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Compartmentalization of sodium in the human brain: a mini-review of ^{23}Na-MRI methods

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Sodium magnetic resonance imaging is a non-invasive technique that provides information about sodium levels in tissues. It has significant applications in brain research due to the important role of sodium in both normal brain function and pathological processes. Total sodium concentration is the most widely used derived metric; it offers insights into sodium content across different brain regions. However, the functional role of sodium is closely linked to its distribution within intra- and extracellular spaces. Sodium osmotic homeostasis affects the intracellular volume fraction, a parameter that can be altered in various neurological disorders. Unfortunately, distinguishing intracellular from extracellular sodium nuclear magnetic resonance signals is challenging, even with the use of contrast agents. In recent years, several methodologies have been proposed to study sodium compartmentalization in humans, typically involving tailored acquisition techniques and modeling approaches. This mini-review provides a brief overview of the challenges, methodologies, and potential applications of compartmentalized sodium MR imaging in human neuroscience.

KEYWORDS

sodium MRI, ^{23}Na MRI, brain, compartmentalization, neurological diseases, biomarkers, modeling

Introduction

Magnetic resonance imaging (MRI) is a non-invasive imaging technique widely used in clinical practice. Conventional MRI is based on hydrogen nuclei because of their large gyromagnetic ratio and abundance in the human body. Notwithstanding the ubiquitous presence of ^{1}H-based MRI and its flexibility for multiple contrasts, other nuclei can offer insights into specific mechanisms. In recent years, the use of heteronuclear MRI, and in particular, of sodium MRI, has significantly expanded. The dynamics of sodium is crucial for several physiological processes, including neuronal excitability, synaptic transmission, and cellular energy metabolism; indeed, approximately 15% of the gray matter energy budget and 44% of the white matter ATP turnover is believed to be used only to maintain the resting potential, neglecting signaling. Overall, up to 50% of the cortical energy budget is assigned to Na^+/K^+ ATPase [1] and is thus needed to maintain sodium and potassium concentration gradients across the cellular membrane.

For sodium, the intracellular and extracellular concentrations are approximately 10–15 mM and 140 mM, respectively [2, 3]. Dysfunctions in sodium homeostasis are associated with various neurological conditions, including multiple sclerosis (MS), Alzheimer's disease (AD), stroke, epilepsy, and brain tumors [4]. Therefore, sodium represents a promising biomarker [5].

Sodium is the most abundant cation, providing the second strongest nuclear magnetic resonance (NMR) signal in the human body after hydrogen, but its lower gyromagnetic ratio (11.3 MHz/T), lower abundance in the human brain, and nuclear spin of 3/2 imply a sensitivity which is only 9.3% of that of the proton. These factors lead to a poor signal-to-noise ratio (SNR) [2], which is partially compensated by the use of ultra-high field strengths (7 T ad above) [6–9]. Sodium is characterized by a quadrupole magnetic moment, leading to two distinct T_2 relaxation times: a slow component of 15–40 m and a fast component of 0.5–8 ms [10–13]. The fast component accounts for approximately 60% of the total sodium NMR signal, requiring MR sequences with very short echo time (TE).

After the first pioneering sodium studies on humans and intact animals, performed in the early 1980s [14, 15], the feasibility of ^{23}Na-MRI in clinical settings has benefited from recent advances in MRI technology and acquisition strategies. In particular, non-Cartesian k-space sampling offers advantages in terms of spatial resolution and acquisition time [16], while ultrashort TE (UTE) or zero TE (ZTE) sequences allow the detection of the short T_2 tissue components [17]. UTE sequences begin the acquisition with a minimal delay after the excitation pulse [18], while in ZTE sequences, the sampling gradients are turned on before the radiofrequency (RF) excitation pulse. In ZTE sequences, the center of the k-space is crossed at zero echo time, and due to the switching of hardware from the transmit to receive mode, the center of the k-space is not sampled. Different strategies have been developed to overcome this problem, such as single-point acquisitions (PETRA) [19]. UTE and ZTE acquisition techniques can be customized in terms of SNR, total acquisition time, and point spread function by adapting the density of the k-space points. Examples include density-adapted radial sequence [20], 3D cones [21], twisted projection imaging (TPI) [16, 22], and FLORET [23]. Non-Cartesian sequence reconstruction methods use regridding, which involves interpolating the sampled data points in a rectilinear grid [24], and performing fast Fourier transform (FFT) or non-uniform FFT [12] on the regridded data [25].

