Long-term reproducibility of GABA levels in the occipital cortex of healthy volunteers

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Target Audience. This abstract is intended for researchers or clinicians who are interested in the use of *in vivo* magnetic resonance spectroscopy (MRS) for the measurement of γ-aminobutyric acid (GABA) concentrations in the human brain.

Purpose. GABA is the primary inhibitory neurotransmitter in the human brain and plays an important role in the regulation of neuronal activity. MRS GABA detection is most commonly performed using spectral editing techniques, such as MEGA-PRESS (1), which enable separation of GABA signal from the background of overlapping resonances. Alternatively GABA detection can be performed using short echo-time MRS methods such as STEAM or SPECIAL (2,3). In either case, GABA detection is challenging because of its relatively low concentration and the large overlapping resonances. Therefore, it is important to characterize the reproducibility of in vivo GABA MRS prior to its application in clinical or neuroscience research. Over short intra-scan intervals, the reproducibility of in-vivo MRS GABA measurements has been well characterized previously. Specifically, for repeated within-session GABA measurements, the reproducibility (coefficient of variation) has been found to range from 7-12% (3,4), and when GABA measurements are repeated in separate sessions up to 8 days apart, the reproducibility ranges from as low as 3.5% (2) to as much as 21% (2,5,6). Over such short time periods, individual GABA levels are believed to be relatively stable, and most of the variations in the observed GABA levels can likely be attributed to measurement error. On the other hand, the reproducibility of in vivo MRS GABA measurements over longer time intervals (greater than 8 days) has not yet been studied, and it is unclear whether GABA levels within individual subjects are stable over longer periods of time. Therefore, the purpose of this study is to investigate the reproducibility MEGA-PRESS edited GABA measurements in the occipital cortex over a period of approximately seven months; the longest interval studied to date.

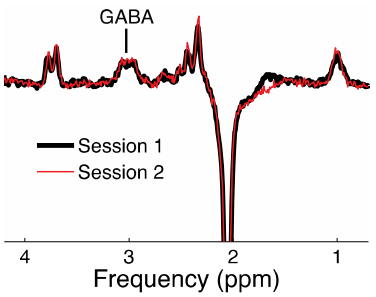

Figure 1. Session 1 and 2 MEGA-PRESS difference spectra from a single subject with a scan interval of 223 days.

Methods. 19 healthy male subjects between (mean age 24 ± 3 years) were recruited to participate in this study. All subjects provided informed, written consent and experiments were approved by the local ethics committee. Participants were scanned twice, with an average interval of 229 ± 42 days (~ 7 months) between scans, on a Siemens Tim Trio 3T MRI-scanner with a body coil transmitter and a 32-channel receive head coil. High resolution T1-weighed MPRAGE structural images were acquired (TR/TE=2420/3.7 ms, 1mm isotropic resolution, 5.5 minute scan), and used to guide placement of a 3x3x3 cm^3 MRS voxel in occipital cortex. GABA edited MRS was performed using MEGA-PRESS (3) with TR/TE=2500/68 ms and 192 averages (8 minute scan time). Data were processed using semi-automated MATLAB processing routines including weighted array coil recombination, removal of motion corrupted averages, frequency and phase drift correction, and manual alignment of edit-on and edit-off spectra. Processed edited spectra were analysed by peak fitting using jMRUI (7) as described previously (8). GABA concentrations were referenced to creatine, which was measured from the sum-spectrum (edit-on + edit-off). To assess reproducibility, we determined the average coefficient of variation between sessions, the Pearson product-moment correlation coefficient (r) between sessions, and the intra-class correlation coefficient.

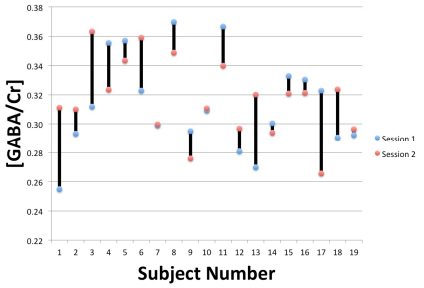

Figure 2. Session 1 and 2 [GABA/Cr] measurements for all subjects.

Results. Figure 1 shows the difference spectra from both sessions for one subject. Figure 2 shows the [GABA/Cr] measurements for both sessions in each of the 19 subjects. The coefficient of variation between sessions ranged from 0.1% to 14.0%, with an average of 5.5 ± 4.4%. Figure 3 shows a scatter plot of session 1 vs. session 2 [GABA/Cr] measurements. A significant positive correlation was observed between sessions (r=0.457, p=0.025). Finally, the intra-class correlation coefficient was calculated to be 0.51, which was statistically significant (p=0.014).

Discussion. We find that MEGA-PRESS measurements of GABA concentrations in the occipital cortex are reproducible in the long term. Indeed, even with a between-scan interval of 7 months, the observed reproducibility is comparable to those reported over short time intervals (< 8 days). The observed intra-class correlation coefficient was statistically significant, meaning that repeated measurements strongly resemble each other (with statistical significance) when between-subject variations are taken into account. In addition to confirming the previous findings that MEGA-PRESS GABA measurements are reproducible, these results also suggest that actual GABA concentrations in the occipital cortex are stable over relatively long periods of time. From this, it is possible to infer that MRS GABA concentrations are a reflection of trait, rather than state, an inference that is supported by the previously observed relationships between GABA and behavior (9). It should be noted that the occipital cortex provides relatively favorable data quality compared with some previously studied regions such as the anterior cingulate (2,5) or the dorsolateral prefrontal cortex (2,4). Therefore, poorer long-term reproducibility might be expected in other brain regions due to increased measurement error.

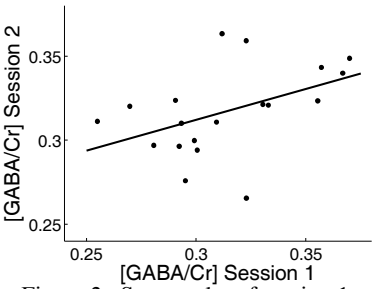

Figure 3. Scatter plot of session 1 vs. session 2 [GABA/Cr] values.

Conclusion. We conclude that GABA concentrations in the occipital cortex as measured by MEGA-PRESS MRS are reproducible over periods as long as 7 months. This result has significant implications for longitudinal MRS investigations of GABA concentrations in the human brain.

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