Evaluation of Sodium (^{23}Na) MR-imaging as a Biomarker and Predictor for Neurodegenerative Changes in Patients With Alzheimer's Disease

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Abstract. *Background/Aim:* Sodium (^{23}Na) MR imaging is a noninvasive MRI technique that has been shown to be sensitive to visualize biochemical information about tissue viability, their cell integrity, and cell function in various studies. The aim of this study was to evaluate differences in regional brain ^{23}Na signal intensity between Alzheimer's disease (AD) and healthy controls to preliminarily evaluate the capability of ^{23}Na imaging as a biomarker for AD. *Patients and Methods:* A total of 14 patients diagnosed with AD were included: 12 in the state of dementia and 2 with mild cognitive impairment (MCI), and 12 healthy controls (HC); they were all scanned on a 3T clinical scanner with a double tuned $^1\text{H}/^{23}\text{Na}$ birdcage head coil. After normalizing the signal intensity with that of the vitreous humor, relative tissue sodium concentration (rTSC) was measured after automated segmentation in the hippocampus, amygdala, basal ganglia, white matter (WM) and grey matter (GM) in both cerebral hemispheres. *Results:* Patients with AD showed a significant increase in rTSC in comparison to healthy controls in the following brain regions: WM 13.6%; $p=0.007$, hippocampus 12.9%; $p=0.003$, amygdala 18.9%;

$p=0.0007$. *Conclusion:* ^{23}Na -MRI has the potential to be developed as a useful biomarker for the diagnosis of AD.

Clinically, Alzheimer's disease (AD) typically begins with impairments in short-term memory and other cognitive functions, which progress and extend to dementia, which interferes with activities of daily living and potentially, a wide range of behavioral changes, and, ultimately, motor difficulties. (1) The process of pathophysiological changes starts many years prior to clinical manifestations of disease such that the spectrum of AD spans from clinically asymptomatic to severely impaired. Therefore, attempts to define AD are merely based on both clinical and biomarker findings (2).

Biologically, AD is characterized by deposition of two major proteins in the brain of affected patients; extracellular amyloid β ($\text{A}\beta$) plaques and intracellular neurofibrillary tangles (NFTs) (1). NFTs are composed of hyperphosphorylated tau protein aggregates, which are responsible for the destabilization of microtubules and axonal transport throughout their accumulation in the neuron cytoplasm (3). Those proteinopathies result in synaptic and neuronal injury and subsequent neurodegeneration through induction of oxidative stress, microvascular dysfunction, as well as consecutive activation of an intracerebral inflammatory response (4). Based on these histopathological hallmarks, a number of biomarkers have been described *in vivo*. Diagnostic biomarkers are direct mirroring of brain AD lesions (amyloidosis or tauopathy) and therefore indicative of the presence of disease at any stage. On the other hand, progression markers; being not necessarily specific to AD, identify ongoing changes (metabolic changes, neuronal loss with atrophy) being indicative of disease progression. Many

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methods have been proposed for this purpose, including sampling of cerebrospinal fluid for biochemical analysis of disease markers, positron emission tomography, and magnetic resonance imaging (MRI) (5). MRI is non-invasive and one of the most widely used neuroimaging techniques in the diagnosis of AD. Structural MRI studies have shown that reduced hippocampal volume is one of the most predictive and sensitive measures of AD in individuals with amnesic mild cognitive impairment (MCI) (1, 6). There is considerable interest in new biomarkers that can identify early evidence of AD to enable treatment initiation and track a patient's response to treatment (5).

Sodium (^{23}Na) MRI is a promising non-invasive imaging technique that might reflect the severity of tissue disintegration and has recently been applied in several pathologies including acute ischemic stroke (7), multiple sclerosis (8), and cerebral neoplasms (9). Thus, it may serve as a disease progression marker.

The potential of sodium MR imaging to detect changes in early AD in conjunction with anatomic proton MR imaging was previously demonstrated and an increased sodium intensity in hippocampus was detected in patients with AD in comparison to healthy controls (10).

The aim of this study was to evaluate the correlation between the sodium signal intensities in different areas of the brain and the volumetric changes in the structural MRI and explore the feasibility of tissue sodium signal intensity as a biomarker for AD progression.

Patients and Methods

Subjects. We prospectively included 14 patients clinically diagnosed with AD in early stage; 12 subjects with mild-to-moderate dementia and 2 subjects with mild cognitive impairment; two women and 12 men, mean age 64 ± 8 years, and 12 age-matched cognitively healthy controls; 10 women and two men, mean age 58 ± 5.8 years.

Clinical assessment was performed in 2017 at the Memory Clinic of the Central Institute of Mental Health (Mannheim, Germany). Neuropsychiatric or general medical causes of impaired cognition were excluded by detailed medical history, physical and neuropsychiatric examination, and standard serum laboratory assessment. Thus, all MCI patients met the MCI Petersen's diagnostic criteria (11, 12) including subjective memory complaints, normal general cognition, only minimally impaired performance in instrumental activities of daily living, absence of dementia, and a measurable impairment in one or more cognitive domains. Cognitive impairment was defined as performance below 1.2 standard deviation in one or more cognitive domains in a standard neuropsychological test battery (13); test battery of the Consortium to Establish a Registry for Alzheimer Disease (CERAD) (14), plus the Wechsler memory scale – logical memory (WMS) immediate and delayed recall, and the trail making test A (TMT-A) and B (TMT-B). In patients with Alzheimer's dementia, an impairment of the activities of daily living was documented by self- or caregiver interview. In all dementia patients, the test battery of the Consortium to Establish

a Registry for Alzheimer Disease (CERADplus) (14), the Wechsler memory scale – logical memory (WMS) immediate and delayed recall, and the trail making test A (TMT-A) and B (TMT-B) showed impairments below 1.2 standard deviation in two or more cognitive domains.

For biomarker assessment, lumbar puncture was performed to determine amyloid pathology in CSF following the NIA/AA criteria for the diagnosis of MCI due to AD or AD dementia (15). Paired samples of CSF and plasma were collected from patients according to the established consensus recommendations (16). Aliquots were stored in polypropylene tubes at -80°C . CSF biomarkers; $\text{A}\beta_{1-42}$, p-tau, and t-tau, were performed in the Neurochemistry Laboratory at the Department of Neurology, University Medical School, Göttingen using established protocols. P-tau levels in CSF were quantified with a commercially available ELISA kit [INNOTEST® PHOSPHO-TAU (181P), Innogenetics N.V (Gent, Belgium)]. $\text{A}\beta_{1-42}$ was detected with a commercially available ELISA kit [INNOTEST® β -AMYLOID (1-42) Innogenetics] for quantitative analysis. APOE genotyping was performed on an Illumina GSA1.0 SharedCustom Content bead array according to the manufacturer's instructions. GenomeStudio 2.0 software (San Diego, CA, USA) was used to determine APOE genotypes and results were exported in PLINK format.

The results of the clinical and biomarker assessment for each patient were discussed at a case conference attended by geriatric psychiatrists and neuropsychologists, the diagnosis of MCI due to AD/prodromal AD (17) or Alzheimer's dementia was assigned by consensus. In age-matched controls, cognitive impairment was excluded in a detailed neuro-psychiatric examination by a clinical experienced geriatric psychiatrist as documented by a MMSE score of 30/30.

MRI data acquisition. All scans were performed at a 3 T MRI system (Magnetom TRIO, Siemens Healthcare Sector, Erlangen, Germany). Standard MRI protocol was acquired using a 12-canal head coil; The scanning protocol included a 2D 1H inversion recovery spin echo sequence (T2-TIRM), $\text{FoV}=(230) \text{ mm}^2$, voxel size= $(1.2 \times 0.9 \times 5) \text{ mm}^3$, $\text{TR}/\text{TI}/\text{TE}=9000/2500/93 \text{ ms}$, $\text{TA}=4 \text{ min } 14 \text{ s}$) and a three-dimensional T1 gradient echo inversion recovery (MP RAGE) was acquired with $\text{TR}/\text{TE}=1900/2.5 \text{ ms}$, flip angle= 20° , $\text{FoV}=23 \text{ cm} \times 23 \text{ cm}$, matrix size= 256×246 , slice thickness= 1.0 mm and voxel size: $1.0 \times 1.0 \times 1.0 \text{ mm}^3$.

An additional ^{23}Na -MRI was acquired with a double-tuned $^1\text{H}/^{23}\text{Na}$ birdcage head coil (Rapid Biomedical GmbH, Rimpf, Germany). The ^{23}Na sequence uses 3D radial density-weighted spokes with $\text{TR}/\text{TE}=100/0.2 \text{ ms}$. The number of spokes was $n=6,000$ with 384 samples each. Gradient amplitude was 4.6 mT/m which resulted in a measurement time of $\text{TA}=10 \text{ mins}$ for an isotropic 3D dataset with a $4 \times 4 \times 4 \text{ mm}^3$ resolution.

MRI data processing. The ^{23}Na image reconstruction was performed offline within MATLAB 2015a (The MathWorks, Inc., Natick, MA, USA) by using a convolution-based regridding algorithm with a Kaiser Bessel window of width=4 and with the application of a Hanning filter in k-space. The reconstructed FoV was $(300 \text{ mm})^3$, and the zero-filling factor was set to 2, resulting a $150 \times 150 \times 150$ voxel-sized image. The ^{23}Na MRIs were coregistered to the MP RAGE image using the statistical parameter mapping software SPM12 (Wellcome Centre for Human Neuroimaging, UCL, London, UK) in MATLAB (Figure 1).

Figure 1. Coronal co-registered ^{23}Na images with 3D T1 MPRAGE (a) from a healthy control (b) from an AD patient.

Figure 2. Exemplary masks of the different segmented brain region; (a) white matter, (b) basal ganglia, (c) frontal lobe cortex, (d) parietal lobe cortex, (e) occipital lobe cortex, (f) temporal lobe cortex, (g) hippocampus and (h) amygdala.

MR images evaluation. Based on the MPRAGE images, different brain regions were segmented using the Free Surfer software version 5.2 (<http://surfer.nmr.mgh.harvard.edu/>) (Figure 2). The volumes of the hippocampus, amygdala as well as the cortex of frontal lobe, parietal lobe and occipital lobe along with the total volume of white matter were computed. The segmentation was

transferrable to the ^{23}Na MRI due to previous image coregistration. The sodium signal intensity in the segmented areas was then evaluated using in-house developed MATLAB script. The sodium signal intensities were normalized to the individual's sodium signal intensity in the vitreous humor and calculated for each brain.

Table I. The computed volumes in the different brain regions in healthy controls (HC) and Alzheimer's disease patients (AD).

	Hippocampus	Amygdala	Frontal lobe	Parietal lobe	Occipital lobe	Temporal lobe	White matter	Basal ganglia
Volume (mm ³)								
HC	7,685.6	2,677.3	134,290.8	85,228.2	32,708.5	79,823.3	402,142.4	19,342.5
AD	4,873.4	1,760.7	125,144.2	77,714.5	32,144.0	67,573.1	402,323.50	17,514.7
p-Value	<0.001	<0.001	0.2	0.1	0.8	0.03	0.8	0.2

Table II. The sodium signal intensities in the different brain regions in healthy controls (HC) and Alzheimer's disease patients (AD).

	Hippocampus	Amygdala	Frontal lobe	Parietal lobe	Occipital lobe	Temporal lobe	White matter	Basal ganglia
Sodium signal intensity (%)								
HC	43%	43%	40%	40%	37%	38%	37%	39%
AD	48%	50%	44%	47%	41%	42%	42%	40%
p-Value	0.005	<0.001	0.048	0.003	0.003	0.009	0.007	0.2

Hippocampus volume was further manually evaluated based on the MTA scale, known as Scheltens' score (18). A white matter lesions grading was conducted using the T2-TIRM axial images. The grading was performed using the scale of Fazekas (19).

Statistical analysis. Statistical analyses were conducted with MATLAB 2015a (The MathWorks, Inc.). A p -value<0.05 was considered to indicate statistical significance.

Descriptive analysis of variables was presented as mean±standard deviation (SD). A paired Student's t -test was used to compare the difference between the respective brain region volumes or the sodium signal intensities in patients and healthy controls for each brain region.

A Pearson's correlation coefficient was obtained to define the correlation between the sodium signal intensity in the hippocampus and the hippocampal volume, the sodium signal intensity in the hippocampus and the MMSE-Score, as well as the correlation between the sodium signal intensity in white matter and the Fazekas grade.

The study was approved by the Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, and written Informed Consent was obtained from all subjects. The study was compliant with the EU General Data Protection Regulations.

Results

The mean MMSE score for the patients was 22.4 ± 3.7 (range=16-28), while that of all healthy controls was 30.

Computed volumetry. In healthy controls, the mean computed hippocampal volume was $7,685.6 \text{ mm}^3$ and that of the patients was $4,873.4 \text{ mm}^3$, $p < 0.001$. The mean computed volume of Amygdala in the healthy controls was $2,677.3 \text{ mm}^3$, while that of the patients was $1,760.7 \text{ mm}^3$, $p < 0.001$.

The mean computed cortical volume in the healthy controls of the frontal lobe was $134,290.8 \text{ mm}^3$, the parietal lobe $85,228.2 \text{ mm}^3$, temporal lobe $79,823.3 \text{ mm}^3$ and occipital lobe $32,708.6 \text{ mm}^3$. In AD patients the mean computed cortical volumes of the frontal lobe, parietal lobe, temporal lobe and occipital lobe were $125,144.2 \text{ mm}^3$, $77,714.5 \text{ mm}^3$, $59,126.4 \text{ mm}^3$ and $28,126.0 \text{ mm}^3$ respectively.

The mean computed volume of basal ganglia in the healthy controls was $19,342.5 \text{ mm}^3$ and in patients was $17,514.7 \text{ mm}^3$. Furthermore, in healthy controls the mean computed volume of white matter was $402,142.8 \text{ mm}^3$ and in the patients was $402,323.5 \text{ mm}^3$. The computed volumetric results are summarized in Table I.

Sodium signal intensities. After normalizing the tissue sodium signal intensity to the signal intensity in the vitreous humor, the tissue sodium signal intensities in healthy controls in Hippocampus were 43% and 43% in amygdala. Forty percent tissue sodium signal intensity was calculated in the cortex of the frontal lobe, 40% in parietal lobe, 37% in occipital lobe, 38% in temporal lobe. In the basal ganglia the tissue sodium signal intensity was 39% and 37% in white matter. On the other hand, the tissue sodium signal intensities measured in the same regions in the AD patients were 48%, 50%, 44%, 47%, 41%, 42%, 40% and 42% respectively. Statistically significant differences in tissue sodium signal intensities were found between HC and AD patients in hippocampus $p = 0.005$, amygdala $p < 0.001$, frontal lobe cortex $p = 0.048$, parietal lobe cortex $p = 0.003$, occipital lobe cortex $p = 0.003$, temporal lobe cortex $p = 0.009$ and white

matter $p=0.007$ (Table II). A moderate negative correlation between the tissue sodium signal intensities in the hippocampus; $r=-0.50$ $p<0.001$.

Visual assessment. All healthy controls showed an MTA score 0. For AD patients MTA score I was observed in three patients, six patients exhibited MTA score II, four patients depicted MTA score III and one patient showed MTA score IV. Positive correlation between MTA score and tissue sodium intensity were found in the hippocampus ($r=0.7$ $p<0.001$).

None of the healthy controls showed white matter lesions in the T2-TIRM images; Fazekas grade 0. Likewise, two patients were evaluated with Fazekas grade 0. Eight patients showed white matter lesions Fazekas grade I, three patients Fazekas grade II and one patient Fazekas grade III. Moderate positive correlation between the Fazekas grade and tissue sodium intensity in white matter ($r=0.4$, $p=0.05$).

Discussion

The aim of the study was to investigate the feasibility of tissue sodium intensity measured with ^{23}Na MRI as a biomarker for AD. Tissue sodium concentration (TSC) provides valuable information on cell function and brain tissue viability and has been evaluated in previous studies for the assessment of neurodegenerative diseases (10, 20).

We observed a significant signal intensity increase in all regions of the cerebrum excluding the basal ganglia in 14 AD patients with a mean of $5\% \pm 1.5\%$. Specifically, there was a 6% signal intensity increase in the hippocampus and 8% signal intensity increase in the amygdala. The sodium signal intensity of the hippocampus positively correlated with the degree of medial temporal atrophy ($r=0.7$ $p<0.001$). These results are in accordance with the small study of Mellon *et al.* (10). Interestingly, in our study other brain regions like the frontal cortex, parietal cortex and occipital cortex as well as the white matter also showed significant differences in tissue sodium intensities. On the other hand, no significant differences in volume in these regions between AD patients and healthy controls were observed. Furthermore, a moderate negative significant correlation between the sodium signal intensity and the MMSE-Score.

Giving that the sodium concentration in grey matter is approximately 80% intracellular volume fraction and 20% extracellular volume fraction (10), moreover a constant 140 mmol/l concentration of extracellular sodium through a diffusional equilibrium with blood and CSF (21), in an early stage of AD increased sodium in tissue could be caused by impairment of the Na^+/K^+ -ATPase due to the neurotoxicity caused by the amyloid beta-peptide ($\text{A}\beta$) that accumulates as insoluble plaques in the brain (22). That could explain the differences in tissue sodium signal intensity between AD patients and HC despite the insignificant differences in

volumes of certain brain regions, which might indicate a phase of the disease prior to neuronal death.

Other brain regions; like hippocampus, amygdala and generally the temporal lobe, which presented significant differences in volumes between AD patients and HC denoting neuronal loss. After neuronal death an increase the interstitial space with increase in the extracellular matrix is to be expected hence a consecutive increase in sodium signal intensity is observed.

In white matter the tissue volume is dominated by the densely packed glial cells while the extracellular space accounts for no more than 6-20% of the total volume (23), giving sodium a tissue equivalent concentration of approximately 18-36 mM (4, 7, 8). In age-related white matter changes where localized lacunar infarction or diffuse alterations are detected (24) and usually associated with cognitive impairment (25).

In this study, a significant correlation between the sodium signal intensity and the grade of white matter lesions ($r=0.4$, $p=0.05$) was observed; which also implicates that the extent of tissue loss due to chronic small vessel ischemia furthermore reflects on the sodium signal intensity due to an increase the interstitial space.

In our study, the normalization of the signal intensity was performed based on the ^{23}Na signal in the patient's vitreous humor. The vitreous humor was chosen as it has high and stable ^{23}Na abundance (26). Previously, CSF was often used for ^{23}Na MRI signal normalization (27). Here, partial volume effects (28, 29) are major risk which is less prominent in the relatively large vitreous humor.

The weighted average of local intracellular and extracellular sodium concentrations in the brain can be assessed by measuring the tissue sodium concentration (TSC) using sodium MRI (30).

The quantification of the TSC is dependent on the signal intensities of ^{23}Na MRI (31). The repetition time (TR) or inversion time (TI) and the echo time of the ^{23}Na -Sequence as well as the T1 and T2 or T2* values are determinant factors for the differences in signal intensities (32). Therefore, there is no significant differences in the intra-individual ^{23}Na -concentrations measured in repeated scans on the same day or after a certain time interval (33). That makes the TSC a potential biomarker to monitor the progression of brain diseases and the outcome of therapeutic interventions.

A major limitation to our study is the small sample size; a larger cohort would be needed to further validate our results. Another limitation was finding an appropriate standard for comparisons between subjects due to missing quantification of the ^{23}Na -MRI images. To overcome this problem, we used the vitreous humour as an internal control for sodium, as they were thought to contain a remarkably constant level of sodium. To our knowledge differences in vitreous humour sodium concentrations in neurodegeneration have not been

reported. Further limitations are ^{23}Na MRI's low resolution which can result in partial volume effects, particularly in small regions of interests like the amygdala. The effects have been described previously by Niesporek *et al.* (28).

In conclusion, our results suggest that ^{23}Na -MRI may be a useful biomarker to detect neuropathological changes associated with AD and might reflect the severity of tissue disintegration. Further studies are needed to validate the use of ^{23}Na -MRI for early diagnosis of AD and for monitoring the course of the disease.

Conflicts of Interest

All Authors declare that they have no conflicts of interest.

Authors' Contributions

S.A.M.: literature review, data collection, analysis and interpretation, statistical analysis, drafted the work, K.H.: data collection, reviewed the manuscript, A.A. and N.P.: image processing. L.H.: patient recruitment, data collection and contributed to drafting the manuscript, L.F.: study design and substantively revised the work, L.S. and G.C.: supervision of the study and substantively revised the work, H.U.K.: conception of the original idea, study design, data interpretation and supported drafting the work. All Authors discussed the results and contributed to the final manuscript.

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