Sodium compartmentalization

Sodium MRI of the brain can follow different approaches according to the information of interest. The basic approach treats the brain as a single compartment and uses UTE or ZTE sequences to collect spin-density weighted (SDW) ^{23}Na MR data. Then, a calibration is performed in order to determine the tissue sodium concentration (TSC). However, changes in TSC can be the result of independent changes within the intracellular and extracellular compartments (IC and EC, respectively). Moreover, pathologies are often associated with changes in the volume fraction [26]. Distinguishing IC from EC sodium requires a combination of acquisition techniques and mathematical models. Most experimental approaches exploit the different relaxation times between bound sodium and free sodium [27], assuming that the intracellular component is mainly composed of bound sodium. Being generally suppression techniques, that is, techniques that selectively suppress or filter a component of the signal, they tend to suffer from low SNR and incomplete suppression.

Sequences

Some sequences have been introduced to isolate IC sodium, but their effectiveness is still debated. These include triple quantum filtering (TQF), double single-quantum (SQ) acquisition, inversion recovery (IR), and bi-exponential weighting.

TQF

The sodium nucleus is a spin 3/2 system with four degenerate spin states (3/2, ½, −½, and −3/2), and is thus characterized by a quadrupolar moment. The transition between the levels can occur via single, double, or triple quantum coherence; SQ relaxation involving the ±3/2 states (outer levels) is faster (T_{2short}) than the relaxation involving the inner levels (T_{2long}). However, if sodium is free (that is, the motional correlation time is much smaller than the Larmor period), the two exponential decays degenerate to a single, longer decay time [13].

The TQF sequence consists of three excitation pulses with the same flip angle and three different phases. The delays between pulses create higher-order coherences, and the read-out signal consists of contributions from all coherence pathways, which can be selected by phase cycling or gradients. The goal is to retain the signal from bound sodium (intracellular) [28]. The intracellular sodium molar fraction (ISMF) and the TSC can be measured directly with MRI, while the intracellular sodium concentration (ISC) and the intracellular volume fraction can be obtained by the combination of the first two quantities (see the *Mathematical models* section). These parameters can give complementary information about tissue state: for example, an increase of TSC and ISC with no increase of ISMF can follow cellular death, while an increase of ISMF with no increase of TSC is associated with cell swelling [29]. TQF presents several problems: low signal from filtering, high SAR from the multiple RF pulses, and the dependence on T_2 leads to low SNR, long acquisition times, and poor quantification. Fiege et al. proposed a method for simultaneous acquisition of single quantum and TQF to reduce total scan time, called SISTINA [30], which was later optimized and enhanced to include relaxometry [31, 32].

Dual SQ acquisition

Bound (intracellular) sodium is characterized by a bi-exponential decay with a T_{2short} component amounting to approximately 60% of the signal [7, 33–41]; the contribution of the T_{2long} component can be obtained by subtracting an SQ image acquired with a short echo time, where the T_{2short} component is suppressed, from one obtained with an ultrashort echo time, including signals from nearly all sodium nuclei. This technique is characterized by lower SAR and higher SNR than TQF at the expense of incomplete suppression of the T_{2long} signal [27].

IR

Inversion recovery acquisition is a widespread technique used to suppress the signal coming from a specific compartment, exploiting

different T_1 relaxations between tissues. The sequence is a standard spin echo preceded by a 180° RF preparation pulse, where the excitation pulse is applied at the specific inversion time (TI) corresponding to the minimum magnetization in the compartment to suppress. While the extracellular space is rich in molecules, it is less dense than cytoplasm. Thus, EC T_1 is expected to be longer than IC T_1 [42], allowing IR-based selective suppression; in IR-based suppression, SAR can be high, SNR low, and suppression incomplete. However, long (soft) inversion pulses reduce SAR. In sodium MRI, relaxation during long RF pulses cannot be ignored because of very low T_2. It has been shown that by tailoring the duration of a soft inversion pulse, the different relaxation properties of IC and EC compartments allow for efficient extracellular signal attenuation while increasing intracellular magnetization at the EC-nulling TI (Soft Inversion Recovery FLuid Attenuation, SIRFLA) [42]. *In vivo* acquisitions at 4.7 T showed an SNR of 18 for brain tissues and an SNR of 3 for the cerebrospinal fluid (CSF) [43].

