Diurnal Stability of MEGA-PRESS measurements of GABA concentration

R. A. Edden[1,2], C. J. Evans[3,4], and D. J. McGonigle[3,5]

[1]Russell H Morgan Department of Radiology and Radiological Sciences, The Johns Hopkins University, Baltimore, MD, United States, [2]FM Kirby Research Center for Functional MRI, Kennedy Krieger Institute, Baltimore, MD, United States, [3]CUBRIC, School of Psychology, Cardiff University, United Kingdom, [4]GE HealthCare, Slough, United Kingdom, [5]School of Biosciences, Cardiff University, United Kingdom

Introduction

As the principle cortical inhibitory neurotransmitter, gamma-aminobutyric acid (GABA) is the target of significant research effort in both the neuroscientific and clinical communities. Robust localised methods for measuring the concentration of GABA in the human brain *in vivo* are now sufficiently precise, not only to detect gross differences between patient populations and healthy controls (e.g. [1]), but also to detect both individual differences between healthy subjects[2] and task-driven changes within individuals[3]. GABA plays a central role in the maintenance of the circadian rhythms in the brain, and animal experiments have shown circadian cortical GABA changes[4]. However, in spite of the obvious implications for future study design, no data have been published investigating whether edited MRS measurements of GABA (plus co-edited macromolecules) vary with the time of day; this study addresses that issue.

Methods

Eight healthy volunteers were recruited for this study, with local ethics board approval. In each subject, GABA-edited MEGA-PRESS spectra were acquired in two regions at five timepoints between 7am and 8pm in the same day (as shown in Figure 1). The sensorimotor volume was centred on the 'hand knob' area of the precentral gyrus, aligned with the upper surface of the cortex in the sagittal plane. The visual region was centred on the median line, rotated in the sagittal plane so as to align with the cerebellar tentorium. The following experimental parameters were used: TE = 68 ms; TR = 1.8s; 16 ms editing pulse; 332 acquisitions; acquisition time 10 min. The edited GABA signal was modelled with a simple Gaussian function and a linear baseline between 2.82 ppm and 3.56 ppm, and quantified relative to the unsuppressed water signal from the same volume which was fitted with a mixed Lorentzian-Gaussian lineshape. A repeated-measures 2-way ANOVA was used to test for main effects of region and timepoint (where timepoint is treated as the repeated measure). Inter- and intra-subject variability was investigated by calculating the CV of measurements for each individual and region, and the coefficient of variation of measurements grouped across all subjects.

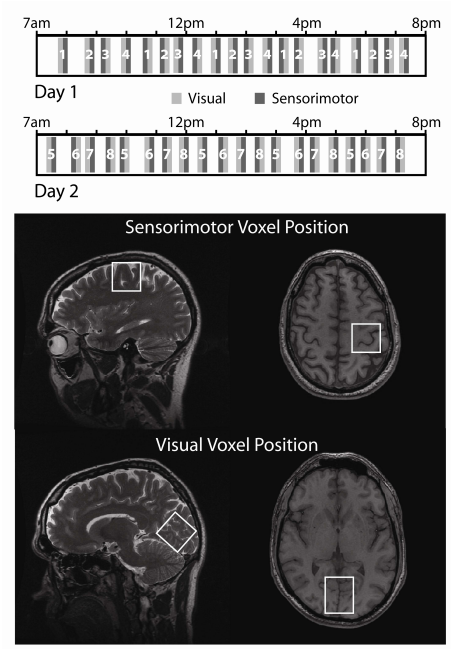

Figure 1: *Location of visual and sensorimotor voxels and timing of MEGA-PRESS GABA measurements.*

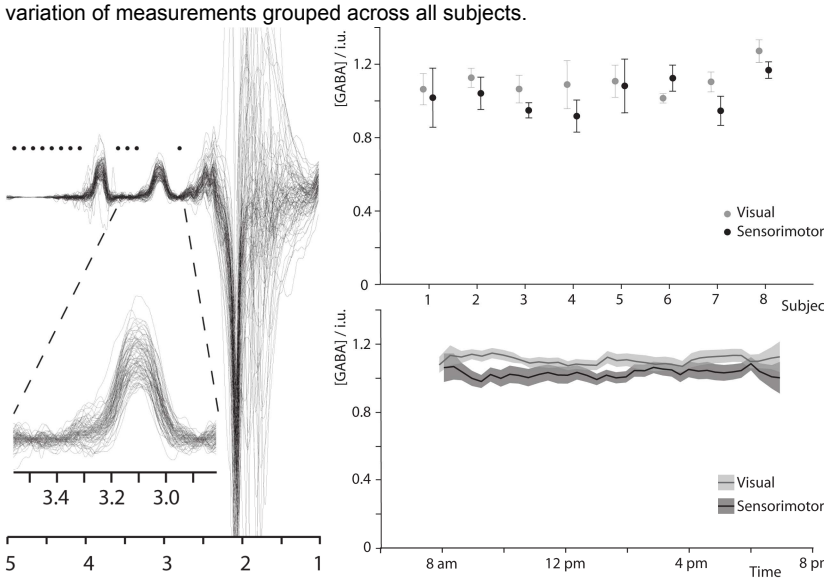

Figure 2: *Overlay of 80 edited spectra, showing reproducible lineshape (left; data have been baseline-corrected through the points •). The plot of mean within-subject GABA concentration by region (above right) shows between-subject variability. No effect of time-of-day is seen in plots of the running mean of eight consecutive measurements (below right); shaded region represents ± 1 SEM.*

Results

All eighty edited spectra were acquired with well-resolved GABA signal (Figure 2; left). No statistically significant effect of timepoint on the GABA concentration was found ($F=1.5$; $df=4$; $p=0.352$; Figure 2, below right). A statistically significant main effect on GABA concentration of region was found ($F=5.56$; $df=7$; $p=0.050$). Individual coefficients of variation (CVs) are shown in the table below. The method appears to be sensitive to inter-subject variability in GABA concentration, since the mean within-subject CV is lower than the between-subject CV in both regions.

Segmentation of the prescribed voxels gave the following results: somatosensory voxel (32±3% grey matter; 54±7% white matter; 14±4% CSF); occipital voxel (32±12% grey matter; 56±7% white matter; 9±3% CSF), which are not significantly different.

Conclusion

This time-of-day GABA stability study leads to three conclusions: that MEGA-PRESS of GABA in occipital and sensorimotor cortex is insensitive to any circadian changes in GABA concentration (and therefore need not be considered in the design of future studies); that GABA concentration is lower in sensorimotor cortex than occipital visual cortex; and that MEGA-PRESS of GABA at 3T is sufficiently sensitive to reveal inter-subject differences in concentration.

Subject	1	2	3	4	5	6	7	8	Mean	Group
CV_{visual}	8%	5%	7%	12%	8%	3%	5%	5%	6.5%	9.1%
$CV_{sensorimotor}$	16%	9%	4%	10%	14%	6%	8%	4%	8.8%	12.0%

Table 1: *Coefficients of variation (over five measurements) for each subject and region. The column* Mean *shows the average of these within-subject CVs. The column* Group *contains the coefficient of variation as calculated across all subjects.*

References

1. RJ Simister et al. Epilepsia 2003;44(4):550-558. 2. SD Muthukumaraswamy et al. Proc Nat Acad Sci. 2009; 106(20):8356-61. 3. A Floyer-Lea et al. J Neurophysiol 2006;95(3):1639-1644. 4. Kanterewicz BI, Golombek DA, Rosenstein RE, Cardinali DP. Brain Res Bull 1993;31(6):661-666.