proton-decoupled, nuclear Overhauser effect enhanced P-31 NMR spectra localized by three-dimensional chemical shift imaging. NMR Biomed;9(4):141-155.
36. Weber-Fahr W, Bachert P, Henn FA, Braus DF, Ende G. 2003 Signal enhancement through heteronuclear polarisation transfer in in-vivo P-31 MR spectroscopy of the human brain. MAGMA;16(2):68-76.
37. Juchem C, Muller-Bierl B, Schick F, Logothetis NK, Pfeuffer J. 2006 Combined passive and active shimming for in vivo MR spectroscopy at high magnetic fields. J Magn Reson;183(2):278-289.
38. Hetherington HP, Chu WJ, Gonen O, Pan JW. 2006 Robust fully automated shimming of the human brain for high-field H-1 spectroscopic imaging. Magn Reson Med;56(1):26-33.
39. Hetherington HP, Avdievich NI, Kuznetsov AM, Pan JW. 2010 RF Shimming for Spectroscopic Localization in the Human Brain at 7 T. Magn Reson Med;63(1):9-19.
40. Gao Y, Strakowski SM, Reeves SJ, Hetherington HP, Chu WJ, Lee JH. 2006 Fast

spectroscopic imaging using online optimal sparse k-space acquisition and projections onto convex sets reconstruction. Magn Reson Med;55(6):1265-1271.

41. Ulrich M, Wokrina T, Ende G, Lang M, Bachert P. 2007 P-31-{H-1} echo-planar spectroscopic imaging of the human brain in vivo. Magn Reson Med;57(4):784-790.
42. Andronesi OC, Ramadan S, Ratai EM, Jennings D, Mountford CE, Sorensen AG. 2010 Spectroscopic imaging with improved gradient modulated constant adiabaticity pulses on high-field clinical scanners. J Magn Reson;203(2):283-293.
43. Menuel C, Guillevin R, Costalat R, Perrin M, Sahli-Amor M, Martin-Duverneuil N, Chiras J. 2010 Phosphorus magnetic resonance spectroscopy: Brain pathologies applications. J Neuroradiol;37(2):73-82.
44. Boyer PD. 1999 Molecular motors - What makes ATP synthase spin? Nature;402(6759):247-+.
45. Du F, Zhu XH, Zhang Y, Friedman M, Zhang NY, Ugurbil K, Chen W. 2008 Tightly coupled brain activity and cerebral ATP metabolic rate. Proc Natl Acad Sci U S A;105(17):6409-6414.
46. Chaumeil MM, Valette J, Guillermier M, Brouillet E, Boumezbeur F, Herard AS, Bloch G, Hantraye P, Lebon V. 2009 Multimodal neuroimaging provides a highly consistent picture of energy metabolism, validating P-31 MRS for measuring brain ATP synthesis. Proc Natl Acad Sci U S A;106(10):3988-3993.
47. Wu RH, Poublanc J, Mandell D, Detzler G, Crawley A, Qiu QC, terBrugge K, Mikulis DJ, Ieee. Evidence of brain mitochondrial activities after oxygen inhalation by P-31 magnetic resonance spectroscopy at 3T. 2007 In: 2007 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Vols 1-16., p 2899-2902.
48. Komoroski RA, Pearce JM, Mrak RE. 2008 P-31 NMR Spectroscopy of phospholipid metabolites in postmortem schizophrenic brain. Magn Reson Med;59(3):469-474.
49. Puri B, Treasaden I. 2009 A human in vivo study of the extent to which 31-phosphorus neurospectroscopy phosphomonoesters index cerebral cell membrane phospholipid anabolism. Prostaglandins Leukot Essent Fatty Acids;81(5-6):307-8.
50. Alberts B, Johnson A, Lewis J. Molecular Biology of the Cell. Science G, editor. New York; 2002.
51. Farooqui AA, Hirashima Y, Horrocks LA. Brain phospholipases and their role in signal transduction. In: Bazan NG, Murphy MG, Taffano G, editors. Neurobiology of Essential Fatty Acids. Volume 318, Advances in Experimental Medicine and Biology. New York: Plenum Press Div Plenum Publishing Corp; 1992. p 11-25.
52. Horrobin DF. 1998 The membrane phospholipid hypothesis as a biochemical basis for the neurodevelopmental concept of schizophrenia. Schizophr Res;30(3):193-208.
53. Shioiri T, Hamakawa H, Kato T, Fujii K, Murashita J, Inubushi T, Someya T. 2000 Frontal lobe membrane phospholipid metabolism and ventricle to brain ratio in schizophrenia: preliminary P-31-MRS and CT studies. Eur Arch Psychiatry Clin Neurosci;250(4):169-174.
54. Rapoport S. 2001 In vivo fatty acid incorporation into brain phospholipids in relation to plasma availability, signal transduction and membrane remodeling. J Mol Neurosci;16:243-261.
55. Barker PB, Butterworth EJ, Boska MD, Nelson J, Welch KMA. 1999 Magnesium and pH imaging of the human brain at 3.0 Tesla. Magn Reson Med;41(2):400-406.
56. Petroff OAC, Prichard JW, Behar KL, Alger JR, Denhollander JA, Shulman RG. 1985 Cerebral intracellular ph by P-31 nuclear magnetic-resonance spectroscopy. Neurology;35(6):781-788.