Bi-exponential weighting

Another approach is to differentiate between bound and free sodium by exploiting the differences in transverse relaxation [44]. The method is still based on multiple-quantum filtering techniques but with the benefit of improved SNR. Two images with different contrasts are acquired and subtracted to generate a bi-exponential weighted image contrast [44]. The first image is an SDW acquired after the first 90° RF pulse, containing the contribution of all sodium ions, and the second one is a single quantum filtering (SQF) acquired after a second 90° RF pulse, containing mostly signals from mono-exponentially (free) relaxing sodium. The difference image can be calculated as follows [44]:

$$S_{DIM} = S_{SDW} - v S_{SQF},$$

where S indicates the signal, DIM is the difference image method, and v is a weighting factor that takes into account the signal losses between the two acquisitions due to T_2^* relaxation, namely:

$$v = \frac{\exp\left(-\frac{TE_1}{T_2^*}\right)}{\exp\left(-\frac{\tau_1}{T_2^*}\right)\exp\left(-\frac{\tau_2}{T_2^*}\right)\exp\left(-\frac{TE_2}{T_2^*}\right)},$$

where TE1 and TE2 are the two echo times of the acquisitions, and τ_1 and τ_2 are the preparation time and the evolution time, respectively. With this method, 3D biexponentially weighted ^{23}Na images can be obtained with an increase of up to 200% of SNR compared to TQF [44].

Mathematical models

An estimate of tissue-specific sodium concentration can be obtained by applying mathematical models to data acquired with the appropriate weighting. The most used method considers two compartments, IC and EC, but the inclusion of more compartments has been proposed. Madelin et al. [2] developed a three-compartment model by dividing the brain into IC, EC, and a solid-like compartment constituted of cell membranes and nuclei, proteins, and other large molecules. The model was further developed by Gilles et al. [45] to include a CSF compartment.

2CM model

The two-compartment (2CM) approach [8, 46] partitions the tissue into homogeneous IC and EC compartments, characterized by volume V_i, sodium amount M_i, and sodium concentration C_i (i = 1 is IC, and i = 2 is EC). The total sodium concentration TSC (C_T in the equations) is

$$C_T = \frac{M_1 + M_2.}{V_1 + V_2}$$

The intracellular volume fraction η and the intracellular sodium molar fraction ISMF (χ in the equations) can thus be written as

$$\eta = \frac{V_1}{V_1 + V_2} = \frac{C_2 - C_T}{C_2 - C_1.}$$

$$\chi = \frac{M_1}{M_1 + M_2} = \frac{C_1}{C_T}\eta.$$

Combining these equations, it is possible to obtain C_1 and η in terms of C_T, χ, and C_2 [29]:

$$\begin{cases} C_1 = \dfrac{\chi C_T C_2}{C_2 - (1-\chi)C_T}. \\ \eta = 1 - (1-\chi)\dfrac{C_T}{C_2} \end{cases}$$

Total sodium concentration C_T and intracellular sodium molar fraction χ are measurable with MRI (e.g., using TQF). C_2 is assumed to be constant in a range between 136 mmol/L and 142 mmol/L [29].

3CM model

The three-compartment model (3CM)adds to IC and EC a solid compartment (SC, index i = 3) that includes cell membranes, nuclei, proteins, and other metabolites. The solid compartment has no sodium content ($M_3 = 0$ mol and $C_3 = 0$ mmol/L) [2, 47, 48]. The volumes can be expressed by equating $V_1 + V_2$ to the fluid (water) volume fraction w, that is generally 0.7 in the white matter and 0.85 in the grey matter and can be considered equal to 0.775 for the total brain [49].

$$V_1 = (w - \alpha)V_{T.}$$

$$V_2 = \alpha V_{T.}$$

$$V_3 = (1 - w)V_{T.}$$

where α is the extracellular volume fraction. With the 3CM model, the unknown variables are the extracellular volume fraction α and the intracellular sodium concentration C_1. Two sodium measurements are required to estimate these quantities, unsuppressed and suppressed in the EC (e.g., via IR). Considering the TSC as S1, and the IC signal as S2, C1 and α can be calculated as [12]:

$$\alpha = \frac{C_T - \frac{C_1 V_1}{V_T}}{C_2},$$

$$C_1 = \frac{C_2 \frac{C_1 V_1}{V_T}}{C_2 w - C_T + \frac{C_1 V_1}{V_T}},$$

where $C_1 V_1/V_T$ is the apparent ISC that is observed with EC suppression, and w can be estimated by segmentation of coregistered proton images.

