Towards Improved Characterization of Brain Tumors by ^{23}Na-MR Neuroimaging at 7 Tesla

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Target Audience: Physicians and scientists interested in clinical applications of non-proton MRI

Purpose: Sodium (^{23}Na)-MRI can provide three different image contrasts, which reflect the average tissue ^{23}Na concentration (NaT contrast) and ^{23}Na ions with short relaxation times (NaR and NaS contrast). The NaR signal is obtained by an inversion-recovery pulse, whereas the NaS contrast is based on weighted subtraction of images at different echo times [1]. Previous work demonstrated a strong association between the Ki-67 proliferation index of brain tumor cells and both, the NaR and NaS signal [1]. This finding emphasizes the added benefit of ^{23}Na-MRI to canonical neuro-oncological imaging as used in clinical routine. In this study, we examined a larger patient population suffering from brain tumors to evaluate the robustness of the Ki-67/NaR association. Furthermore, ^{23}Na-MRI is compared to conventional T1-weighted gadolinium enhanced (T1w GAD+), T2-weighted (T2w) and FLAIR imaging.

Methods: ^{23}Na-MRI was conducted on a 7 Tesla MR system (Magnetom 7T, Siemens Healthcare, Erlangen, Germany) using a double-resonant (^{1}H / ^{23}Na) quadrature birdcage coil (Rapid Biomed GmbH, Rimpar, Germany). ^{23}Na-MR sequences were based on a 3D density-adapted projection reconstruction technique [2]. To detect the tissue ^{23}Na signal (NaT) relaxation weighting was minimized using a short echo time (TE = 0.35 ms) and a long repetition time (TR = 160 ms; readout duration: T_{RO} = 10 ms; flip angle $\alpha = 90°$). A nominal spatial resolution of 3 x 3 x 3 mm^3 was achieved in an acquisition time of T_{AQ} = 10 min 40 s. A second echo (TE_2 = 12 ms) was used to calculate a weighted subtraction image (NaS) as described previously [1]. To suppress signal from extracellular fluids such as cerebrospinal fluid, an inversion recovery sequence (NaR) was applied with the following parameters: TE = 0.75 ms; TR = 185 ms; T_{RO} = 16.7 ms; inversion time: TI = 41 ms; T_{AQ} = 9 min 52 s; nominal spatial resolution: 4.4 x 4.4 x 4.4 mm^3. Canonical T1w GAD+, T2w and FLAIR imaging was performed on a 3 Tesla MR system (Tim Trio 3T, Siemens Healthcare, Erlangen, Germany).

N = 20 patients suffering from naïve brain tumors WHO grade 1 to 4 were measured including 2 Pilocoytic Astrocytomas (PA), 2 Astrocytomas (A), 1 Oligodendroglioma (OD), 4 Anaplastic Astrocytomas (AA), 2 Anaplastic Oligodendrogliomas (AOD), 1 Anaplastic Ependymoma (AE), 1 Gliomatosis Cerebri (GC), 7 Glioblastomas (GBM). For all patients, histopathologic evaluation of tumor specimens was performed including Ki-67 monoclonal antibody staining. Ki-67 is a cellular marker for proliferation [3] and is known to correlate with tumor growth [4,5]. ^{23}Na and ^{1}H images were co-registered to the individual standard space using FLIRT (part of FSL) [6]. Tumors were manually masked in FSLView by a board-certified experienced neuroradiologist.

Results: Correlation analyses revealed a strong correlation between the NaR signal of the tumor and its Ki-67 index ($r = 0.85$, $p < 0.001$; Fig. 1a) and between the NaS signal and the Ki-67 index ($r = 0.87$, $p < 0.001$; Fig. 1b). This is visualized by the distinct distributions of the NaS signal for exemplary Ki-67 rates (Fig. 2). There was no correlation between histopathologic tissue parameters and NaT (Fig. 1c), conventional T1w GAD+ (Fig. 1d), T2w and FLAIR imaging (data not shown).

