# The association of CEST effects at -1.6ppm with tissue fate in stroke models

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**Purpose** Recent studies have observed an NOE-mediated CEST effect at -1.6ppm in rat brain and in humans imaged at ultra-high fields [1-3]. The signal at -1.6ppm has been reported to decrease immediately following stroke onset in rats [2, 4]. The purpose of this study was to explore the association of effects at -1.6ppm with tissue outcome in stroke models.

**Methods** Six male Wistar rats underwent MCAO and MRI was performed at 1h and 2h post-MCAO on a 9.4T Agilent spectrometer as follows: pulsed CEST scheme at four different average powers ($B_1$=0.27uT, 0.55uT, 0.82uT, and 1.1uT) with 51 offset frequencies, CBF maps using pseudo-continuous ASL, and ADC using DWI in three directions [3]. The ROIs used in this study were as follows; ischaemic core: within both the presenting and final infarct identified using guidance from ADC and CBF maps; infarct growth: within the final infarct but not within the presenting infarct; oligaemia: tissue present in the perfusion deficit but not the final infarct; and a mirrored contralateral mask. The CEST data were first analysed using Lorenztian difference analysis (LDA). A two-pool Bloch-McConnell (BM) model, comprising a water pool and a symmetric semisolid effects pool, was fitted to the data, and the simulated water+semisolid baseline was subtracted from the acquired data. The mean residual was found for the peak at -1.6±0.2ppm, and -3.5±1.5ppm across animals. This was done for each $B_1$ in order to better-characterise the effects at -1.6ppm before commencing fully-model-based analysis, described next. CEST data were fitted to a five-pool BM model comprising a water pool, an amide pool at 3.5ppm, a symmetric semisolid MT pool, an NOE pool at -3.5ppm, and a pool at -1.6ppm. The apparent NOE ratios, NOER*(-3.5ppm) and NOER*(-1.6ppm), were extracted [5] and normalised to the contralateral mean. One-way ANOVA was used for comparisons between ROIs followed by *post-hoc* pairwise testing corrected for multiple comparisons.

**Results** A $B_1$ power of 0.55uT yielded the largest LDA signal (Fig. 1) at -1.6ppm (1.78% in the contralateral ROI, 3.10% in the ischaemic core), whereas adjacent powers resulted in a smaller signal. An LDA spectrum of the data acquired at $B_1$=0.55uT (Fig. 2) shows that the oligaemia ROI exhibits a pronounced peak at -1.6ppm compared to the contralateral ROI, which was explored further using a 5-pool BM model. Relative NOER*(-1.6ppm) varied significantly between ROIs (ANOVA p=0.03) (Fig. 3). In the ischaemic core relative NOER*(-1.6ppm) was elevated (mean±95% CI) (1.6±0.6), and was approximately unity in the oligaemia ROI. The absolute value of NOER*(-1.6ppm) exhibited a high level of variation compared to effects at -3.5ppm, with a contralateral SD of 88% v.s. 8.4%.

**Fig. 1**

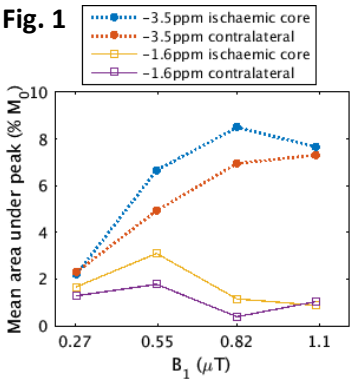



**Fig. 2**

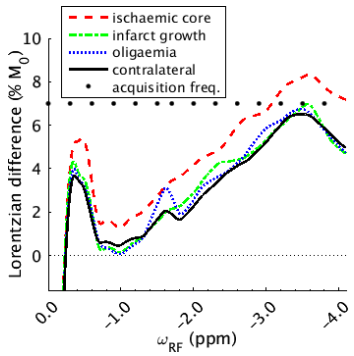
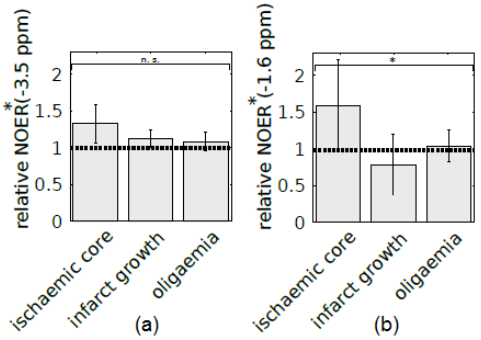



**Fig. 3**




**Discussion and conclusion** The ischaemic core signal did not describe the decrease observed in other studies, which could be due to the comparatively lower $B_1$ used herein. The elevated signal level at -1.6ppm in oligaemic tissue that was observed through LDA was not observed in the BM model results. The variability in the model-fitted results suggest that it was difficult to extract an effect consistently, likely owing to the small number of offsets near -1.6ppm. The data suggest that effects at -1.6ppm might be associated with tissue outcome in stroke.

**[1]** Zhang et al., *Magn Reson Med,* 78(2) 588–597, 2017; **[2]** Zhang et al., *Magn Reson Imaging*, 34(8) 1100–1106, 2016; **[3]** Zaiss et al., *NeuroImage*, 179 144-155, 2018; **[4]** Tee et al., *Proc. Intl. Soc. Mag. Reson. Med.* vol. 25 no. 3782, 2017.; **[5]** Tee YK et al., *J. Magn. Reson.,* 222, 88-95, 2012.