4CM model

The four-compartment model (4CM) [45] is a further refinement of the 3CM. Here, the CSF is considered a distinct compartment (i = 4), and

$$V_1 = \alpha_1 V_T,$$

$$V_2 = \alpha_2 V_T,$$

$$V_3 = (1 - w) V_T,$$

$$V_4 = \alpha_4 V_T,$$

where α_i is the volume fraction of each liquid compartment, that is $\alpha_1 + \alpha_2 + \alpha_4 = w$. The model uses the same assumptions of 3CM and considers $C_4 = C_2 \approx 140$ mmol/L. The model is conceptually similar to 3CM but includes a more realistic segmentation. The variables are C_1, and the volume fractions α_i. The estimation requires the simulation of the signal and a multi-pulse sequence exploiting the different relaxation between compartments [45].

Compartmentalized sodium MRI in brain diseases

^{23}Na-MRI is sensitive to physiological and pathological processes that happen during the progression of several neurological diseases [50, 51]: in fact, many brain disorders show sodium concentration anomalies associated with sodium–potassium pump dysfunction or cellular membrane impairment, allowing a sodium MRI to target specific features of the pathology. Anomalies in overall sodium are often caused by an increase in the intracellular sodium concentration or the extracellular volume fraction. Therefore, differentiating the compartments can help and improve the diagnostic information of sodium imaging.

Anomalies in sodium levels play a crucial role in the pathophysiology of multiple sclerosis [52]. The most common form of MS is characterized by a first period of relapsing/remitting (RR) symptoms that later converts into a secondary progression phase (SPMS). RRMS is primarily characterized by demyelination, resulting in impairment of action potential conduction. The demyelinated axons can experience an overexpression of sodium channels along their membranes. Albeit this process re-establishes signal transduction and contributes to clinical remission in RRMS, it is responsible for higher sodium influx, resulting in an increased energy demand to maintain resting potential and sodium homeostasis. Moreover, intra-axonal sodium accumulation contributes to axonal degeneration by reversal of the sodium/calcium exchanger that increases intra-axonal calcium (Ca), ultimately causing irreversible damage, whose accumulation leads to SPMS [53–55].

Considering the fundamental role of sodium in MS, ^{23}Na-MRI has been widely employed. TSC has been studied in normal-appearing white matter (NAWM), normal-appearing grey matter (NAGM), CSF, and MS lesions [55–58]. Various studies have shown an increase of TSC in lesions as well as in cortical gray and white matter across primary, secondary, and relapsing-remitting multiple sclerosis (RRMS) [55–57]. Additionally, sodium levels are linked to clinical measures of disability and impairment [57]. Studies on lesions have demonstrated that TSC is elevated in contrast-enhancing lesions, T_1 hypointense lesions, and T_1 isointense lesions, while non-enhancing lesions with a reduced apparent diffusion coefficient (ADC) exhibit TSC levels that are comparable to those in NAWM. This consistency in TSC suggests that the tissue structure may be preserved early on, prior to any breakdown of the blood–brain barrier (BBB). Thus, TSC may represent a sensitive biomarker of chronic tissue abnormalities, BBB disruption, and vasogenic edema in contrast-enhancing lesions. Normal levels of TSC in lesions with a decreased ADC may indicate that the lesions are in an early stage [10, 59, 60].

The well-demonstrated increase of TSC in MS can be driven by intracellular sodium accumulation, expansion of the extracellular space, or both [57]. Strategies based on single-quantum, inversion recovery, and triple-quantum filtering have been used to disentangle the intracellular contribution [8]. Findings suggest that intracellular sodium concentration can give complementary information about MS lesions and inflammatory processes. Petracca et al. [8] found an increase in ISC in both WM and GM of RRMS patients; a decrease of the intracellular volume fraction was observed in several clusters in WM and GM, while changes at the whole-brain scale were significant only in WM. Interestingly, lesion burden and disability were correlated to TSC and intracellular volume fraction but not to ISC, suggesting that the latter is a consequence of early neuro/axonal metabolic dysfunction, while the former reflects tissue loss [8]. Studies on lesions have demonstrated a different intracellular concentration between hyperacute, acute, and chronic ones [61, 62], suggesting the sensitivity of ISC to reveal inflammatory mechanisms during the first stage of the disease (see Table 1).