57. Berg J, Tymoczko J, Stryer L. Biochemistry. Freeman WH, editor. New York; 2002.
58. Lodish H, Berk A, Zipursky S. Molecular Cell Biology. Freeman WH, editor. New York; 2000.
59. Xiong ZG, Chu XP, Simon RP. 2006 Ca2+-permeable acid-sensing ion channels and ischemic brain injury. J Membr Biol;209(1):59-68.
60. Petroff EY, Price MP, Snitsarev V, Gong H, Korovkina V, Abboud FM, Welsh MJ. 2008 Acid-sensing ion channels interact with and inhibit BKK+ channels. Proc Natl Acad Sci U S A;105(8):3140-3144.
61. Chesler M. 2003 Regulation and modulation of pH in the brain. Physiol Rev;83(4):1183-1221.
62. Yermolaieva O, Leonard AS, Schnizier MK, Abboud FM, Welsh MJ. 2004 Extracellular acidosis increases neuronal cell calcium by activating acid-sensing ion channel 1a. Proc Natl Acad Sci U S A;101(17):6752-6757.
63. Iotti S, Frassineti C, Alderighi L, Sabatini A, Vacca A, Barbiroli B. 1996 In vivo assessment of free magnesium concentration in human brain by P-31 MRS. A new calibration curve based on a mathematical algorithm. NMR Biomed;9(1):24-32.
64. Halvorson HR, Vandelinde AMQ, Helpern JA, Welch KMA. 1992 Assessment of magnesium concentrations by P-31 NMR invivo. NMR Biomed;5(2):53-58.
65. Aussedat J, Lortet S, Ray A, Rossi A, Heckman M, Zimmer HG, Vincent M, Sassart J. 1992 Energy metabolism of the hypertrophied heart studied by 31P nuclear magnetic resonance. Cardioscience;3(4):233-239.
66. Marseilles M, Eicher JC, Gomez MC, Cottin Y, Cohen M, Walker P. 1996 Improvement of skeletal muscle oxidative metabolism after heart transplantation in heart failure patients. A 31P NMR study. Sci Sports;11(1):28-33.
67. Bowers JL, Lanir A, Metz KR, Kruskal JB, Lee RGL, Balschi J, Federman M, Khettry U, Clouse ME. 1992 NA-23-NMR and 31P-NMR studies of perfused mouse-liver during nitrogen hypoxia. Am J Physiol;262(4):G636-G644.
68. Zakian KL, Koutcher JA, Malhotra S, Thaler H, Jarnagin W, Schwartz L, Fong YM. 2005 Liver regeneration in humans is characterized by significant changes in cellular phosphorus metabolism: Assessment using proton-decoupled P-31- magnetic resonance spectroscopic imaging. Magn Reson Med;54(2):264-271.
69. Sharma R, Sinha S, Danishad KA, Vikram NK, Gupta A, Ahuja V, Jagannathan NR, Pandey RM, Misra A. 2009 Investigation of hepatic gluconeogenesis pathway in non-diabetic Asian Indians with non-alcoholic fatty liver disease using in vivo (P-31) phosphorus magnetic resonance spectroscopy. Atherosclerosis;203(1):291-297.
70. Kemp GJ, Meyerspeer M, Moser E. 2007 Absolute quantification of phosphorus metabolite concentrations in human muscle in vivo by P-31 MRS: a quantitative review. NMR Biomed;20(6):555-565.
71. van Elderen SGC, Doornbos J, van Essen EHR, Lemkes H, Maassen JA, Smit JWA, de Roos A. 2009 Phosphorus-31 Magnetic Resonance Spectroscopy of Skeletal Muscle in Maternally Inherited Diabetes and Deafness A3243G Mitochondrial Mutation Carriers. J Magn Reson Imaging;29(1):127-131.
72. Lim EL, Hollingsworth KG, Thelwall PE, Taylor R. 2010 Measuring the acute effect of insulin infusion on ATP turnover rate in human skeletal muscle using phosphorus-31 magnetic resonance saturation transfer spectroscopy. NMR Biomed;23(8):952-957.
73. Holtzman D, Mulkern R, Tsuji M, Cook C, Meyers R. 1996 Phosphocreatine and creatine kinase in piglet cerebral gray and white matter in situ. Dev Neurosci;18(5-6):535-541.

