A double-tuned $^1\text{H}/^{23}\text{Na}$ dual resonator system for tissue sodium concentration measurements in the rat brain via Na-MRI

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Short Title:

Dual resonator system for quantitative Na-MRI in rat brain

Abbreviations

MRI	magnetic resonance imaging
SNR	signal-to-noise ratio

1 Abstract

A method for quantifying the Tissue Sodium Concentration (TSC) in the rat brain from ^{23}Na -MR images was developed. TSC is known to change in a variety of common human diseases and holds considerable potential to contribute to their study; however, its accurate measurement in small laboratory animals has been hindered by the extremely low signal to noise ratio (SNR) in ^{23}Na images. To address this, the design, construction and characterisation of a double-tuned $^1\text{H}/^{23}\text{Na}$ dual resonator system for ^1H -guided quantitative ^{23}Na -MRI is described. This system comprised of an SNR-optimised surface detector coil for ^{23}Na image acquisition, and a volume resonator producing a highly-homogeneous B_1 field (<5% inhomogeneity) for the Na channel across the rat head. The resonators incorporated channel-independent balanced matching and tuning capabilities with active decoupling circuitry at the ^{23}Na resonance frequency. A quantification accuracy of TSC of < 10mM was achieved in Na-images with 1.2 μl voxel resolution acquired in 10 minutes. The potential of the quantification technique was demonstrated in an *in vivo* experiment of a rat model of cerebral stroke, where the evolution of the TSC was successfully monitored for 8 hours after the stroke was induced.

1. Introduction

The availability of high field magnetic resonance imaging (MRI) scanners in the past decade has renewed interest in so-called “X-nuclei” imaging (X-nuclei = nuclei other than ^1H), where the increase in field strength produces a larger degree of polarisation of the nuclear spins and hence a larger signal to noise ratio (SNR) in the resultant images. The interest in sodium in particular stems from the knowledge about the cellular sodium-potassium pump, a trans-membrane enzyme which regulates the intracellular sodium concentration, keeping it at approximately 10 mM compared to an extracellular concentration of ~140 mM. In many diseases, these concentrations are known to change and hence measurements of sodium concentration in tissue can provide information on the status of the tissue, potentially aiding in disease diagnosis or therapy monitoring. For example in stroke, the bioenergetic failure which occurs within minutes of the ischaemic event disrupts the Na^+/K^+ -ATPase pump function (which, depending on the cell type, is responsible for between one and two thirds of the cell’s energy expenditure), having a consequent effect on the intracellular and hence total tissue sodium concentration (TSC). Animal models of cerebral ischaemia have been used to study the underlying physiological mechanisms of tissue damage following a stroke, and hence considerable recent interest has focussed on the possible use of Na-MRI in this area. For example, several studies have attempted to identify a viability threshold for the TSC, above which tissue may be considered to be irreversibly damaged, but below which tissue may still be viable and therefore amenable to a therapeutic intervention [1-3]. However, limitations in the spatial and temporal resolution of images obtained in these studies, coupled with the fact that it was only possible to measure relative rather than absolute TSC values, have resulted in contradictory data in the published literature relating to the TSC time course evolution [4-7]. Consequently the viability threshold hypothesis has not been verified to date, nor indeed has a determination been reached as to the ultimate usefulness of Na-MRI in stroke.

For stroke studies, the acute phase covering the immediate hours after the stroke occurred is of primary importance, since it is only during this time period that stroke patients may be offered a therapeutic intervention (typically within 4 hours of start of stroke). Hence a stable system capable of monitoring the evolution of the

