Published in final edited form as:

J Magn Reson Imaging. 2013 September ; 38(3): 745–750. doi:10.1002/jmri.24009.

Regional difference in GABA levels between medial prefrontal and occipital cortices

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Abstract

Purpose—To avoid the confounding effects of variations in tissue composition this study measured regional GABA differences using two voxels with the same tissue composition.

Materials and Methods—Eighteen healthy adult volunteers were scanned using a 3 Tesla GE clinical scanner with a J-coupling based editing sequence. Spectroscopy voxels were placed in the medial prefrontal (MPFC) and occipital lobes (OCC) with essentially the same gray and white matter fractions.

Results—A 16% ($p=0.0001$) significantly higher GABA to creatine ratio was found in the OCC (0.1103 ± 0.0050) compared with the MPFC (0.0953 ± 0.0041). When normalized to tissue water, GABA concentrations in the OCC were 14% higher than in the MPFC.

Conclusion—A difference in GABA concentration was found between the OCC and MPFC voxels in healthy subjects when controlling for tissue composition.

Keywords

N-acetylaspartate (NAA); creatine; glutamate + glutamine (Glx); gamma-aminobutyric acid (GABA); prefrontal cortex; occipital cortex; white matter; gray matter

INTRODUCTION

Changes in the main inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in humans have been associated with physiological conditions, psychiatric disorders, neurological conditions, and the use of various medications (1–11) and references in (12). However, measuring GABA levels via magnetic resonance spectroscopy (MRS) is difficult because of the spectral overlap of the weak GABA signals by stronger signals of various other origins (1–3 and references therein). Essentially, all GABA spectroscopic techniques make use of the J coupling between the protons on the GABA C4 carbon and the protons on the C3 carbon; the most widely used technique has been two-step spectral editing (2,3). These methods have been used to measure the GABA to creatine ratio in many studies, most of which have focused on the occipital cortex (OCC) where static magnetic field distortion can be well corrected (1–7). GABA to water ratios have also been measured for absolute

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The authors report no conflict of interest, financial or otherwise.

quantification of GABA although quantification of GABA has many limitations such as potential variations in T_2 decay of both GABA and tissue water.

The role of GABA in psychiatric disorders has spurred recent interests in extending GABA editing methods to the frontal lobe of human brain (10,13). It is of great interest and importance to compare GABA concentrations between the occipital and frontal lobes. Comparing concentration of strong MRS signals—such as N-acetylaspartate (NAA), creatine and choline—from different brain regions is usually conducted using chemical shift imaging techniques combined with tissue segmentation (14,15). Comparing GABA concentrations in the occipital and frontal lobes by chemical shift imaging, however, poses two serious technical challenges. First, chemical shift imaging of GABA requires that the editing pulse act properly across the entire slice (16). This is very difficult for the two step editing method employed in this study. It is especially difficult for an axial slice covering both the occipital and frontal regions of interest due to the large static magnetic field shift between these two regions caused by the nasal cavity. With clinical scanners, a full high order correction of static magnetic field distortion in these slices is very difficult if not impossible. Second, because of the low cortical concentrations of GABA, only a very limited number of relatively large image pixels can be measured by chemical shift imaging within the time constraints of most clinical studies, making it difficult to distinguish regional differences in GABA from differences due to gray and white matter fractions.

The apparent difference in GABA distribution in brain has multiple origins. From a neurochemical point of view the distribution of the GABA synthesizing enzyme glutamic acid decarboxylase is well known to be very different across the brain. Many metabolites including GABA have different levels in gray and white matter. While spatial distribution of intense signals from NAA, creatine and choline can be analyzed from a large number of voxels there is a general difficulty in analyzing regional difference in dilute metabolites such as GABA where large voxels encompassing both gray and white matter have to be used to gain sufficient SNR. The goal of this work is to show that the complications in comparing regional difference in dilute metabolites due to variations in tissue composition can be avoided by choosing large voxels with the same tissue type composition, therefore, revealing difference in concentration not caused by tissue type composition. With a typical GABA voxel size of 18 cc for a usable signal-to-noise ratio (SNR) at 3 Tesla, the measurement of two separate voxels in a single session is feasible. This study compares regional GABA differences using two voxels of essentially the same gray and white matter fractions, one in the medial prefrontal cortex (MPFC), and the other in the occipital lobe (OCC), thus circumventing the difficulties noted above. The study sought to explore differences in GABA concentrations between the MPFC and OCC voxels in adult healthy subjects, and to establish baseline measures for our future studies that may use the OCC as an internal control. Since NAA, creatine, choline and Glx (glutamate+glutamine) are simultaneously detected by the GABA editing sequence, results from these metabolites are also reported.

MATERIALS AND METHODS

Eighteen healthy volunteers (13 M, 5 F; 22–57 years old; average age: 30.5 years (SD=9.4 years)) recruited in compliance with the Institutional Review Board (IRB) of the National Institute of Mental Health (NIMH). Scans were performed on a 3 Tesla GE whole body scanner (General Electric Medical Systems, Milwaukee, Wisconsin, USA) running the 15M4 software platform. A Medical Advances (Intermagetics General Corporation, Milwaukee, Wisconsin, USA) RF quadrature transmit/receive coil was used with an inner diameter of 25 cm and a length of 20 cm. Scan sessions began with a T_1 weighted anatomical scan by a three dimensional spoiled gradient echo sequence (repetition time TR

= 7.3 ms, echo time TE = 2.7 ms, flip angle 12°; in plane resolution 0.9 mm × 0.9 mm; matrix size 192 × 256; field of view 240 mm × 240 mm; slice thickness 2 mm; total scan time 2 min 32 s).