74. Holtzman D, Mulkern R, Meyers R, Cook C, Allred E, Khait I, Jensen F, Tsuji M, Laussen P. 1998 In vivo phosphocreatine and ATP in piglet cerebral gray and white matter during seizures. Brain Res;783(1):19-27.
75. Bischof MG, Mlynarik V, Brehm A, Bernroider E, Krssak M, Bauer E, Madl C, Bayerle-Eder M, Waldhausl W, Roden M. 2004 Brain energy metabolism during hypoglycaemia in healthy and Type 1 diabetic subjects. Diabetologia;47(4):648-651.
76. Mason GF, Chu WJ, Vaughan JT, Ponder SL, Twieg DB, Adams D, Hetherington HP. 1998 Evaluation of P-31 metabolite differences in human cerebral gray and white matter. Magn Reson Med;39(3):346-353.
77. Hetherington HP, Spencer DD, Vaughan JT, Pan JW. 2001 Quantitative P-31 spectroscopic imaging of human brain at 4 tesla: Assessment of gray and white matter differences of phosphocreatine and ATP. Magnetic Resonance in Medicine;45(1):46-52.
78. Buchli R, Martin E, Boesiger P, Rumpel H. 1994 Developmental changes of phosphorus metabolite concentrations in the human brain - a P-31 magnetic resonance spectroscopy study in vivo. Pediatric Research;35(4):431-435.
79. Doyle VL, Payne GS, Collins DJ, Verrill MW, Leach MO. 1997 Quantification of phosphorus metabolites in human calf muscle and soft-tissue tumours from localized MR spectra acquired using surface coils. Physics in Medicine and Biology;42(4):691-706.
80. Bertoni-Freddari C, Fattoretti P, Giorgetti B, Solazzi M, Balietti M, Di Stefano G, Casoli T. Decay of mitochondrial metabolic competence in the aging cerebellum. In: DeGrey ADN, editor. Strategies for Engineered Negligible Senescence: Why Genuine Control of Aging May Be Foreseeable. Volume 1019, Annals of the New York Academy of Sciences; 2004. p 29-32.
81. Bertoni-Freddari C, Fattoretti P, Giorgetti B, Solazzi M, Balietti M, Meier-Ruge W. 2004 Role of mitochondrial deterioration in physiological and pathological brain aging. Gerontology;50(3):187-192.
82. Schapira AHV. 2006 Mitochondrial disease. Lancet;368(9529):70-82.
83. Murashita J, Kato T, Shioiri T, Inubushi T, Kato N. 1999 Age-dependent alteration of metabolic response to photic stimulation in the human brain measured by P-31 MR-spectroscopy. Brain Res;818(1):72-76.
84. Rae C, Scott RB, Lee M, Simpson JM, Hines N, Paul C, Anderson M, Karmiloff-Smith A, Styles P, Raddac GK. 2003 Brain bioenergetics and cognitive ability. Dev Neurosci;25(5):324-331.
85. Forester B, Berlow Y, Harper D, Jensen J, Lange N, Froimowitz M, Ravichandran C, Iosifescu D, Lukas S, Renshaw P and others. 2010 Age-related changes in brain energetics and phospholipid metabolism. NMR Biomed;23(3):242-50.
86. Kadota T, Horinouchi T, Kuroda C. 2001 Development and aging of the cerebrum: Assessment with proton MR spectroscopy. Am J Neuroradiol;22(1):128-135.
87. Moreno-Torres A, Pujol J, Soriano-Mas C, Deus J, Iranzo A, Santamaria J. 2005 Age-related metabolic changes in the upper brainstem tegmentum by MR spectroscopy. Neurobiol Aging;26(7):1051-1059.
88. Husted CA, Matson GB, Adams DA, Goodin DS, Weiner MW. 1994 In vivo detection of myelin phospholipids in multiple sclerosis with phosphorus magnetic resonance spectroscopic imaging. Ann Neurol;36(2):239-241.
89. Steen C, Koch M, Mostert J, De Keyser J. 2008 Phosphorus spectroscopy of normal-appearing white matter in multiple sclerosis. Mult Scler;14:S222-S222.
90. Laptook AR, Corbett RJT, Uauy R, Mize C, Mendelsohn D, Nunnally RL. 1989 Use of P-31 magnetic-resonance spectroscopy to