Alzheimer's disease is characterized by extracellular deposits of β amyloid peptides (Aβ). *Postmortem* studies have shown a correlation between Aβ accumulation and ion imbalance [69–71]; disruption of Na^+ homeostasis is induced by Aβ oligomers and is responsible for neuronal network destabilization in the early stage of the disease [71]. TSC was found to be high in AD patients, suggesting that sodium imbalance during the progression of the disease might have a key role in energy failure [72, 73]. However, recent *ex vivo* studies have shown that sodium increase in brain tissue does not correspond to an increase in the CSF, indicating that anomalies can be associated with the intracellular pool [69]. However, no direct evidence exists for this hypothesis so far.

Stroke is one of the most common causes of death and the leading cause of long-term disability. During a stroke, the blood flow in the brain is compromised, resulting in a breakdown of cellular energy production, followed by the piling of sodium and calcium in the intracellular compartment. A measure of intracellular sodium would have the benefit of being related to the direct pathological consequence of stroke. A study on non-human primates has shown

TABLE 1 Applications and main findings of sodium compartmentalization techniques in multiple sclerosis and brain tumors.

Study	RF coil	Field	QA or specific steps	Method	Application	Metrics	Main findings
Petracca et al., 2016 [8]	Custom-built nested coil (^{23}Na birdcage + ^{1}H 8-channel stripline) [63]	7T	B0 and B1 corrections	SQ, TQF	MS	TSC, ISC, ISMF, ISVF, ESC	Increased TSC and ISC were found in global WM in MS. At the regional level, decreased ISVF was found within WM clusters of increased TSC, and few clusters of ISC increase were detected. Higher TSC and ISC were found in global GM in MS, and no statistically relevant differences were found for ISVF. At the regional level, decreased ISVF was found in cortical and deep GM regions that showed a TSC increase, while ISC increases were detected only in a few areas.
Biller et al., 2016 [61]	Dual-tuned (^{23}Na/^{1}H) birdcage coil (RAPID Biomedical GmbH, Rimpar, Germany)	7T	Hamming filter to reduce Gibbs ringing	IR	MS	TSC, ISC	Differences in sodium levels were found between acute and chronic MS lesions in the brain. Acute lesions tended to show higher sodium levels and ISC, reflecting active inflammation, while chronic lesions might exhibit lower sodium and ISC levels, corresponding to the shift toward neurodegeneration and reduced inflammation.
Mennecke et al., 2022 [62]	Dual-tuned (^{23}Na/^{1}H) birdcage coil (RAPID Biomedical GmbH, Rimpar, Germany)	3T	-	SIR	MS	TSC, ISC	Hyperacute lesions showed increased TSC and SIR signals (associated to IC), while other lesions showed increased TSC with an attenuation of the SIR signal, suggesting that the main cause of TSC can be related to the expansion of the EC compartment. Sodium enhancement was shown to be reversible, suggesting its correlation to inflammatory mechanisms.
Boada et al., 2003 [64]	Custom-built, dual-tuned (^{23}Na/^{1}H) birdcage coil [65]	3T	B1 correction	SQ, TQF	Brain tumor (Primary brain tumor)	TSC (single quantum), ISC (triple quantum)	SQ images revealed lesion location and highlighted the extent of partial volume effects caused by the high sodium concentration commonly present in the necrotic foci associated with this type of pathology. TQ sodium showed a signal void at the site of the necrotic center and edema, with small regions of mild hyperintensity in the lesions. TQF might be sensitive to areas of recurrent or new tumors.
Boada et al., 2004 [66]	Custom-built, dual-tuned (^{23}Na/^{1}H) birdcage coil [65]	3T	B1 correction	TQF	Brain tumor	TSC, ISC	TQF images showed a significant signal void in the necrotic center of the tumor and in the area of edema. A hyperintensity was present in the lesions in areas corresponding to recurrent tumors.
Nagel et al., 2011 [6]	Dual-tuned (^{23}Na/^{1}H) birdcage coil (RAPID Biomedical GmbH, Rimpar, Germany)	7T	Measures of T1 and T2*in brain parenchyma and CSF in healthy subjects Assessments of T1 and T2*	IR and Difference of images	Brain tumor (Singular supratentorial brain tumors)	TSC, ISC	High proliferation rate tumors were associated with increased signals related to intracellular sodium.

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TABLE 1 (*Continued*) Applications and main findings of sodium compartmentalization techniques in multiple sclerosis and brain tumors.

