# To NOE or not to NOE? - A study about the use of the Nuclear Overhauser Effect in $^{31}$P MRSI of the brain at 7T

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**Introduction:** The Nuclear Overhauser effect (NOE) is an often employed technique in $^{31}$P spectroscopy to enhance the intrinsically low signal intensities. However, considerable spread is present in NOE enhancement values per metabolite[1-3], raising concerns that NOE might add uncertainty, negating the SNR gain. We hypothesized that spread in NOE enhancement values is mainly attributable to fitting inaccuracies of signals with low intensity and error propagation in the calculation of NOE. To test this hypothesis we performed repeated measurement with both methods, i.e. standard $^{31}$P MRSI ('noNOE') and NOE-enhanced MRSI ('NOE') in the brain of 7 healthy volunteers at 7T.

**Theory**: The NOE enhancement, defined as [NOE-noNOE]/noNOE, can be considered as an indirect measure of method agreement. As described by Bland and Altman[5], lack of repeatability can interfere with the agreement between two methods. If one method has poor repeatability, i.e. large variation in repeated measurements on the same subject, the agreement between the two methods will also be poor. The 95% limits of agreement (LoA) between the noNOE and NOE method were determined per metabolite (measure independent of systematic differences between methods) as were the 95% repeatability coefficients (RC) of the metabolites of each method itself. These values can be compared to each other to assess if an observed lack of agreement between the methods is explained by lack of repeatability (i.e. if 95% LoA≈95% RCs), or if there must be some other factor reducing the agreement between the methods (i.e. if 95% LoA>>95% RCs)[5].

**Methods:** 7 Healthy volunteers were measured at a 7T MR system using an 8-rung high-pass birdcage coil tuned to $^{31}$P which fitted within an 8-channel $^{1}$H array head coil[5,6]. $B_0$ and $^{1}$H RF shimming were performed to optimize the $B_0$ homogeneity and to maximize the $^{1}$H transmit RF amplitude ($B_1^+$) in the occipital region. The amplitude of proton saturating pulses (WALTZ-4) to generate a constant NOE was set to reach at least 30Hz in the occipital region by using absolute B1 maps. 3D pulse acquire $^{31}$P MRSI was acquired 4 times consecutively (acquisitions 1 and 3: noNOE; 2 and 4: NOE). FOV: 240x240x240 mm, matrix: 12x12x8, 0.3 ms block pulse, FA: 45°, TA: 7:48min per MRSI dataset. All measurements were performed within SAR limits. Three non-neighbouring voxels were selected per subject in the occipital lobe. Metabolite Report (Siemens Healthcare) was used to fit these $^{31}$P spectra, and the Cramér-Rao lower bound (CRLB) of the fitting accuracy was determined for each metabolite. Linear mixed models were used to determine the RCs and to test if $B_1^+$ was associated with NOE enhancement.

**Results:** Small differences in spectral patterns between repeated measurements using the same method and larger differences between noNOE and NOE could be observed visually (fig. 1). For all metabolites except αATP the fitting accuracy (CRLB) was significantly better with NOE than without (table). The 95% LoA were comparable to the 95% RC of the individual methods for all metabolites except PE. Absolute RCs of noNOE and NOE were similar, but because of the signal increase, relative repeatability improved with positive NOE. In a Bland-Altman plot this is seen as a shift of the means to the right and a decrease of the relative RCs, which is well visible for PE, Pi and NAD (fig. 2). Local $B_1^+$ (above 30Hz for NOE) was not significantly associated with NOE enhancement.