TSC with a high temporal resolution (ideally < 10-20 minutes per acquisition) is required. For rodent brain imaging, optimising the SNR necessitates the use of a surface coil placed close to the brain. Although such a coil can be used to both transmit the B_1 field and detect the signal, the use of such transceiver coils is not ideal due to the highly inhomogeneous nature of the B_1 field which renders accurate quantification of the TSC very difficult. The use of adiabatic radiofrequency pulses can be used to mitigate the effects of B_1 -field inhomogeneity. However these come at the expense of longer minimum time to echo (TE) values, which negatively affect the quantification accuracy due to the presence of a short T_2 -relaxation component of sodium nuclei *in vivo* (~ 1 ms). Although volume resonators may be used to produce very homogeneous B_1 fields, their limited signal sensitivity significantly reduces the achievable SNR [8]. The optimal solution for accurate TSC quantification consists of a volume resonator for B_1 field transmission and a separate surface coil for detection [9]. The benefits of this set-up have been demonstrated previously as part of single-tuned ^1H [8], ^{23}Na [9], and double-tuned $^1\text{H}/^{129}\text{Xe}$ [10] transmit-only receive-only (TORO) coil systems. However, such a TORO solution, while common in clinical MRI, has proved difficult to realise in rodent imaging due to the small sizes involved: with coil dimensions of the order of only 20 mm in diameter, the two resonators interact strongly with each other, significantly reducing the achievable SNR. To avoid such SNR losses, the transmit-only volume resonator must be electro-magnetically decoupled from the detector coil, which imposes a considerable challenge on the design of the surface detector coil. A further complication arises from the desire to acquire both ^1H and ^{23}Na images using the same coil arrangement, in order to facilitate image co-registration, requiring the development of a dual-tuned $^1\text{H}/^{23}\text{Na}$ volume resonator.

The aim of the current study was twofold: first, to develop a TORO system comprising of a dual-tuned $^1\text{H}/^{23}\text{Na}$ volume resonator optimised for transmit homogeneity and a ^{23}Na surface detector coil optimised for SNR; second, to develop a technique for generating TSC parametric maps using a UTE pulse sequence and a correction scheme for the surface coil's inherent detection sensitivity profile. The quantification accuracy was assessed using a range of test phantoms and the technique applied to an *in vivo* model of cerebral ischaemia to demonstrate the potential of the technique.

2. Methodology

2.1 Double-tuned $^{23}\text{Na}/^1\text{H}$ dual resonator system

The foremost design criterion for the dual resonator system was to generate an optimally homogeneous ^{23}Na B_1 field with the volume resonator, while receiving high SNR with a surface coil in order to maximise the accuracy of the TSC quantification. A secondary design criterion for the double-tuned $^1\text{H}/^{23}\text{Na}$ volume resonator was to maximise the efficiency of the ^1H channel, which ultimately was used for the acquisition of high resolution ^1H images for registration with the low resolution ^{23}Na images. A similar optimisation of the ^{23}Na channel was not required, since this channel was not used for signal detection and all desired ^{23}Na transmit B_1 fields (and hence flip angles) could be obtained by the large variability in power that could be delivered to the resonator.

A 12-rung double-tuned $^{23}\text{Na}/^1\text{H}$ birdcage volume resonator was developed for use on a 7 T MRI system (70/30 BioSpec, Bruker BioSpin GmbH, Germany), which generated a linearly polarised B_1 -field at the respective Larmor frequencies (79.4 and 300.3 MHz). A high-pass rather than a low-pass birdcage design was used in order to avoid the use of extremely small capacitance values which would be required for the latter; at 7 T and for rat dimensions, tuning capacitance values of < 2 nF would be necessary for a low-pass birdcage design, which are inherently difficult to manufacture with the high degree of accuracy required to ensure perfect balancing of each saddle around the birdcage structure. The resonator (pictured in Figure 1) was wrapped on a fibreglass former of internal diameter 72 mm, sufficient to fit a large rat (up to 800g). The birdcage structure was covered by a radiofrequency shield of outer diameter 112 mm, comprised of a series of longitudinal copper strips interconnected with 1 nF chip capacitors (CHB, Temex, France) to minimize the possibility of eddy current generation. This shield was necessary in order to prevent interaction with the nearby gradient coils, which would induce eddy currents and tend to destabilise the finely-tuned resonance properties of the resonator. The dual-frequency mode was achieved by inserting trap circuits into each saddle, where a trap capacitance of 15 pF was required and each trap circuit was finely tuned by adjusting the trap inductors (2 windings, 0.8mm wire diameter, 6mm loop diameter). The capacitance required at the other end of each saddle was 62.8 pF.

The capacitive and inductive components at the cable connection points for the ^1H and ^{23}Na channels and at opposite sites were removed from the saddle segment and replaced by two 820pF series capacitors. The variable tuning capacitors (2 to 120 pF, NMTM120CE, Voltronics) were mounted in between the resonator and the RF shield. The ^1H and ^{23}Na connection points were designed to be located with a 90° shift with respect to each other, resulting in a perpendicular orientation of the ^{23}Na and ^1H B_1 fields generated by the structure. The resulting geometric decoupling of the B_1 fields inherent to this design served to minimise cross-talk between the channels, thereby minimising the RF power dissipation of the ^{23}Na B_1 field in the ^1H channel and *vice versa*. To this end, the structure's symmetry was maintained during tuning by mechanically coupling both tuning trimmer capacitors through the use of a cog-based mechanical coupling mechanism attached to the resonator's former, so that the tuning rod changed both tuning capacitors simultaneously, thereby maintaining the circuit balance.