Discussion and Conclusion: In this study, we are able to reproduce previous findings [1] on the association between the relaxation-weighted ^{23}Na signals (NaR and NaS) and the Ki-67 proliferation index of brain tumors, despite the differing tumor subtypes between both studies. A local cellular energetic breakdown mainly of the Na^+/K^+ ATPase, changes in Na^+/H^+ exchange kinetics [7] and a sustained cell depolarization initiating cell division might represent the pathophysiological correlates of this association [8]. All mechanisms result in an elevated intracellular Na^+ concentration, which is reflected by the NaR and NaS contrast. NaT, T2, T1 GAD+ and FLAIR signals of tumor tissue failed to exhibit correlations with the Ki-67 proliferation index. This underlines the limited specificity [9] in tumor characterization of these sequences but also emphasizes the added value of NaR and NaS imaging to conventional neuro-oncological MRI. Figure 3 exemplarily demonstrates the benefit of ^{23}Na-MRI in neuro-oncology: Both, the PA and the GBM exhibit vivid contrast enhancement and elevated NaT signals. However, the NaR contrast revealed a low signal in the low grade tumor and a high signal in the GBM. This allowed for correctly diagnosing a PA (histology proven) and discarding the differential diagnosis of a GBM. ^{1}H-MRI GAD+ data were of limited use in the diagnosis. The fact that ^{23}Na-MRI does not require contrast media further underlines its potential for clinical applications in neuro-oncology.

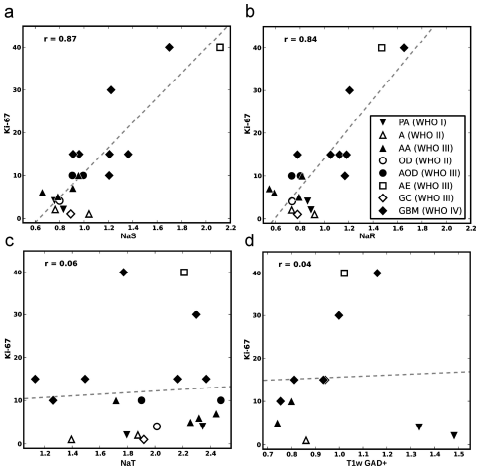

Fig. 1: Correlation analyses showed an association between NaS and Ki-67 (**a**) and between NaR and Ki-67 (**b**). There was no correlation between Ki-67 and NaT (**c**), T1w GAD+ (**d**), T2w or FLAIR imaging (data not shown).

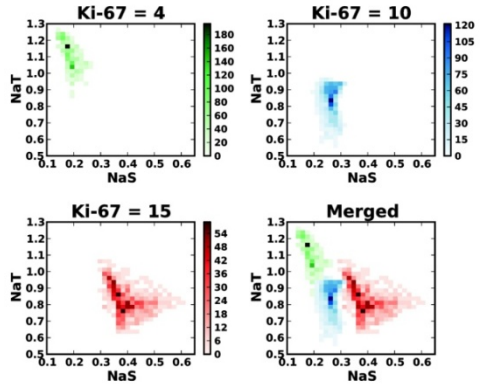

Fig. 2: Based upon their correlation, the 2D-histograms demonstrate a distinct NaS distribution for exemplary Ki-67 proliferation indices [%]. Bins are intensity-coded.

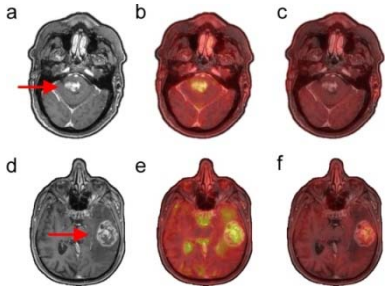

Fig. 3: Exemplary T1w GAD+ (**a, d**), NaT (**b, e**) and NaR (**c, f**) data of a *Pilocytic Astrozytoma* (PA, WHO 1, **a-c**) and a *Glioblastoma* (GBM, WHO 4, **d-f**) demonstrate the benefit of ^{23}Na-MRI: In contrast to T1w GAD+ imaging, the ^{23}NaR contrast enables a distinction between PA (low signal, **c**) and its main differential diagnosis of a high grade glioma (high signal, **f**).

References

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