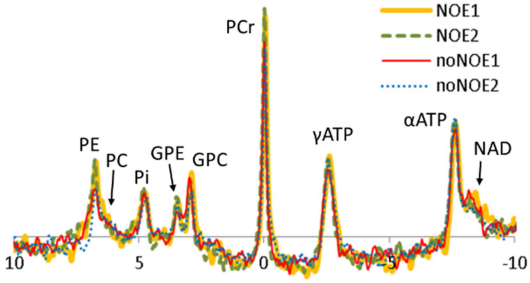


*Fig. 1 $^{31}$P spectra of repeated measurements. (G)PE: (glycero)phoshoethanolamine, (G)PC: (glycero)phosphocholine, Pi: inorganic phosphate, PCr: phosphocreatine, ATP: adenosine triphosphate, NAD: nicotinamide adenine dinucleotide*

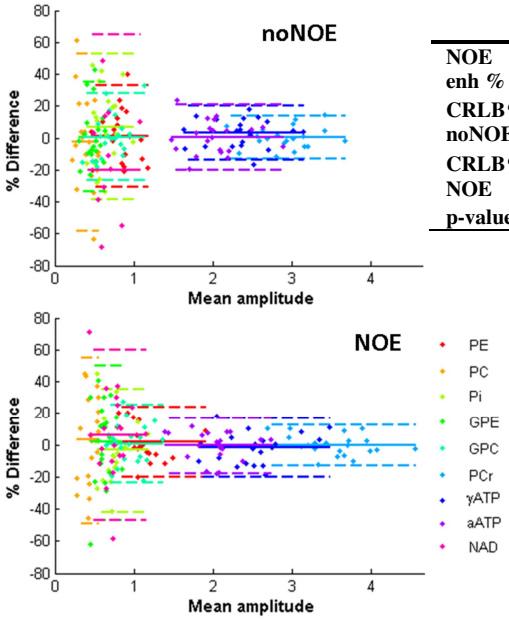


*Fig. 2 Relative Bland-Altman plots of the repeated noNOE and NOE measurements. The difference between the two repeated measurements is expressed relative to their mean. Solid lines represent means; dashed lines show the mean +/- 95% relative RC.*

| | PE | PC | Pi | GPE | GPC | PCr | γATP | αATP | NAD |
|---|---|---|---|---|---|---|---|---|---|
| **NOE enh %** | 39±22 | 19±31 | 21±20 | 30±22 | 36±20 | 22±5.4 | 7.1±7.2 | 0.2±4.9 | 21±23 |
| **CRLB% noNOE** | 9.4±1.7 | 20.2±5.8 | 13.2±2.6 | 15.0±3.4 | 11.0±2.7 | 3.3±0.8 | 2.4±0.4 | 2.9±0.7 | 27±7.4 |
| **CRLB% NOE** | 6.8±1.0 | 16.7±4.1 | 10.8±1.8 | 11.7±2.6 | 8.1±1.8 | 2.7±0.6 | 2.3±0.3 | 2.8±0.7 | 21±5.5 |
| **p-value** | <0.001 | 0.001 | <0.001 | <0.001 | <0.001 | <0.001 | 0.001 | 0.56 | <0.001 |

**Discussion and conclusion:** Positive NOE enhancements improved fitting accuracy and relative repeatability. Similarly, the relative repeatability of metabolites with endogenously higher signal amplitudes (PCr, γATP and αATP) was better. A larger amplitude range simply improves the detection of changes in metabolite levels. The similarity of the 95% LoA between the methods and the 95% RCs of each method indicates that NOE just enhances the signal of the metabolites, without introducing additional variation. The finding of a higher 95% LoA of PE compared to its 95% RCs might be due to local spatial differences in dipolar relaxation time, which affect the NOE[7], but this needs further investigation.

Once the minimum $^{1}$H $B_1^+$ needed for constant NOE with a specific saturation scheme is determined, and this minimum power level is reached over the full volume of interest - which requires $B_1$ shimming at ultra-high fields - NOE is beneficial for $^{31}$P MRSI in the brain at 7T. It does not introduce variation for most metabolites, but rather improves their accurate detection and fitting.

**References**: [1] Lei et al. *Magn Reson Med* 2003;49:199. [2] Tyler et al. *NMR Biomed.* 2009;22:405, [3] Lagemaat et al. *Magn Reson Med.* 2014; doi:10.1002/mrm.25209. [4] Bland and Altman, *Stat Methods Med Res* 1999;8:135. [5] Van de Bank et al. *ISMRM* 2014;#4810. [6] Orzada et al *ISMRM* 2009;#2999. [7] Mathur-De Vré et al. *Magn Reson Imaging* 1990;8:691.

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