Figure 1: The in-house built $^1\text{H}/^{23}\text{Na}$ birdcage volume resonator with RF-shield on the left side

To enable the use of a ^{23}Na receive-only surface coil in conjunction with the birdcage resonator, the latter was actively decoupled during the receive phase. Although it is possible to geometrically decouple coils, for example by arranging the orientation of the plane of the surface coil parallel to the B_1 -field of the birdcage, the accurate geometric decoupling of identically-tuned resonators is difficult to set-up in practice without the use of a network analyser beside the MRI system, and thus it is impractical for *in vivo* experimentation to rely exclusively on this approach.

Consequently, in addition to the use of geometric decoupling by aligning the coils by eye in the MRI system, the use of active decoupling was incorporated into the design of each radiofrequency coil. In this way, an active decoupling signal from the MRI scanner was used to switch the coils on- or off-resonance at the appropriate time during the imaging pulse sequence. This was achieved by incorporating a PIN-diode switched trap circuit into the resonance structure, designed such that the coil was on-resonance as long as the PIN-diode was reverse-biased, i.e. the coil had to be switched off-resonance by applying a suitable DC voltage (+5/-35V), which was supplied by the MRI scanner. The DC potential was separated from RF ground through the use of high value capacitors (1 nF, CHB, TEMEX, France) while the RF potential was separated from DC ground using RF chokes (4.7 μ H, IM4, Vishay, France).

To characterise the performance of the birdcage volume resonator, a series of bench-level tests were carried out. The ^{23}Na and ^1H relative B_1 field strengths were measured for a circular 2D slice with 3 cm diameter covering the centre of the resonator using an automated positioning system with a measurement resolution of ± 0.1 mm, wherein the resonator was driven by an output port of a network analyser (E5061A, Agilent, USA) while the RF field at every position within the region of interest was measured with a custom-designed, small, weakly coupling pick-up loop of diameter 12 mm. The voltage *emf* induced in this coil was rectified using a pair of Schottky diodes and a low pass filter, so that signal losses and distortions due to sensor-resonator interactions could be prevented, with the resultant signal fed back into the network analyser. The loaded and unloaded quality factors (“Q-factors”) were measured using s_{11} reflection network analyser measurements, with loaded conditions simulated with phantoms containing physiological concentrations of NaCl in an agar gel suspension. The degree of isolation achieved through the use of the active decoupling circuitry was determined using s_{21} transmission network analyser measurements.

2.2 Receive-only ^{23}Na surface detector coil

The circuit diagram for the receive-only ^{23}Na surface detector coil is presented in Figure 2. This coil was constructed from 1.5 mm diameter copper wire, with two co-centric winding loops of diameters 20 mm and 30 mm. The use of two such loops with a 3 mm gap between the windings was found to optimise the detected SNR for a

coil suitable for rat brain imaging; reducing the gap and increasing the number of windings tended to reduce the SNR. The windings, which were initially planar, were wrapped around a 42 mm diameter cylinder to better fit the anatomy of the rat head, which increases the detection sensitivity with depth into the sample. Split tuning capacitors in the coil's circuit (C_{t1} and C_{t2} in Figure 2: 56 pF and 47pF, CHB series, TEMEX, France) were used for balancing purposes. The resonator was variably tuneable via a trimmer capacitor, C_t (0.5 to 6 pF, NMQM6GE, Voltronics, USA). The matching and tuning circuit was mounted on a strip board (42 x 120 mm², AJB16, Farnell, Ireland) to which the resonance loop was soldered. Non-magnetic coaxial cable with matching BNC connectors (RG316 and 11BNC50-2-13-133NE respectively, Huber and Suhner, Switzerland) were used to transmit the RF signal from the receiver coil to the preamplifier of the Bruker MRI system. Active decoupling was achieved using a similar PIN-diode (UM9401SM, Microsemi, USA) switched trap circuit idea as that used for the birdcage resonator. Again, to block the RF from dissipating in the DC supply cable, 4.7 μ H Rf chokes (IM4, Vishay, France) were introduced into the DC path which acted as low impedance for the DC current but high impedance for the RF current. Similarly, the separation of the DC and RF ground was achieved via two blocking capacitors (1 nF, CHB, TEMEX, France) inserted into the trap circuit in series with the trap circuit inductor.