Study	RF coil	Field	QA or specific steps	Method	Application	Metrics	Main findings
Fiege et al., 2013 [30]	Dual-tuned (^{23}Na/^{1}H) birdcage coil (RAPID Biomedical GmbH, Rimpar, Germany)	4T	B1 correction	SQ, TQF	Brain tumor	TSC, ISC	TQF images displayed a significant reduction in signal from abnormal regions, indicating a local decrease in sodium ions that are capable of establishing TQ coherences. The combined sodium images can validate the existence of pathology, suggesting possible dysfunction of the Na + K+–ATPase and/or alterations in the ion exchange mechanisms of tumor cells, which may result in elevated levels of intracellular sodium.
Biller et al., 2016 [67]	Dual-tuned (^{23}Na/^{1}H) birdcage coil (RAPID Biomedical GmbH, Rimpar, Germany)	7T	-	SIR	Brain tumor	TSC, ISC, ISC/TSC	The ratio between intracellular and total sodium concentration was found to be a predictor of IDH mutation status and could be a useful metric to improve the classification of brain tumors and their stages.
Nunes-Neto et al., 2018 [48]	Custom-built, 8-channel dual-tuned ^{23}Na/^{1}H coil	3T	-	IR	Brain tumor (gliomas)	EVF	Increases in EVF within the solid components of tumors were possibly related to differences in cell packing, loss of gap junctions between tumor cells, and ion migration from intracellular spaces, potentially leading to cellular shrinkage.
Worthoff et al., 2020 [32]	Dual-tuned (^{23}Na/^{1}H) birdcage coil (RAPID Biomedical GmbH, Rimpar, Germany)	4T	B0, B1, flip angle maps (Bloch–Siegert method)	SQ, TQF	Brain tumor (gliomas)	TSC, ISC, ISMF, ISVF	Detailed sodium relaxometry, quantitative analysis, and modeling of intra- and extracellular sodium parameters show abnormalities in cerebral gliomas and are related to the IDH mutational status.
Bathia et al., 2022 [68]	Dual-tuned (^{1}H-^{23}Na) birdcage coil (Advanced Imaging Research, Cleveland, OH, United States of America)	3T	-	Dual echo	Brain tumor (pediatric gliomas)	TSC	Higher TSC is found in supratentorial gliomas than in adjacent uninvolved brain tissue. Dual echo ^{23}Na MRI shows additional benefit in distinguishing tumors from the surrounding tissue and CSF.

For each study, the table reports the RF coil used, magnetic field, QA, or specific acquisition or processing steps of the study, MR approach, clinical application, metrics extracted, and a synthetic report of main findings.
ESC: extracellular sodium concentration; EVF: extracellular volume fraction; IDH: isocitrate dehydrogenase; IR: inversion recovery; ISC: intracellular sodium concentration; ISMF: intracellular sodium molar fraction; ISVF: intracellular sodium volume fraction; SIR: soft inversion recovery; SQ: single quantum; TQ: triple quantum; TQF: triple quantum filtering; TSC: total sodium concentration.

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that the duration of brain ischemia can be associated with a threshold on the TSC beyond which tissue reperfusion would be of little benefit [74]. Studies on humans have demonstrated how sodium can be considered a promising biomarker for tissue viability and cell integrity, and how its integration into clinical practice can have an impact on future diagnosis and treatments [75–77]. It is likely that knowledge about IC sodium would help personalized decisions on reperfusion.

Epilepsy is characterized by recurring seizures, causing a large inflow of sodium. Intracellular ^{23}Na-MRI is thus an obvious biomarker to quantify the physiological effects of seizures. Moreover, cell shrinkage and cerebral atrophy have been reported in epileptic areas [78, 79]. Both phenomena are associated with an increase in the extracellular volume fraction, resulting in an increase of TSC in the epileptogenic zone [80]. An increase in TSC in epileptogenic zones suggests intracellular sodium accumulation, even in interictal periods [81], and demonstrates long-term changes in sodium levels [80, 82]. A decrease in TSC was observed in a patient who suffered non-convulsive seizures during the scan, suggesting transient neuronal swelling and reduction of extracellular volume fraction [82]. Some recent studies [80, 83] investigated the ratio between $T_2^*{}_{short}$ and $T_2^*{}_{long}$, showing an increase of the short component mainly localized to epileptogenic zones, whereas TSC was increased in all regions. These results suggest that a differential weighting of intracellular/extracellular sodium can be sufficient to highlight specific pathophysiological phenomena.