characterize evolving brain-damage after perinatal asphyxia. Neurology;39(5):709-712.

91. Levine SR, Helpern JA, Welch KM, Vande Linde AM, Sawaya KL, Brown EE, Ramadan NM, Deveshwar RK, Ordidge RJ. 1992 Human focal cerebral ischemia: evaluation of brain pH and energy metabolism with P-31 NMR spectroscopy. Radiology;185(2):537-44.
92. Helpern JA, Vande Linde AM, Welch KM, Levine SR, Schultz LR, Ordidge RJ, Halvorson HR, Hugg JW. 1993 Acute elevation and recovery of intracellular [Mg2+] following human focal cerebral ischemia. Neurology;43(8):1577-81.
93. Ramadan NM, Halvorson H, Vande-Linde A, Levine SR, Helpern JA, Welch KM. 1989 Low brain magnesium in migraine. Headache;29(9):590-3.
94. Lodi R, Lotti S, Cortelli P, Pierangeli G, Cevoli S, Clementi V, Soriani S, Montagna P, Barbiroli B. 2001 Deficient energy metabolism is associated with low free magnesium in the brains of patients with migraine and cluster headache. Brain Res Bull;54(4):437-441.
95. Boska MD, Welch KMA, Barker PB, Nelson JA, Schultz L. 2002 Contrasts in cortical magnesium, phospholipid and energy metabolism between migraine syndromes. Neurology;58(8):1227-1233.
96. Barbiroli B, Martinelli P, Patuelli A, Lodi R, Iotti S, Cortelli P, Montagna P. 1999 Phosphorus magnetic resonance spectroscopy in multiple system atrophy and Parkinson's disease. Mov Disord;14(3):430-435.
97. Hoang TQ, Dubowitz DJ, Moats R, Kopyov O, Jacques D, Ross BD. 1998 Quantitative proton-decoupled P-31 MRS and H-1 MRS in the evaluation of Huntington's and Parkinson's diseases. Neurology;50(4):1033-1040.
98. Smith CD, Gallenstein LG, Layton WJ, Kryscio RJ, Markesbery WR. 1993 P-31 magnetic-resonance spectroscopy in Alzheimer's and Pick's disease. Neurobiol Aging;14(1):85-92.
99. Pettegrew JW, Panchalingam K, Hamilton RL, McClure RJ. 2001 Brain membrane phospholipid alterations in Alzheimer's disease. Neurochemical Research;26(7):771-782.
100. Forlenza OV, Wacker P, Nunes PV, Yacubian J, Castro CC, Otaduy MCG, Gattaz WF. 2005 Reduced phospholipid breakdown in Alzheimer's brains: a P-31 spectroscopy study. Psychopharmacology;180(2):359-365.
101. Heindel W, Bunke J, Glathe S, Steinbrich W, Mollevanger L. 1988 Combined H-1-MR imaging and localized P-31-spectroscopy of intracranial tumors in 43 patients. J Comput Assist Tomogr;12(6):907-916.
102. Heindel W, Friedmann G. 1988 Image-guided localized P-31 NMR-spectroscopy in brain tumors. Tumordiagnostik & Therapie;9(4):166-166.
103. Hubesch B, Sappeymarinier D, Roth K, Meyerhoff DJ, Matson GB, Weiner MW. 1990 P-31 MR spectroscopy of normal human brain and brain tumors. Radiology;174(2):401-409.
104. Arnold DL, Emrich JF, Shoubridge EA, Villemure JG, Feindel W. 1991 Characterization of astrocytomas, meningiomas, and pituitary adenomas by phosphorus magnetic resonance spectroscopy. J Neurosurg;74(3):447-53.
105. Maintz D, Heindel W, Kugel H, Jaeger R, Lackner KJ. 2002 Phosphorus-31 MR spectroscopy of normal adult human brain and brain tumours. NMR Biomed;15(1):18-27.
106. Keshavan MS, Stanley JA, Montrose DM, Minshew NJ, Pettegrew JW. 2003 Prefrontal membrane phospholipid metabolism of child and adolescent offspring at risk for schizophrenia or schizoaffective disorder: an in vivo P-31 MRS study. Mol Psychiatry;8(3):316-323.
107. Rzanny R, Klemm S, Reichenbach JR, Pfleiderer SOR, Schmidt B, Volz HP, Blanz