Figure 2: Circuit diagram of the receive-only ²³Na surface coil with the active decoupling circuit indicated in red (RFC is a Radio Frequency Choke, R_D is the Diode Resistance (47 Ω), and the 1 nF capacitors are DC blocking capacitors).

The coil characterisation was performed using similar tests as used for the birdcage volume resonator. The s_{21} -attenuation was measured for the on- and

off-resonance coil modes using a 20 mm diameter pick-up loop. The difference in transmission attenuation at the 79.4 MHz resonance frequency was used as a measure of active decoupling. The coil was further compared to a commercial transceiver $^1\text{H}/^{23}\text{Na}$ surface coil (Bruker BioSpin GmbH, Germany), with coil sensitivity profiles measured across images of a test phantom containing a 4 M NaCl solution obtained with a standard 2D FLASH sequence.

2.3 *In Vivo MR Image Acquisition and Reconstruction*

An optimized 2D Ultra-short Echo Time (UTE) sequence (ParaVision 5.0, Bruker BioSpin GmbH, Ettlingen, Germany) was used to acquire high quality ^{23}Na *in vivo* images. Using this technique, a TE of 853 μs was achieved, which helped to minimise T_2 -weighting effects on the measured signal intensity. T_1 -weighting effects were also minimised through the use of a relatively long TR of 200 ms, considering that the T_1 for ^{23}Na *in vivo* is in the region of 40 ms [11, 12]. Typical TR values quoted in the literature for Na-MRI range from 100 to 120 ms, aimed primarily at maximising the SNR through the use of multiple signal averaging within a reasonable acquisition time [13, 14]. In the current study, it was highly desirable to avoid any possible effects of T_1 -weighting on the TSC quantification, particularly in view of the realistic expectation that the T_1 values might change during the 8 hour time course of the experiment covering the acute stroke phase. The sequence parameters were further optimised for gradient duty cycle to allow for the acquisition of stable *in vivo* ^{23}Na images with the required high spatio-temporal resolution for this extended imaging time without overheating the system (*Table 1*). To maximise the SNR per unit time, the bandwidth was set to 15 kHz, the lowest value possible with the electronics on the 7 T Bruker system used for the *in vivo* experiments. A large field of view (FOV) of 20 x 20 cm was imaged to further prevent gradient overheating and minimise gradient delay-related artefacts, which can occur in the k -space centre due to temporal deviations as little as 50 μs in the gradient delay times. The use of such a large FOV reduced the requirement for strong gradient changes steps, thereby reducing the effect of these gradient-related issues. To achieve an in-plane spatial resolution of 1mm, 256 matrix elements were acquired across this FOV. The use of such a large FOV allowed for 8-times undersampling of the k -space data to reduce the acquisition time; streaking artefacts introduced by the k -space undersampling, which

were evident primarily in the outer regions of the images, were effectively removed by cropping the images to display only the object of interest (that is, the phantoms or rat brain). The number of multiple slices that could be acquired within the TR of 200 ms was restricted to five and hence accurate slice positioning was required in each rat in order to cover the entire stroke lesion. This was achieved by positioning the ^{23}Na slice stack in the middle of the frontal cortex using the ^1H images as a guide. The availability of good quality anatomical images is vital in this regard, necessitating the use of a dual-tuned resonator for *in vivo* qNa-MRI applications. The 2D-radial data sets were reconstructed using a nearest neighbour regridding algorithm implemented in Matlab[®] (The Mathworks, Natick, MA, USA) using code developed in-house. The regridded data were filtered using a Hanning window before inverse Fourier transformation.

Table 1: Sequence parameters used for *in vivo* ^{23}Na and ^1H imaging of the brain ^{*}.