Traumatic brain injury (TBI) is the result of acute events in which an external force damages the brain. TBI causes stretch-induced damage to the cell membranes along the axons, causing mechanical damage and mechanoporation [84], triggering ionic and proteolytic cascades, and ultimately resulting in disruption of ionic homeostasis. Sodium imbalances following mild TBI are associated with patient outcomes [85]. Surprisingly, a decrease of TSC in TBI was reported [84, 85], contrary to what could be expected. A recent longitudinal study [86] has investigated TSC levels 3 months after the injury, when no significant variations of TSC were found, suggesting normalization of the sodium ionic equilibrium.

Brain tumors represent another important application for ^{23}Na-MRI. The most aggressive are characterized by rapid cell proliferation and angiogenesis: both of these factors are linked to a reduced Na^+-K^+-ATPase activity [87], resulting in an increase of the intracellular sodium concentration. Cellular proliferation can also be associated with an increase in extracellular volume fraction [88]. The level of Na^+ in malignant tumors is higher than in healthy tissues [46, 89–95]. IC sodium is thus a potential biomarker for cancer staging. Moreover, EC volume fraction is expected to increase following treatment. Therefore, compartmentalized sodium measurements are a promising biomarker for evaluating response to treatment. Studies on compartments have demonstrated a decrease in the signal associated with intracellular sodium (see Table 1) [30, 48, 64, 66, 96]. However, Nagel et al. [6] reported an increased IR signal (associated with intracellular sodium) for tumors with high proliferation rates: a positive correlation between the MIB-1 proliferation rate and the IR signal was found, and no correlation considering TSC values was found. These results suggest the potential of compartmentalization to discriminate among different types of brain tumors [6, 67] and their progression [68].

Technical remarks

The disentanglement of IC and EC sodium needs specific acquisition sequences and mathematical models. The scanning sequences developed for selective acquisition from a single compartment suffer from some limitations: they are based on the idea that intracellular and extracellular pools are composed of bound sodium and free sodium, respectively, and have different relaxation properties, but this hypothesis is likely an oversimplification, leading to partial or poor compartment specificity [97]. Moreover, all scanning approaches for compartmentalized sodium quantification suffer from poor SNR and a very long scanning time.

Sodium imaging is, in general, impaired by hardware and technical limitations. The challenge with RF technology for sodium MRI lies in the ability to detect small signals with very short T_2 relaxation times [98, 99], thus requiring high sensitivity and fast switching between transmit and receive modes. While most sodium coils used to be custom-built or handmade, commercial RF coils, including ^{23}Na/^{1}H birdcage coils and surface coils, are now available. Surface coils are more sensitive, but limited coverage and highly inhomogeneous B_1 field impair quantitative studies [98, 100]. In recent years, phased array sodium RF receive coils have been introduced. The efficient design of phased array receive coils and the added benefit of potential parallel imaging are attractive, but these coils necessitate correction methods for accurate sodium quantification [26, 101–103]. Acquisition strategies may also be optimized; recent studies have proposed methods to reduce scan time using postprocessing with convolutional neural networks [77] or fingerprinting to simultaneously acquire sodium density and sodium relaxation parameters and improve sodium MRI resolution [104–107].

Part of the ongoing research still relies on simulations and phantom studies. Phantoms with varying sodium and agar concentrations can simulate the relaxation behavior of compartments and aid in optimizing sequence parameters. However, further development is required regarding the quality of agar phantoms and the development of more stable alternatives to enhance optimization and sodium quantification [108].

Finally, improvements are expected from the diffusion of deep-learning-based methods for denoising or model optimization and fitting, but the relatively limited size of ^{23}Na datasets requires tailored solutions [109].

Conclusion

The first MRI studies on compartmentalization of ^{23}Na were presented more than 20 years ago. Because sodium compartmentalization is directly linked to cellular homeostasis, it can provide unique, relevant, and specific clinical information about tissue integrity and physiology in several serious pathologies, including cancer and neurodegenerative or neuroinflammatory diseases.

However, technical difficulties of scanning and postprocessing, as well as scanning time, currently make compartmentalized sodium

imaging a tool for clinical research that is not expected to expand to clinical practice in the near future.

Author contributions

IE: investigation, visualization, and writing – original draft. MG: visualization and writing – review and editing. FG: conceptualization, funding acquisition, supervision, visualization, and writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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