SODIUM IMAGING IN THE BRAIN

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HIGHLIGHTS

Sodium
- is an important ion for healthy brain functioning
- is the second most abundant MR visible nucleus in tissue
- requires specialized hardware and pulse sequences to image it in the brain
- may be a novel biomarker of cellular metabolism in neurological disorders

INTRODUCTION

Magnetic resonance imaging (MRI) is a powerful, and lucky for us, flexible tool for the interrogation of brain disorders because of the variety of molecular properties that can create unique image contrast, as well as the different MR-visible nuclei for assessing complementary aspects of tissue metabolism. MRI is well known for its measurements of water. After hydrogen (^{1}H), sodium (^{23}Na) is the second most abundant MRI observable nucleus in living tissue. The sodium ion plays a key metabolic role in the brain for the conduction of action potentials, osmotic balance, etc. An important aim of MRI is to provide "in vivo pathology" that identifies not only whether a brain region is abnormal, but importantly also yields specific clues as to the nature of the underlying differences at the micro-structural level (e.g. demyelination, axon loss, etc). This is key for understanding the basis and diversity of a clinical disorder, identifying links of brain structure with cognitive (dis)ability or other performance (e.g. motor), and yielding quantitative biomarkers to follow disease progression or treatment effects.

CHALLENGES WITH IMAGING SODIUM

First, sodium is a spin 3/2 nucleus with an electric quadrupole moment that produces very rapid bi-exponential signal decay (T_2 of brain at 4.7T: 2.9 ms - 60% and 29 ms - 40%) and rapid longitudinal relaxation (T_1 ~ 36 ms); recall that ^{1}H is a spin 1/2 nucleus. Second, ^{23}Na has a lower gyromagnetic ratio (reduced sensitivity) and a much smaller concentration (20-60 mM in normal brain tissue) than ^{1}H (110 M), yielding much less signal (~0.02%). To accommodate reduced signal, comparably low-resolution images must be generated for sufficient signal-to-noise ratio (SNR); higher field magnets are also important to enhance much needed SNR. Sodium MRI cannot compete with ^{1}H MRI for anatomical detail but may contribute other unique information. Third, ^{23}Na excitation and detection requires specialized hardware such as a broadband RF amplifier and appropriately tuned RF coils (i.e. Larmor frequency of 34 MHz for ^{23}Na at 3T, compared to 127 MHz for ^{1}H) – most clinical MRI scanners do not come with this, although this is a more common option for modern high field scanners (animal scanners usually have this capability). Simple birdcage RF coils are effective. Fourth, centre-out k-space acquisition techniques are needed to reduce the echo-time (TE) to sub-ms, thereby minimizing excessive signal loss as a result of the very short T_2 relaxation of sodium. The short T_1 is advantageous as it permits 3D imaging in a reasonable time by allowing short repetition times (TR). One drawback of straight 3D-radial acquisition is that *many* 'spokes' are required to fill k-space, but other strategies such as twisted projection imaging, TPI [1] (**Figure 1)**, can reduce the number of required acquisitions dramatically. Scan times are on the order of 5-30 minutes depending on the nominal resolution, method, and field strength. The use of 2D gradient-recalled echo, even though it is readily available on clinical scanners, is ill-advised as the TEs are too long and the image quality suffers far too much. Careful selection of acquisition parameters is paramount.

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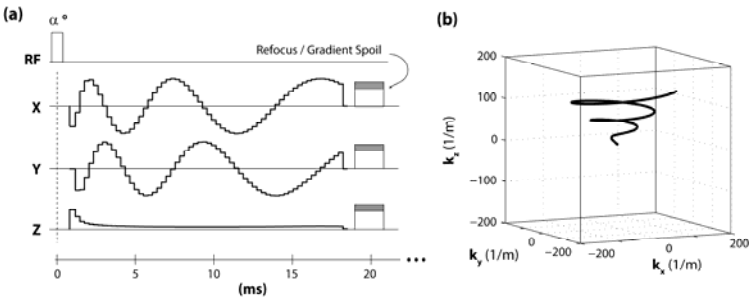

Figure 1 : Sodium imaging needs specialized sequences like twisted projection imaging (TPI) with very short echo time to acquire sufficient signal. The gradient waveforms in **(a)** determine the 3D k-space sampling trajectory shown in **(b)**. Only one trajectory is shown.