	^{23}Na	^1H
<i>Sequence</i>	2D UTE	2D RARE
<i>FoV</i>	20 cm x 20 cm	8 cm x 8 cm
<i>MTX</i>	256 x 256 (100 projections).	256 x 256
<i>ST</i>	2 mm	2 mm
<i>TA</i>	10 min	5 min
<i>TE</i>	853 μs	64 ms (RARE-factor 8)
<i>TR</i>	200 ms	3262 ms
<i>FA</i>	90°	90°/ 180°
<i>BW</i>	15 kHz	50 kHz

^{*}. The following parameters are listed: Field of View (FoV), Matrix Size (MTX), Slice Thickness (ST), Acquisition Time (TA), Echo Time (TE), Repetition Time (TR), Flip Angle (FA), Band width (BW)

2.4 TSC Quantification

To quantify the TSC (combined intracellular and extracellular Na^+) in the rat brain, the following approach was used. In addition to scanning the sample (i.e. the rat head), a separate scan was acquired of a homogeneous reference phantom. In both scans, an 8 mm diameter cylindrical fiducial vial, permanently attached to the top of the surface detector coil, was included in the scanning field of view. Using this system, the sensitivity profile of the surface coil could be compensated for (assuming a relatively homogeneous B_1 -field generated by the birdcage resonator), while also allowing for the quantification of the TSC, as implemented using code developed in-house in Matlab[®] (The Mathworks, Natick, MA, USA) and explained in the following sections.

The homogeneous reference phantom was comprised of a 40 mm diameter cylindrical container filled with 120 mM NaCl dissolved in distilled water and suspended in a 1 % agarose gel. The reference and sample images were first co-registered relative to the position of the surface coil. This was accomplished using the image of the fiducial vial, which contained 50 mM NaCl dissolved in distilled water and suspended in a 1 % agarose gel. The homogeneous fiducial vial also exhibited the sensitivity profile of the detector coil, which allowed for the use of a semi-automated three-dimensional registration procedure. After co-registering the reference (R) and sample (S) images, a quotient image (Q) was computed as:

$$Q_j = \frac{S - \overline{N_S}}{\sigma(N_S)} \cdot \frac{\sigma(N_R)}{R - \overline{N_R}}, \quad (1)$$

where N_S and N_R are the Regions of Interest (RoIs) representing sample and reference noise, chosen as square regions with 250 pixels at the upper left corner in each image, and σ are the respective standard deviations of the noise. The averaged noise magnitudes were usually different in sample and reference images, and led to a ^{23}Na concentration offset when they were not taken into account, as observed previously [15]. Therefore, it was necessary to divide the SNR values by each other rather than dividing pure image intensities. The sample, reference, and quotient images are presented in Figures 3(a), (b) and (c) respectively, where the sample in this case consisted of a test concentration phantom composed of five compartments containing different ^{23}Na concentrations (four cylindrical vials surrounded by a fifth compartment). An increase in the noise intensity is evident, particularly outside the sample, resulting from the amplification following the division operation (Figure 4(c)). The dark band above the test concentration phantom in Figure 3(c) arose due to the different sizes of the reference and test concentration phantoms (thinner wall for the former), which resulted in signal closer to the coil for the reference phantom, in turn resulting in the dark band following calculation of the quotient image, but did not affect the quantification of the compartments in the test concentration phantom.

(a)

(b)

(c)

Figure 3: (a) SNR map of the sample, in this case a test concentration phantom, which was divided by (b) the co-registered SNR map of the reference phantom, to compute (c) a sensitivity-corrected quotient image.

To compensate for sample-dependent loading of the detector coil, the pixel values in the quotient image were modified by the signal measured in an area of known ^{23}Na concentration within the sample. For experiments involving the test concentration phantom, the compartment containing 130 mM was used for this purpose. For *in vivo* experiments, the value of the TSC of the healthy rat brain was used; this value has been well established in the literature, with a value of 45 ± 4 mM measured by MRI and validated by the gold standard *ex vivo* ^{22}Na radionuclide method [16]. The same TSC value has also been measured in quantitative ^{23}Na MRI studies of the healthy human brain [17, 18]. Thus the signal averaged across a RoI located in the contralateral side of the rats' brain was assumed to represent a TSC value of 45 mM, since it was known that this part of the brain was not exposed to a reduction in cerebral blood flow following the stroke [19]. A similar reference approach was adopted in two recent studies [11] [20].

