

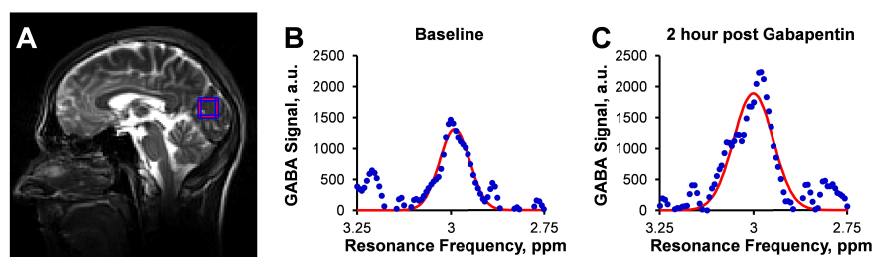
## 7T MRS of brain GABA Pre and Post Gabapentin Administration in Health Males

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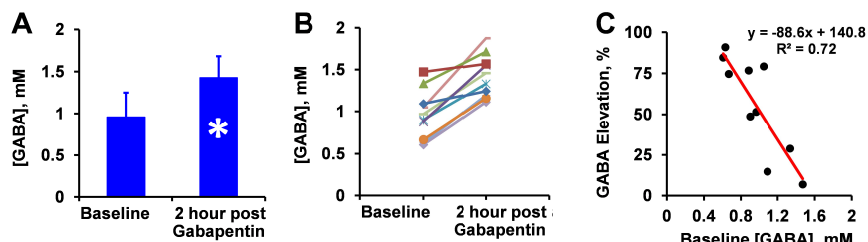
**Introduction:** Gamma-Aminobutyric acid (GABA) is the major neurotransmitter for fast inhibitory synaptic transmission. GABA is present in 30-40% of all synapses and activation of its receptors increases membrane conductance to ions that leads to depressant effect. Owing to widespread presence and utilization, GABA is potentially involved in all functions of the central nervous system (CNS), as well as in all CNS diseases. Because of its critical role in multiple diseases, GABA concentration may serve as a surrogate marker for the diagnosis of several neuropsychiatric conditions and evaluation of therapeutic efficacy of GABAergic agents. Thus, there has been tremendous interest in quantifying these neurotransmitters based on proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS). Gabapentin (Neurontin®, Pfizer, Inc), an antiepileptic drug, has been shown to modulate the GABA concentration *in vivo* in the brain, to improve seizure control in individuals with epilepsy, and is widely prescribed for the management of neuropathic pain. However, the treatment efficacy varies in individuals. In this study, using a MEGA PRESS based GABA editing sequence [1,2] at 7T, the feasibility of measuring GABA changes after oral administration of gabapentin in healthy volunteers has been investigated.

**Methods:** All the experiments were performed on a Siemens 7T whole body scanner with a vendor supplied circularly polarized (CP) volume RF coil. All the studies were approved by the institutional review board of University of Pennsylvania. <sup>1</sup>H-MRS scans were performed on healthy volunteers (n=10; 27.7 ± 7.6 years of age) before and 2 hours post oral administration of gabapentin (900mg). Another set of healthy similarly aged

volunteers (n=9) were scanned twice without taking any drug. Localized manual shimming of the B<sub>0</sub> field was performed on a brain voxel in the visual cortex (12cc, Figure 1.A) to obtain localized water line width of ~30Hz or less. Single voxel spectra (SVS) were obtained with a PRESS sequence using following parameters: spectral width = 4 kHz, number of points = 2048, averages = 100, TR = 3s and TE = 69ms for GABA edited spectroscopy. Total acquisition time was 10min. The editing pulses are frequency selective and invert the GABA -CH<sub>2</sub> protons attached to C2 (at 1.9ppm) and turned "on" and "off" on alternate scans. Subtraction of these scans provides GABA signals (Figure 1.B-C) from -CH<sub>2</sub> protons attached to C3 (at 3ppm). A variable power RF pulses with optimized relaxation delays (VAPOR) water suppression block was played out before the SVS acquisition. In the SVS scans with the editing pulse off, GABA signals are buried under the Cr peak. SVS spectra were processed from the raw free induction decay data by exponential apodization (10Hz to 20Hz), Fourier transformation, phase correction and baseline removal. Brain metabolite peaks were fitted, integrated and normalized by water reference signal (acquired at TE = 20ms) for absolute quantification of GABA concentration pre and 2 hours post gabapentin administration.



**Figure 1.** Sample GABA edited spectra (fitted as red lines) pre and post gabapentin (B and C) from a visual cortex voxel indicated in A.



**Figure 2.** An average of 55.7% of GABA increment (A and B, \* p=0.001) was observed 2 hour-post gabapentin administration (oral, 900mg). The percentage of increment is negatively proportional to the baseline GABA concentration (C).

**Results:** Similar brain GABA levels ( $1.08 \pm 0.26$  mM and  $1.10 \pm 0.26$  mM) were observed in the two scans from healthy males scanned twice. The mean  $\pm$  SD percent difference between scan when no drug is given was  $6.1 \pm 5.0\%$ , whereas gabapentin administration led to an average increase (range 7%-91% increase) in visual cortex GABA concentration of 55.7% (from  $0.96 \pm 0.29$  mM to  $1.43 \pm 0.25$  mM, \*p=0.001). The percentage of increment is negatively proportional to individual's baseline GABA concentration ( $R^2=0.72$ ), indicating that gabapentin may be more effective on individuals that has lower level of brain GABA concentration.

**Conclusion:** We successfully implemented MEGA PRESS based GABA editing sequence at 7T. The reproducibility of GABA measurement between day scans is demonstrated to be ~6%. An average of 55.7% of GABA elevation is found due to the oral administration of gabapentin in healthy volunteers. The elevated GABA levels are found to be inversely proportional to individual's baseline GABA level, which indicates that the gabapentin treatment response may depend on the baseline GABA levels of the subjects.

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**Reference:** [1] Mescher M, et al, NMR Biomed 11:266-272 (1998); [2] Bielicki G., et al, NMR Biomed 17:60-68 (2004).