Estimation of GABA and Glutamergic Contents in Occipital Lobe and Cerebellum By1H MR Spectroscopy

Saadallah Ramadan[1], Tapan Biswas[2], Keith Heberlein[3], Mark Brown[4], and Alexander Lin[5]

[1]*School of Health Sciences, University of Newcastle, Callaghan, New South Wales, Australia,* [2]*Biswas X Ray & Scan Center, West Apcar gardens, Asansol, India,* [3]*Siemens Medical Solutions, Charlestown, MA, United States,* [4]*Training and Development Center, Siemens Healthcare, Cary, NC, United States,* [5]*5Center for Clinical Spectroscopy, Brigham and Women's Hospital, Boston, MA, United States*

Introduction: γ-amino butyric acid (GABA) is the major inhibitory neurotransmitter of the mammalian adult brain, occurring in 30-40% of all synapses (second only to glutamate as a major brain neurotransmitter). Due to its major inhibitory role, GABA plays an important role in neuropsychiatric diseases and their treatment (1), as well as in pain progression and monitoring (2). Glutamate (Glu) is the most abundant inhibitory neurotransmitters of the adult mammalian central nervous system, the metabolic precursor of GABA, and plays a central role in pain transmission (3,4). Glutamine (Gln), however, is known to be a precursor and storage form of glutamate and is located in astrocytes at lower concentration than Glu. Both glutamate and GABA are synthesized in the brain from the Krebs citric acid molecule alpha-keto glutarate — a reaction known as the "GABA shunt". GABA is synthesized from glutamic acid and is catabolized back into the citric acid cycle.
Due to the different functions of different brain regions, it is expected that concentrations of GABA and Glx (Glu+Gln) to vary with brain function. Thus, the cerebellum is known to be involved in the coordination of voluntary motor movement, balance, equilibrium and muscle tone, while the occipital lobe is believed to be the primary concern of the occipital lobe is visual perception, recognition of printed words and colors(5).
Based on the above, it is informative to study the amounts of Glx and GABA in two functionally different regions if the brain, such as cerebellum and occipital lobe and try to correlate these concentrations with reported functions.

Methods: GABA and Glx were quantified in a 20x30x20 mm^3 voxel in the occipital lobe (n=14, mean age: 38 yrs) and cerebellum (n=10, mean age: 37 yrs) on a 3T clinical MR scanner (Trio Tim System, Siemens Healthcare, Germany) using a 12 channel head matrix coil by means of MEGA PRESS editing sequence(6). The voxel was localized on a 3D MRI 1mm isotropic MPRAGE. Spectroscopic parameters were: TE 70ms, TR 2 s, weak water suppression using WET, spectral width=2000 Hz, 128 averages, and 512 data points were acquired in 256 ms, RF offset was set 1.7 pm less than water (3.0 ppm). Two scans were acquired in which the frequency selective editing pulses were interleaved between 1.9ppm (on resonance: proton coupled to the edited GABA proton at 3.0ppm, bandwidth 42 Hz) and symmetrically at 1.9ppm with respect to water (4.7ppm), i.e. at 7.5 ppm. Scan time was 9 minutes. All subjects were consented according to local Institutional Review Board ethics guidelines.
Data processing: The on/off-resonance spectra were subtracted on scanner, Fourier transformed and manually peak fitting in the frequency domain was carried out between 1.5-4.0 ppm by a Gaussian peak lineshape. Four peaks were fitted: Glx (3.8, 2.3 ppm), GABA(3.0ppm), and NAA(2.0ppm). GABA and Glx concentrations were quantified as a ratio to NAA in the edited spectrum. Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale et al., 1999; Fischl et al., 2002).

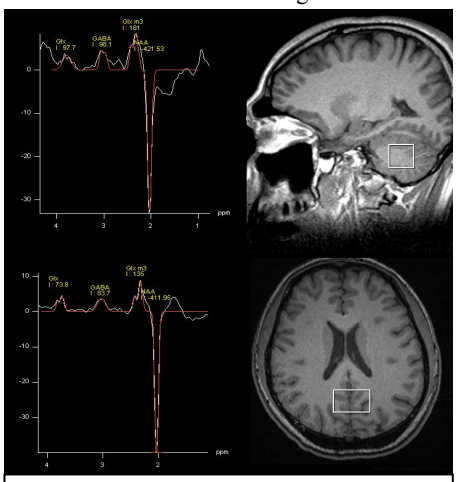

Figure 1. Representative spectra from occipital and cerebellum brain regions.

Results and Discussion:
A typical voxel positioning in occipital lobe and cerebellum, and resulting edited spectra are shown in Figure 1.

Average voxel segmentation for cerebellum was 47% white matter (WM) and 52% gray matter (GM), while for occipital lobe it was 45% WM and 44% GM. Remaining percentage was assumed to be CSF.

The plot of ratio of two Glx peaks (3.8 and 2.3ppm) and GABA (3.0ppm) to NAA with their standard errors is shown in Figure 2. The plot shows clearly higher ratios in the cerebellum.

It has been reported by Choi et al (7) that mean GABA concentration in gray and white matter was determined to be 1.30±0.36 µmol/g and 0.16±0.16 µmol/g, respectively. This is in agreement with our finding and the ratio go WM and GM.

No attempt was made to account for the contamination of the co-edited macromolecules, which resonates at 3ppm and is coupled to 1.7 ppm (8). The irradiated frequency (1.9ppm) for GABA is very similar to the 1.7ppm for macromolecule, and selectively editing GABA requires a higher magnetic field.

NAA can be used as a common reference in both brain regions. This is supported by a finding by Jacobs et al that NAA concentrations in occipital and cerebellum are similar (9). Increased GABA/Glx observed in the cerebellum relative to the occipital lobe could be due to functional/cellular differentiation of these two brain regions.

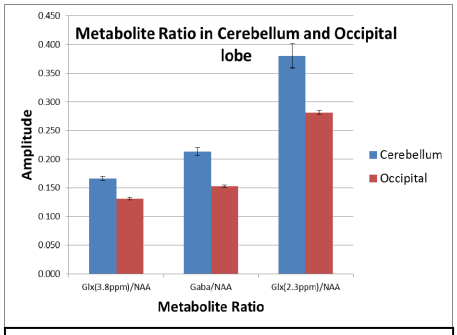

Figure 2. Glx and GABA ratio to NAA in occipital lobe and cerebellum.

Conclusion: GABA/NAA and Glx/NAA ratios in cerebellum were found to be higher than those in occipital lobe, probably due to different functionalities of these two different brain regions.

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