The ratio of the mean signal magnitudes in the reference (F_R) and sample (F_S) images was computed for RoIs in the quotient image corresponding to the area of known ^{23}Na concentration $c(F_S)$ in the sample image (i.e. corresponding to the 130 mM compartment or the contralateral brain for the phantom or *in vivo* experiments, respectively). The correction factor accounting for the variable loading was then computed as:

$$cor = \frac{\overline{F_R} - \overline{N_R}}{\sigma(N_R)} \cdot \frac{\sigma(N_S)}{\overline{F_S} - \overline{N_S}} \quad (2)$$

To quantify the TSC in each voxel, j , the correction factor was applied to the pixel values in the quotient image, Q_j and multiplied by the chosen reference ^{23}Na concentration value, *conc*:

$$TSC_j = Q_j \cdot cor \cdot conc. \quad (3)$$

To assess the quantification accuracy and confirm that T_2 -weighting effects were minimal, two phantoms were scanned. The first was the test concentration phantom discussed previously. The second phantom had the same physical structure, but with each of the four compartments containing 500 mM NaCl suspended in 0, 1, 2 and 3 % agarose gels respectively, each surrounded by a 5 % agarose gel suspension again with 500 mM NaCl concentration.

2.5 TSC Measurements after Stroke

In vivo experiments were performed under license from the UK Home Office and were subject to the Animals (Scientific Procedures) Act, 1986. The intraluminal thread model of middle cerebral artery occlusion (MCAO) was used to induce an experimental stroke, wherein the right MCA was occluded in one male Sprague Dawley rat (bodyweight ~ 310 g). The contralateral hemisphere served as a control during the experiments. Blood pressure, heart rate, body temperature, and blood gases were monitored and maintained within normal limits. At the end of scanning experiment the animal was killed by transcardial perfusion fixation using 4 % paraformaldehyde in a phosphate buffer. Following fixation, the brain was harvested, processed, and embedded in paraffin wax and subsequently sectioned at 6 μ m and stained with haematoxylin and eosin for histological analysis.

The continual real-time monitoring of the physiological parameters of the rat was critically important in order to maintain its stability during the long duration (typically ~ 8 h) of the experiment. From previous experience with this model of cerebral ischemia, penumbra tissue was expected to occur primarily in the dorsolateral regions of the MCA territory cortex which receives collateral blood flow from the anterior cerebral artery. End artery subcortical (striatal) tissue within the MCA territory was believed to be permanently damaged from a very early stage after stroke onset [19]. The TSC time course was extracted from two manually selected ROIs (cortex and subcortex) within the ischaemic lesion and from one ROI on the contralateral normal hemisphere.

3. Results

3.1 RF Coil Characterisation

The characteristic coil parameters for the volume resonator are presented in Table 2. A decoupling of -34.4 dB was achieved for the ^{23}Na channel using active decoupling alone; typically, a value in excess of -30dB is considered to be sufficient isolation between channels [8]. A B_1 -field homogeneity of $\pm 3.8\%$ for the ^1H channel and $\pm 4.5\%$ for the ^{23}Na channel was achieved across the circular area with 3 cm diameter. The ^{23}Na B_1 field map is shown in Figure 4.

Table 2: System parameters of the double-tuned $^{23}\text{Na}/^1\text{H}$ birdcage coil.

	Q_{unloaded}	Q_{loaded}	B_1 field homogeneity γ	Dynamic Range (MHz)	Decoupling from ^{23}Na (dB)	Decoupling from ^1H (dB)	^{23}Na Active Decoupling (dB)
^{23}Na channel	82	64	3.8 %	78.8 - 79.9	-	-40.4	-34.4
^1H channel	142	56	4.5 %	294 - 306	-31.1	-	-

Figure 4: ^{23}Na B_1 -field homogeneity for the $^1\text{H}/^{23}\text{Na}$ birdcage coil. The diameter of the measured circular area (colour area in this figure) was 6.5 cm, while the white bar represents 1 cm length. B_1 -field homogeneity was determined over a circle of diameter 3 cm located at the centre: $^1\text{H} \pm 3.8\%$ $^{23}\text{Na} \pm 4.5\%$; and over a 5 cm diameter $^1\text{H} \pm 6.8\%$ $^{23}\text{Na} \pm 7.8\%$.

