Age and Regional Dependent Changes of Glutamate in Human Brain: In vivo quantitation with MR spectroscopy

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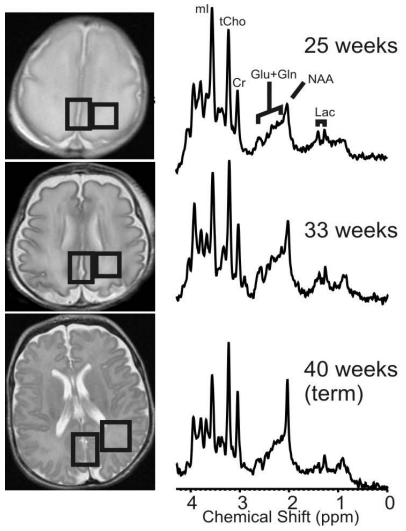
Introduction: Glutamate (Glu) is the most abundant excitatory neurotransmitter in the mammalian brain. Abnormal glutamate regulation is associated with neuronal dysfunction and has been linked with neurological disorders such as epilepsy, schizophrenia, and other mental and emotional conditions. The goal of this study was to measure age-dependent changes of glutamate concentrations in the human brain.

Methods: All single-voxel PRESS spectra (TR=1.5s, TE = 35ms, 128 averages) of occipital grey matter (GM) and parietal white matter (WM) acquired in this institution with "normal" MRI report and unremarkable clinical follow-up were reviewed. Subjects were either enrolled in various research studies or had clinical indications for MRI/S. This included suspicion of encephalitis, metabolic disorders, seizures, hypoxic-ischemic episodes, and others. All spectra were first reviewed for quality. Spectra with a linewidth of 6 Hz or larger were not included in the analysis. The final analysis included data from 416 patients ranging in age from 25 weeks post-conceptional age (15 weeks premature) to 20 years. All studies were carried-out on a 1.5T MR system (Signa LX, GE, Milwaukee, Wis). A standard head coil was used for acquisitions in older subjects (≈15-20 years) whereas for younger children and for newborns custom-designed smaller pediatric and newborn head coils (1) were used to ensure a good signal-to-noise ratio (SNR). LCModel software (S. Provencher Inc.) was used for processing and quantitation. Concentrations were corrected for the varying fractions of cerebrospinal fluid in the regions of interest. The signal from unsuppressed water was used as internal reference. The water content of the developing brain changes rapidly from ≈92% at 27 weeks post-conceptional age (PCA) to ≈85% six months after birth and then declines more gradually to ≈82% and ≈73% in pure grey and white matter (2). From the data summarized by Lentner et al. (2) a look-up table for water content as a function of PCA was generated by linear interpolation and used for absolute quantitation of grey and white matter spectra. Age of subjects was measured as PCA to adjust for different gestational age at birth. Metabolite concentrations were fitted to various functions (not described in detail).



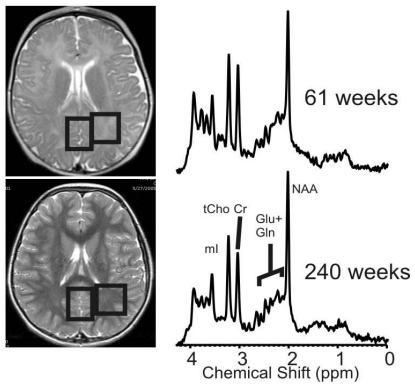


Fig. 1: *MR images indicating regions of interest and spectra of parietal WM (GM spectra not shown).*

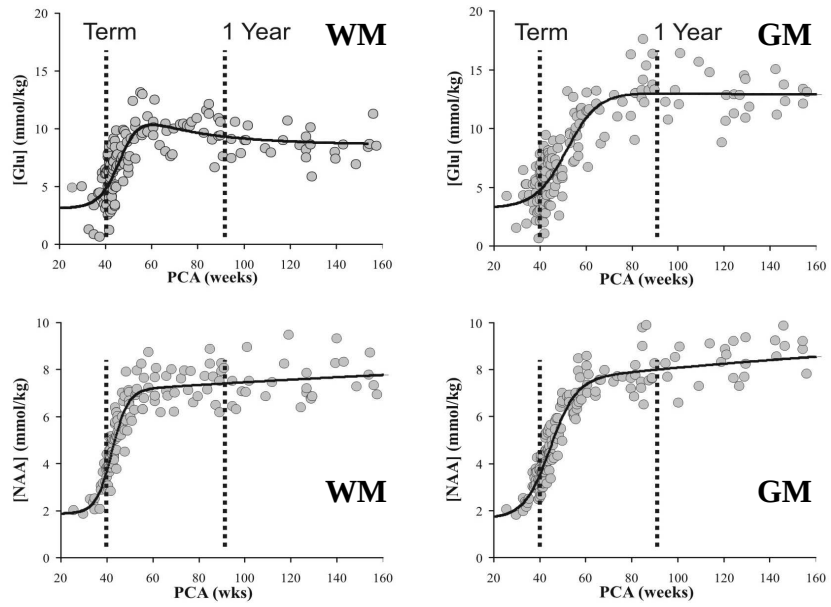


Fig. 2: *Glu and NAA concentrations in the developing human brain.*

Results: Glutamate concentrations increased from 3.7 ±2.0 µmol/gr at term to adult levels of 8.6±1.1µmol/gr in WM and from 4.4±1.5 µmol/gr to 12.9±1.3µmol/gr in GM within the first year of life (**Fig. 1,2**). The highest rate of net glutamate synthesis in WM was observed at 6 weeks after birth (0.46µmol/gram/week) and in grey matter 12 weeks after birth (0.36µmol/gr/week). In WM, glutamate reached a transient maximum (≈10.3µmol/gr) 20 weeks post-term and thereafter decreased slightly. In GM, glutamate reached a plateau at one year post-term. A significant decrease thereafter was not observed. NAA concentrations showed similar age-dependent changes. But a transient maximum in WM was not observed (**Fig. 2**). Glutamine (Gln) remained constant (3.9±1.4 µmol/gr (WM) and 4.9±1.5 (GM)). The mean covariance between Glu and Gln was -0.35±0.20 in this study.

Discussion: Within brain tissue, most of the glutamate is stored in the neuropil. The time courses of glutamate concentration suggest that maturation of glutamatergic neurons and the maximum density of their axon/dendrite network in the human brain is reached within the first year of life. Quantitation of Glu and Gln at clinical field strength is compromised by their complex structures and partial overlap. However, Glu and Gln are not identical and their separation in this study benefited from the use of special coils for small children with high signal-to-noise and the good shim achieved in brains of small children.

Acknowledgment: Rudi Schulte Research Institute.

References: 1. Bluml, S., et al.. Radiology, 2004. 231(2): p. 594-601. 2. Lentner, C., Geigy Scientific Tables, Ciba-Geigy, Editor. 1981, Ciba-Geigy: Basel, Switzerland. p. 220, 222, 223.