B, Kaiser WA. 2003 31P-MR spectroscopy in children and adolescents with a familial risk of schizophrenia. Eur Radiol;13(4):763-770.

108. Jensen JE, Miller J, Williamson PC, Neufeld RWJ, Menon RS, Malla A, Manchanda R, Schaefer B, Densmore M, Drost DJ. 2006 Grey and white matter differences in brain energy metabolism in first episode schizophrenia: P-31-MRS chemical shift imaging at 4 Tesla. Psychiatry Res;146(2):127-135.
109. Smesny S, Rosburg T, Nenadic I, Fenk KP, Kunstmann S, Rzanny R, Volz HP, Sauer H. 2007 Metabolic mapping using 2D P-31-MR spectroscopy reveals frontal and thalamic metabolic abnormalities in schizophrenia. Neuroimage;35(2):729-737.
110. Stanley JA, Kipp H, Greisenegger E, MacMaster FP, Panchalingam K, Pettegrew JW, Keshavan MS, Bukstein OG. 2006 Regionally specific alterations in membrane phospholipids in children with ADHD: An in vivo P-31 spectroscopy study. Psychiatry Res;148(2-3):217-221.
111. Stanley JA, Kipp H, Greisenegger E, MacMaster FP, Panchalingam K, Keshavan MS, Bukstein OG, Pettegrew JW. 2008 Evidence of Developmental Alterations in Cortical and Subcortical Regions of Children With Attention-Deficit/Hyperactivity Disorder A Multivoxel In Vivo Phosphorus 31 Spectroscopy Study. Arch Gen Psychiatry;65(12):1419-1428.
112. Pettegrew JW, Levine J, Gershon S, Stanley JA, Servan-Schreiber D, Panchalingam K, McClure RJ. 2002 P-31-MRS study of acetyl-L-carnitine treatment in geriatric depression: preliminary results. Bipolar Disord;4(1):61-66.
113. Hamakawa H, Murashita J, Yamada N, Inubushi T, Kato N, Kato T. 2004 Reduced intracellular pH in the basal ganglia and whole brain measured by P-31-MRS in bipolar disorder. Psychiatry Clin Neurosci;58(1):82-88.
114. Laxer KD, Hubesch B, Sappey-Marinier D, Weiner MW. 1992 Increased pH and inorganic phosphate in temporal seizure foci demonstrated by [31P]MRS. Epilepsia;33(4):618-23.
115. der Grond J, Gerson J, Laxer K, Hugg J, Matson G, Weiner M. 1998 Regional Distribution of Interictal 'P Metabolic Changes in Patients with Temporal Lobe Epilepsy. Epilepsia;39(5):527-536.
116. Chu WJ, Hetherington HP, Kuzniecky RI, Vaughan JT, Twieg DB, Faught RE, Gilliam FG, Hugg JW, Elgavish GA. 1996 Is the intracellular pH different from normal in the epileptic focus of patients with temporal lobe epilepsy? A 31P-NMR study. Neurology;47:756-760.
117. Chu WJ, Hetherington HP, Kuzniecky RI, Simor T, Mason GF, Elgavish GA. 1998 Lateralization of human temporal lobe epilepsy by 31P NMR spectroscopic imaging at 4,1T. Neurology;51:472-479.
118. Hetherington HP, Kim JH, Pan JW, Spencer DD. 2004 H-1 and P-31 spectroscopic imaging of epilepsy: Spectroscopic and histologic correlations. Epilepsia;45:17-23.
119. Simor T, Chu WJ, Hetherington H, Kuzniecky R, Elgavish G. Tailored temporal lobectomy induced improvements in 4.1T 31PNMR SI generated phosphorous metabolite indices in temporal lobe epilepsy. 1997; Vancouver, Canada. p 33.
120. Pan JW, Bebin EM, Chu WJ, Hetherington HP. 1999 Ketosis and epilepsy: P-31 spectroscopic imaging at 4.1 T. Epilepsia;40(6):703-707.
121. Hetherington HP, Pan JW, Spencer DD. 2002 H-1 and P-31 spectroscopy and bioenergetics in the lateralization of seizures in temporal lobe epilepsy. J Magn Reson Imaging;16(4):477-483.
122. Andrade CS, Otaduy MCG, Valente KDR, Maia DF, Park EJ, Valerio RMF, Tsunemi MH, Leite CC. 2011 Phosphorus magnetic

resonance spectroscopy in malformations of cortical development. Epilepsia;52(12):2276-2284.

TABLES

Table 1 Characteristics of phosphorus-31 (^{31}P) and hydrogen-1 (^{1}H) nuclei for magnetic resonance spectroscopy (MRS)

Nucleus	Nuclear Spin	Gyromagnetic ratio [MHz/T]	Precession frequency at 3T [MHz]	Natural abundance [%]	Relative sensitivity [%]
^{1}H	½	42.571	127.7	99.98	100
^{31}P	½	17.235	51.7	100	6.6

Table 2 Metabolites identified in ^{31}P-MRS *in vivo* in the human brain and their characteristics

Metabolite	Symbol	T1 [s] in 1,5 T	T2 [ms] in 2 T	Concentration [mM]
Phosphomonoesters	PME	1.2	70	3-4
Inorganic phosphate	Pi	1.1	80	1
Phosphodiesters	PDE	1.3	20	9-14
Phosphocreatine	PCr	2.4	150	3-4
γ- adenosine triphosphate	γ-ATP	0.9	30	3
α- adenosine triphosphate	α-ATP	1.1	30	3
β- adenosine triphosphate	β-ATP	1.0	20	3

Table 3 Metabolites identified on ^{31}P-MRS, their position in the horizontal axis in parts per million (ppm), and their roles in cerebral physiology

Metabolite	Chemical shift [ppm]	Role
PME (PE + PC)	+6.5	Membrane anabolism
Pi	+4.9	Intracellular pH
PDE (GPE + GPC)	+2.6	Membrane catabolism
PCr	0	Energetic metabolism
γ-ATP	-2.7	
α-ATP	-7.8	Energetic metabolism
β-ATP	-16.3	(Mg^{2+})

FIGURES AND LEGENDS

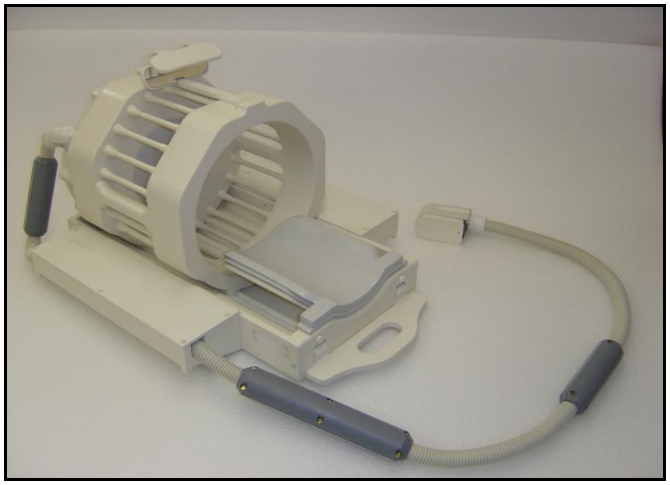

Fig - 1 Dual-tune 31P/1H birdcage head coil (AIRI, Cleveland, USA) used to acquire the ^{31}P-MRS. Although a surface coil could be used to evaluate the brain, specially the occipital region, the signal in the more distant areas from the coil cannot be satisfactorily detected with the same quality as it is obtained with the head coil.

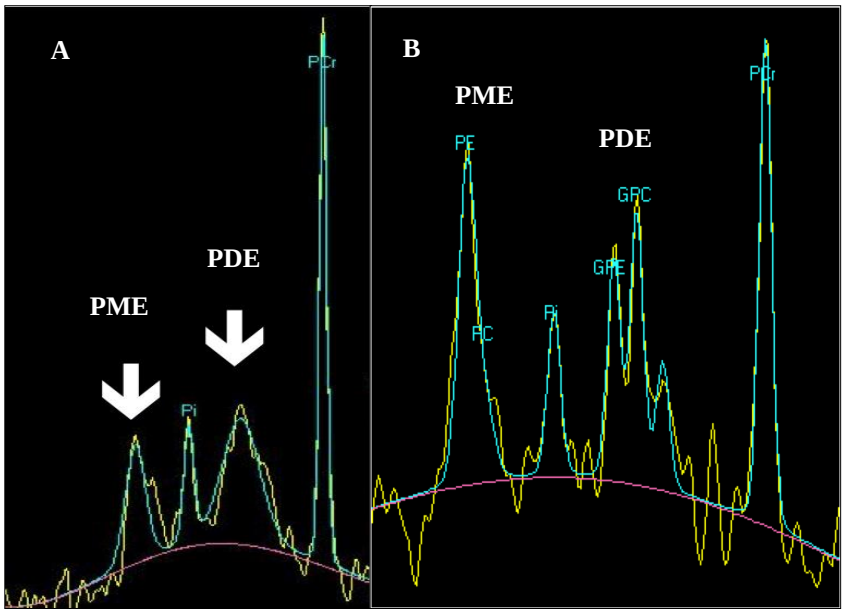

Fig - 2 Expansion of one region of interest of ^{31}P-MRS shows, from left to right: phosphomonoesters (PME), inorganic phosphate (Pi), phosphodiesters (PDE) and phosphocreatine (PCr). Spectrum without (A) and with (B) the use of decoupling technique and nuclear Overhauser enhancement (nOe) with irradiation through ^{1}H channel. It can be observed that the PME and PDE peaks (arrows) get thinner and increase in the spectrum B. The PDE are constituted by glycerophosphoethanolamine (GPE) and glycerophosphocholine (GPC), and the PME represent the sum of phosphoethanolamine (PE) and phosphocholine (PC).