The results for the ^{23}Na surface detector coil are presented in Table 3. A decoupling of -36 dB was measured with the pick-up coil. The active decoupling between the receive-only surface coil and the volume resonator was measured for the worst case scenario of complete geometric coupling between the two coils, i.e. the B_1 -field from the volume resonator oriented orthogonally to the plane of the surface coil: the decoupling was better than -23 dB during the transmit period, when the surface coil was switched off-resonance. In practice, the coils were geometrically decoupled by visually aligning the plane of the surface coil parallel with the B_1 field of the volume resonator when setting up phantom or *in vivo* experiments, and so the actual decoupling typically achieved was < -35 dB. The dual resonator system was compared to an existing commercial transceiver surface coil (TXRX). The

comparison of the coil profiles measured in the images obtained from both coil set-ups using the 2D FLASH imaging sequence are presented in Figure 5, where the improvement in the in-house built coil at depth can be seen. A 3-fold increase in SNR was measured at a depth of 12 mm, a depth typical of the brain within the rat head. It should be noted that this increase in SNR was achieved with the additional benefit of a uniform transmit B_1 field, allowing for accurate quantification of the sodium concentration, which is not possible with a transceiver surface coil.

Table 3: System parameters of the ^{23}Na receive-only surface detector coil.

Q_{unloaded}	Q_{loaded}	Pick-up coil decoupling (in dB)	Receive active decoupling (in dB)	Transmit active decoupling (in dB)
142	125	-36	-25	-23

Figure 5: Comparison of the SNR profiles measured in a 4 M NaCl solution phantom using the ^{23}Na receive-only coil and commercial $^{23}\text{Na}/^1\text{H}$ transceiver surface coil. The flip angle was adjusted at approximately 90° across the entire sample for the transmit-only receive-only (TORO) system and to the sample surface for the transceiver (TXRX) system.

3.2 TSC Quantification accuracy

A quantified parametric map of ^{23}Na concentration in the test concentration phantom, together with a comparison of the set versus measured TSC values, is presented in Figure 6(a) and (b), demonstrating the linearity of the quantification technique. The range of ^{23}Na concentrations used in this phantom was chosen to be representative of that which occurs in both healthy and diseased brain tissue, to test the quantification accuracy under realistic conditions. Using the optimised UTE sequence's image

acquisition parameters (i.e. voxel sizes of 1.2 μl acquired in 10 minutes), a quantification accuracy of less than 10 mM was achieved. The suppression of T_2 -weighting effects was tested on a second phantom containing different agarose gel concentrations but the same ^{23}Na concentration. The resulting ^{23}Na concentration map is presented in Figure 6(c), showing that no differences in the quantified ^{23}Na concentrations were measured (Figure 6(d)) for this range of gel concentrations (corresponding to T_2 relaxation values in the range of approximately 20 – 50 ms, as measured by ^{23}Na relaxometry)

Figure 6: (a) Quantitative ^{23}Na concentration map of the test concentration phantom. (b) The quantified ^{23}Na concentrations as a function of set ^{23}Na concentrations, illustrating good linearity across the physiologically and pathophysiologically relevant range of ^{23}Na concentrations. (c) The ^{23}Na concentration map for the T_2 -relaxation times replicating phantom. (d) Measured ^{23}Na concentrations as a function of set (500 mM) agarose gel concentration. Note the independence of the measured ^{23}Na concentration from the gel concentration for 0 to 5 % gels. Note also the ^1H signal difference between solution and gel compartments in the inset ^1H T_2 -weighted image. Colour bars are in units of mM.

3.3 In Vivo Stroke Experiment

TSC maps computed for the *in vivo* stroke study are presented in Figure 7, showing the evolution of the TSC across the five imaged brain slices. To segment out the brain from the head, ^1H images acquired with the volume resonator were used to generate a mask representing the edge of the brain, which was then superimposed on the ^{23}Na images and used to cut-away non-brain regions. Clear increases in TSC

during this time period are evident in these maps, from a normal value of ~ 45 mM to approximately 140 mM by 7 hours post-MCAO. The maps also reveal regional variations in TSC increase, for example between the ischaemic subcortical and cortex regions: while the former exhibited an increase in TSC within 1 hour of the MCAO, the latter did not begin to increase until after 4 hours post-MCAO. The averaged TSC values over subcortical (core), cortical (periphery), and contralateral normal tissue were extracted from respective ROIs in TSC maps and graphed in Figure 8. The location of the ROIs were determined by reference to a standard rat brain atlas [21]. In contralateral normal tissue, TSC remained constant over the entire scanning time, whereas increasing TSC was measured in both the periphery and the core stroke regions. Major regional differences were observed in the onset time of TSC increases, with delay times approaching 2 hours measured in the peripheral regions.

Figure 7: The evolution of TSC after MCAO for 5 coronal slices (rows) across 7.7 hours (columns) in the stroke rat brain. Times after MCAO are labelled above each column. Note the TSC changes in the ischemic right hemisphere (left side on these TSC maps) after MCAO. Also note the delayed TSC increase in the cortex (red arrow) compared to the subcortex (white arrow).

Figure 8: TSC in manually-selected ROIs corresponding to regions of subcortex (black), cortex (blue), and contralateral normal tissue (red) as a function of time in the acute phase after MCAO. Note that TSC at 1hour after MCAO was higher in subcortex and lower in cortex compared to TSC in contralateral normal tissue, whereas TSC in contralateral normal tissue remained constant.

Discussion

The SNR deficit inherent to all X-nuclei MR imaging must be tackled not only through the use of high field MRI systems, but also with dedicated radiofrequency coil systems capable of delivering sufficient SNR to produce high spatial resolution images in reasonable acquisition times. The need to dual-tune X-nuclei coils with the ^1H frequency, coupled with the required channel isolation, has resulted in most attention being paid to coils for ^1H applications where SNR continues to be an issue. However, the dual resonator system developed in the current study demonstrates that significant improvements in SNR and penetration depth can be achieved through careful coil design. The quantification accuracy, which is a particularly important feature for longitudinal stroke studies, benefits significantly from the use of a homogeneous B_1 field producing a uniform flip angle distribution across the sample. While this has been well known for some time, the ability to concomitantly maintain a high SNR with such rodent coil systems has proved difficult to achieve. Measuring and compensating for flip angle variations is possible for ^1H -MRI, but such strategies are difficult to perform in practice for ^{23}Na -MRI due to the lower SNR and hence are prone to significant error. On the other hand, compensating for the inherent detection sensitivity profile of the surface detector coil is relatively straightforward to perform, as demonstrated here.

The quantification accuracy of < 10 mM achieved in the current study for image voxels of $1.2 \mu\text{l}$ acquired in 10 minutes demonstrates to the ability of the Na-

MRI technique to reveal subtle changes in TSC *in vivo*. Although the TSC was measured to increase from a healthy value of 45 mM to approximately 140 mM, the ability to detect differences in TSC evolution in spatially distinct brain regions may shed further light on the pathophysiology of the acute stroke phase. For example, the observed delayed increase of TSC between ischaemic cortical and subcortical regions may indicate penumbral tissue in areas of delayed increase, that is tissue which is at risk of infarction but is still amenable to a therapeutic intervention. Further experiments are required to verify this hypothesis. A further refinement of the methodology would be the use of a 3D rather than 2D UTE sequence, which would be expected to further increase the achievable SNR due to a decrease in TE.

The intra-luminal thread model of cerebral ischaemia is particularly well suited to study the subtle changes in TSC in the acute phase of a stroke as it produces a reproducible infarct in the brain, and further it reduces the incidence of artefacts due to inflammation and oedema at the imaged slice location since the surgical site for introducing the filament into the vasculature is some distance from the site of ischaemia. However, equally important, the model allows for the rapid transfer of the rat into the MRI system after the surgery is performed, allowing for the acquisition of TSC time course data from as early as 30 minutes after stroke onset time. Indeed, in the current study, the first data point after MCAO was sampled significantly earlier than in previously reported MCAO rat studies, where delays of between 2 to 4 hours have been reported [6, 22]. (although the former study did report a delay of 1.1 hour for one rat) As a result, the evolution of the TSC in the crucial early phase after MCAO was not measured which may have lead to erroneous conclusions about regional TSC changes in these studies.

In conclusion, a dual coil system for performing quantitative ^{23}Na -MRI in small rodents was developed, which demonstrated excellent B_1 -field homogeneity and SNR performance compared to similar coil systems reported in the literature and compared to a commercially-available transceiver coil. The stability of the coil system was ensured by incorporating variable and balanced tuning and matching capabilities at each channel on the birdcage volume resonator and also at the ^{23}Na surface detector coil. The system achieved a quantification accuracy of < 10 mM for image voxels of only $1.2\ \mu\text{l}$ acquired in 10 minutes, and was successfully used to monitor the increase in tissue sodium concentration in ischaemic tissue following the

induction of an experimental stroke in the rat brain. The system could be easily applied to the study of other diseases and conditions such as cancer, Alzheimer's disease, aging, arthritis and paramyotonia.

Acknowledgements

This work was financially supported by Science Foundation Ireland (SFI) under the Research Frontiers Program, grant number "05/RFP/PHY006".

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