SODIUM MRI OF THE BRAIN

The first sodium images of the human brain were created in 1985 [2]. Since then, there are only about 22 published studies of human brain pathology on tumour [3-11], stroke [12-17], hemorrhage [18], Alzheimer's disease [19], Huntington's disease [20], and multiple sclerosis [21-24]. It should be noted that over half of these studies have been published within the last five years or so indicating a surge of interest in sodium MRI, likely coupled with the proliferation of ultra-high field MRI. The rationale for investigating sodium has been: a suspected link between the pathological process and sodium ion channels, a change in sodium compartmentation (e.g. shift from extra- to intra-cellular), and/or sodium accumulation within the tissue. **Figure 2** shows some examples of sodium images of the human brain from a selection of papers.

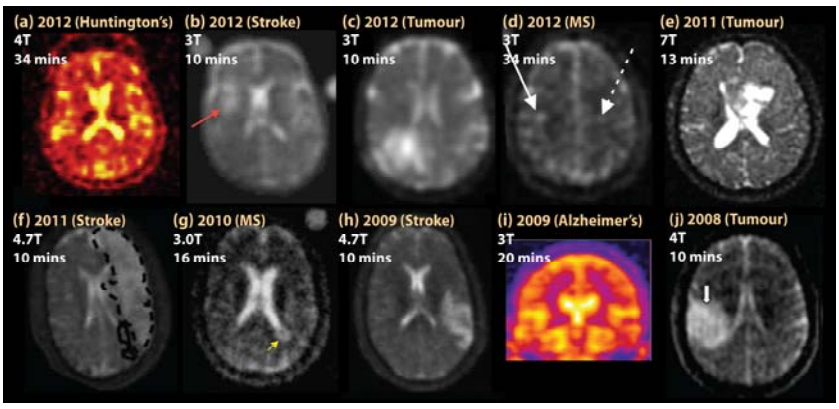

Figure 2 : From 2008-2012, 10 sodium MRI papers (including our two **(f)** and **(h)**) studying human brain pathology have been published: **(a)** [20], **(b)** [17], **(c)** [10], **(d)** [24], **(e)** [11], **(f)** [12], **(g)** [21], **(h)** [16], **(i)** [19] and **(j)** [3]. This is equal to the total number of papers published in the preceding 23 years. The field strength and image acquisition time are shown for each image.

The primary or even 'sole' concern of most sodium MRI studies thus far has been the quantification of tissue sodium concentration (TSC). This requires the minimization of ^{23}Na signal modulation by anything (such as relaxation) other than the concentration of ^{23}Na. The commonly used sequence for "TSC" contains short and non-selective ('hard') 90^{o} RF excitation pulses to shorten TE to < 1 ms to minimize T_2^* signal loss and 'long' (for ^{23}Na) TR in the range of 100–150 ms to minimize the effects of T_1 saturation. However, absolute quantification of TSC may not be the only valuable feature of ^{23}Na MRI.

Standard ^{1}H MRI draws its power from relaxation based contrast, and it is possible that the unique relaxation mechanism of ^{23}Na MRI (i.e. nuclear alignment in the electric field gradients produced by macromolecular structures) may also provide valuable information [25]. Other forms of contrast, which has been a focus of our research, include inversion recovery [26], T_1-weighted [27], T_2^*-weighted [28], and multiple quantum filtering [29,30] to presumably weight the acquired sodium signal towards macromolecular dense environments such as intra-cellular space. These techniques may provide greater specificity but suffer even further losses of SNR and hence undergo considerable scan time/resolution penalties. Despite the challenges, sodium MRI may become a useful and unique biomarker in various neurological disorders.

A SAMPLING OF REFERENCES FOR SODIUM MRI OF HUMAN BRAIN

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