Two spectroscopy voxels (3 l/r × 3 a/p × 2 s/i cm) were scanned in each session. The first was placed over the midline in the frontal lobe just anterior to the ventricles (MPFC). The second voxel was placed over the midline in the occipital lobe just posterior to the ventricles (OCC) (Fig 1). The location of the OCC voxel was chosen to approximately include the same amount of gray and white matter as in the MPFC voxel. The GABA editing sequence was a modified standard PRESS sequence (1,17), TE = 68 ms; TR = 1.5 s; total number of acquisitions NS = 1024; in-scanner averaged acquisitions for phase cycling NEX = 2. The editing pulse had a top-hat profile with a bandwidth ranging from 2.0 ppm to 0.6 ppm that covered both the GABA protons on C3 at 1.89 ppm and partially covered the glutamate and glutamine protons on C3 and C4 (17). The editing pulse was switched on (edited) and off (non-edited) during respectively even- and odd numbered scans. Each scan of 26 minutes was an in-scanner average of two acquisitions resulting in a total of 256 edited and 256 non-edited scans and saved separately.

The anatomical images were segmented with SPM5 (18) to determine the fraction of gray matter, white matter, and cerebrospinal fluid (CSF). A program written in IDL (ITT Visual Information Solutions, White Plains, NY, USA) was used to extract the coordinates of the spectroscopy data files and their respective tissue fractions from the segmentation results (17). The spectroscopy data were processed in the time domain as follows: the water reference scan at the end of each spectroscopy scan was fitted with Hankel Singular Value Decomposition (HSVD) (19) and the phase of the fitted water signal was used to deconvolve the time domain data to correct for residual eddy currents. To correct for subject motion, the spectroscopy data were evaluated by comparing the amplitude of the residual water signal of each of the 512 individual scans. A scan was rejected if its amplitude deviated more than 10% from the average. To further correct for subject motion the phase of each residual water signal was used to phase correct each scan (17). The same HSVD algorithm was then used to remove the residual water from the spectroscopy data, and the scans were averaged to one non-edited scan and one subtracted scan that revealed the GABA C4 signal. In the non-edited scan the NAA, choline, and creatine signals were fitted in the time-domain with a Marquardt-Levenberg non-linear fitting algorithm using IDL. The model function used a shared lineshape for all three metabolites consisting of a combination of Lorentz and Gauss damping and a shared parameter for frequency offset. The relative frequency positions of NAA, choline, and creatine were taken from literature (15). GABA shift and coupling parameters (15) and fit parameters of the non-edited signal were used to construct a reference signal of the expected shape of the GABA doublet in the edited signal: a doublet with equal amplitude, with a separation of 14 Hz, position from GABA shift values and the the shared offset parameter, and the lineshape from the main metabolite fit. This lineshape was used to eliminate the additional degree of freedom in the fit that would increase the deviation of the GABA to creatine ratio. For visual presentation the processed time domain data was line broadened by a 6.6 Hz Blackman-Harris window and transformed to the frequency domain. The edited GABA signal consisted of a combination of GABA and macromolecules group M7 (20) that are J coupled to group M4 at 1.7 ppm and is sometimes referred to as GABA+ (21). GABA correlations between the two brain areas within individual subjects were also assessed via linear regression analysis of the GABA levels measured in each of the two areas.

RESULTS

Figure 1 shows the location of the MPFC and the OCC voxel and the segmentation of the anatomical image by SPM in a typical scan. Figure 2 shows a typical set of processed GABA spectra acquired from the MPFC. The fitted non-edited spectrum is displayed in the top panel, and the fitted difference spectrum is displayed in the bottom panel. The range of the gray matter fraction for all the volunteers was determined from tissue segmentation; it ranged from 0.47 to 0.63 with an average of 0.535 and a standard deviation of 0.020 for the MPFC voxel. For the OCC voxel, the gray matter fraction ranged from 0.40 to 0.61 with an average of 0.522 and a standard deviation of 0.026 (Table 1). As shown in Table 1, no significant difference was observed in tissue composition between the two voxels. Because the experiment was designed to have a narrow range of variation in tissue composition, no significant correlation was seen between the gray matter fraction and the creatine to water ratio, or between the GABA to creatine ratio for both voxels.

The GABA to creatine ratios are plotted in the left panel of Figure 3. The GABA to creatine ratio was 0.0953 ± 0.0041 for the MPFC voxel, and 0.1103 ± 0.0050 for the OCC voxel ($p=0.0001$). We also investigated intra-subject regional correlation of the GABA to creatine ratio (see Fig 3, right panel), however no significant correlation was observed with the Pearson's correlation coefficient r equal to 0.356. ($p = 0.2$). The creatine to water ratios were $1.48 \times 10^{-3} \pm 6.6 \times 10^{-5}$ for the MPFC voxel and $1.42 \times 10^{-3} \pm 6.4 \times 10^{-5}$ for the OCC voxel; the values did not differ significantly ($p=0.2$). When normalized to tissue water, GABA concentrations in the occipital lobe voxel were 14% higher than in the medial prefrontal lobe voxel. Significant differences were observed in the NAA to creatine ratio between the MPFC (1.42 ± 0.04) and the OCC (1.78 ± 0.06) ($p=2 \times 10^{-9}$), and in the choline to creatine ratio between the MPFC (0.801 ± 0.04) and the OCC (0.576 ± 0.04) ($p=9 \times 10^{-10}$). No significant difference was observed in the co-edited glutamate plus glutamine (Glx) to creatine ratio. The co-edited Glx to creatine ratio in the MPFC voxel was 0.0812 ± 0.0035 , and that in the OCC voxel was 0.0802 ± 0.0044 ($p=0.74$). