

# Nuclear Overhauser Enhancement Imaging of Glioblastoma Patients at 7 Tesla: Region Specific Correlation with Diffusion Weighted MRI

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**Target Audience:** Researchers and clinicians in the field of MRI who are interested in the use of chemical exchange saturation transfer (CEST) contrast in oncology.

**Purpose:** Recently, Nuclear Overhauser Enhancement (NOE) mediated CEST studies turned out to provide additional information in glioblastoma imaging compared to standard MR sequences [1-3]. The observed signal drop in tumor tissue and peritumoral areas is assumed to be due to changes in protein density, protein mobility, pH or protein folding states while the contribution of each individual cause remains uncertain. The purpose of this study was to explore possible origins of the NOE signal in terms of protein density and tumor cellularity by region specific correlation with apparent diffusion coefficients (ADC), since ADC has shown to correlate with cellularity in gliomas [4,5].

**Methods:** Fifteen patients (4 female, 11 male) with newly diagnosed histologically proven glioblastoma were enrolled in this prospective study before surgery. NOE-mediated CEST-contrast was acquired at 7 Tesla (7T) with the sequence parameters as described in Paech et al. (2014) [3]. Asymmetric magnetization transfer ratio ( $MTR_{asym}$ ) was conducted at 3.3ppm. Contrast enhanced T1 (CE-T1), T2, susceptibility weighted images (SWI) and diffusion weighted MRI (DW-MRI) were acquired at 3T and coregistered. Two regions of interest (ROI) were investigated in each patient throughout the whole tumor volume: The hyperintense tumor on CE-T1 excluding necrotic parts (Fig. 1A, red line) and the T2 edema (Fig. 1B, green line). Furthermore false hypointense ADC values caused by micro-bloods within the glioblastoma were identified on SWI and excluded in both ROIs. ADC and  $MTR_{asym}$  values were correlated voxelwise within both ROIs separately using Spearman's rank order correlation, yielding two region specific correlation coefficients ( $r_{Sp}$ ) for every patient.

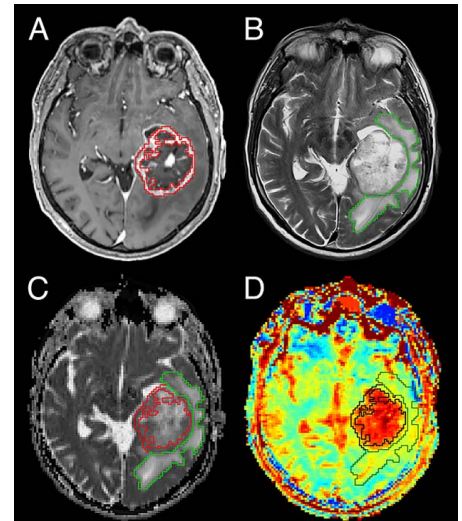
**Results:** In the area of CE-T1 tumor, 2 patients tended towards a weak positive correlation between ADC and  $MTR_{asym}$  ( $r_{Sp}=0.19$  and  $0.28$ ,  $p<0.001$ ) and 2 patients showed a weak negative correlation ( $r_{Sp}=-0.17$  and  $-0.31$ ,  $p<0.05$  and  $<0.001$ ). In the other 11 patients, the correlation was either not significant ( $p>0.05$ ,  $n=6$ ) or  $r_{Sp}$  was too small to claim any association between ADC and  $MTR_{asym}$  ( $n=5$ ). Within the margins of T2 edema eight out of the 15 patients classify as weakly ( $r_{Sp}=0.16$ ;  $0.18$ ;  $0.20$ ;  $0.20$ ;  $0.23$ ;  $0.26$ ;  $0.29$ ) or as moderately ( $r_{Sp}=0.53$ ,  $p<0.001$ ) positive correlating. In the other 7 patients, the correlation in T2 edema was either not significant ( $p>0.05$ ,  $n=4$ ) or  $r_{Sp}$  was too small to claim any association between ADC and  $MTR_{asym}$  ( $n=3$ ).

**Discussion:** As a principal finding, the lack of correlation in the area of CE-T1 tumor suggests that ADC and NOE have distinct underlying principles. At the same time, the results for T2 peritumoral edema do show a tendency towards weakly positive correlations of ADC and  $MTR_{asym}$  values. Generally, low  $MTR_{asym}$  values represent high NOE-mediated exchange rates and vice versa [3]. Therefore low ADC values within the peritumoral edema might correspond with high NOE-effects because of the increased cellularity and thus altered protein content in these voxels. High ADC values on the other hand represent areas of increased water content (and thus reduced overall protein concentration) that will consequently contribute to a lower NOE-effect. Our findings have to be validated both in a larger patient group and by histopathological correlations to determine the contribution of cell density to the NOE-mediated CEST-effect and to fully understand their origin.

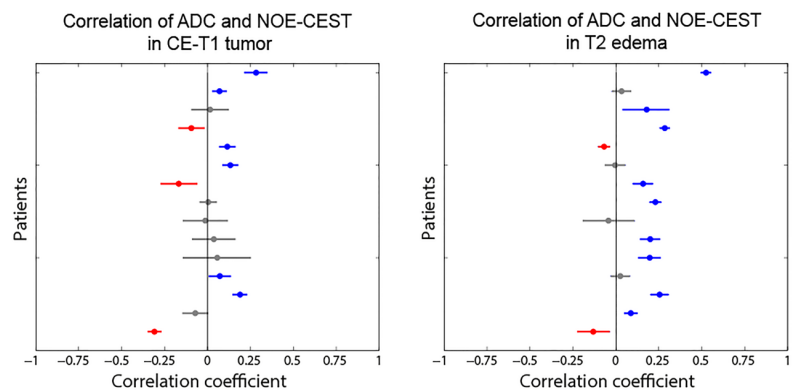
**Conclusion:** This study reveals that the NOE-mediated contrast provides information about glioblastoma that is different from the one obtained in diffusion weighted images. However, for the area of T2 edema, cellularity emerges as one possible contributor to changes in the NOE-signal.

## References:

- [1] Zaiss M., et al., MR imaging of protein folding in vitro employing Nuclear-Overhauser-mediated saturation transfer. NMR in Biomedicine, 2013
- [2] Jones CK, et al., Nuclear Overhauser enhancement (NOE) imaging in the human brain at 7T. NeuroImage, 2013
- [3] Paech D., et al., Nuclear Overhauser Enhancement Mediated Chemical Exchange Saturation Transfer Imaging at 7 Tesla in Glioblastoma Patients. PLoS ONE, 2014
- [4] Sugahara T, et al., Usefulness of diffusion-weighted MRI with echo-planar technique in the evaluation of cellularity in gliomas. JMRI, 1999
- [5] Ellingson BM, et al., Validation of functional diffusion maps (fDMs) as a biomarker for human glioma cellularity. JMRI, 2010



**Figure 1. Segmentation of the regions of interest in a 61-year-old glioblastoma patient and exemplary slice:** A) CE-T1 weighted image with CE-T1 tumor ROI. B) T2 weighted image with T2 edema ROI. C) ADC map and D) NOE mediated  $MTR_{asym}$  contrast displaying both ROIs.



**Figure 2. Patient-individual Spearman correlation coefficients ( $r_{Sp}$ ) with 95% confidence intervals:** Positive correlations are marked blue, negative correlations are red, correlations with  $p>0.05$  are displayed in grey. There is a trend towards a positive correlation in the area of T2 peritumoral edema (T2 edema). In the enhancing tumor (CE-T1 tumor), no tendency towards any correlation can be observed.