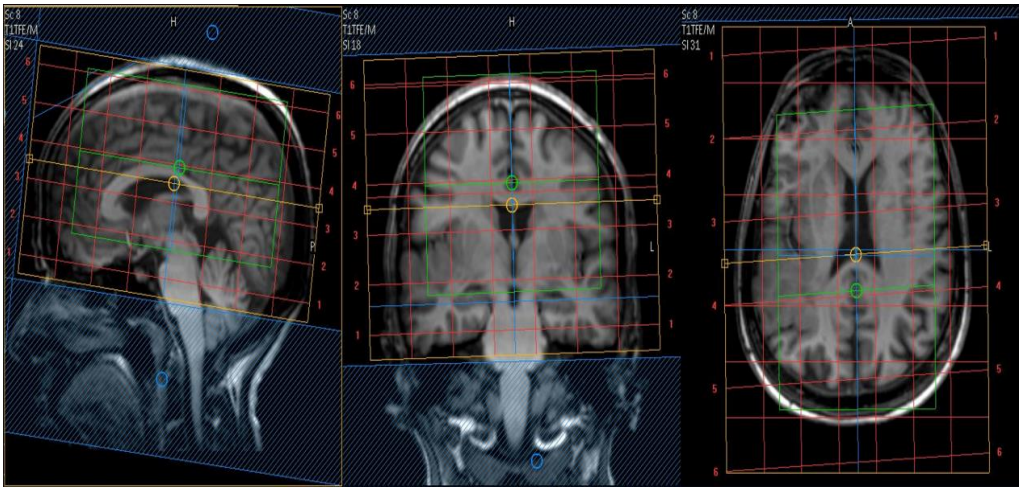

Fig - 3 Planning of a ^{31}P-MRS experiment in a patient with an extensive area of cortical dysplasia in the right cerebral hemisphere. Positioning of the ^{31}P-MRS grid in multiplanar T1-fast field echo (T1-FFE) images with a multivoxel matrix of six slices, seven columns and eight lines (orange box), according to the anatomical landmarks. The small green box centered on the image corresponds to the shimming area. The blue saturation slabs were positioned to avoid any overlapping artifacts in the area of interest. The individual voxels were 25 x 25 x 20 mm in size, with effective nominal volumes of 12.5 cm^3.

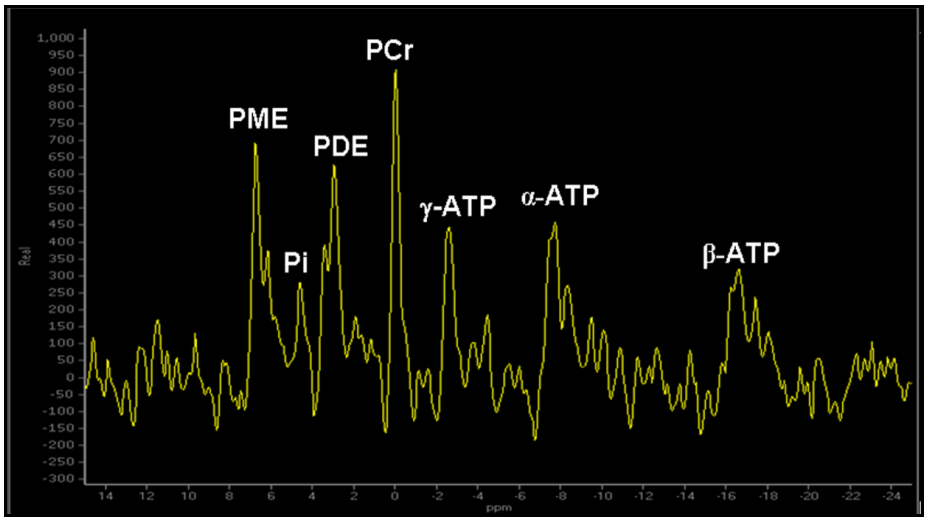

Fig - 4 Typical ^{31}P-MRS of the human brain shows, from left to right, the following metabolites: PME (phosphomonoesters), Pi (inorganic phosphate), PDE (phosphodiesters), PCr (phosphocreatine), and γ-, α-, and β- ATP (adenosine triphosphate).

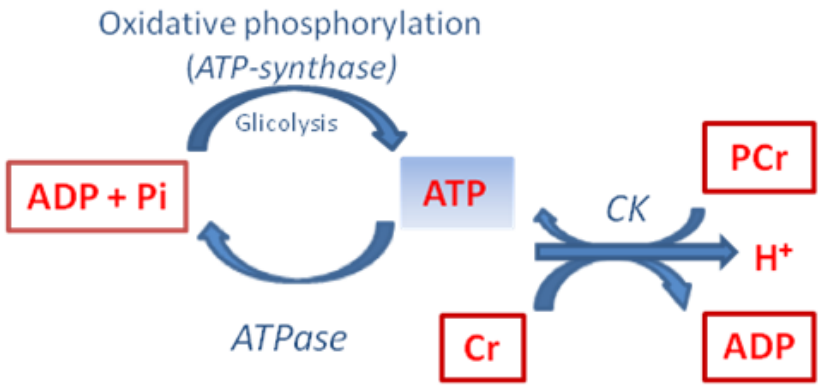

Fig - 5 Schematic representation of the synthesis of ATP (adenosine triphosphate) from the reaction catalyzed by creatinekinase (CK), which uses PCr (phosphocreatine) as a substrate and generates creatine (Cr). The ATP synthesis also results from the mitochondrial activity through the reaction of oxidative phosphorylation, mediated by ATP synthase, and to a lesser extent from the glycolysis mechanism. The ATP, in turn, is degraded by the enzyme ATPase, producing ADP (adenosine diphosphate) and Pi (inorganic phosphate).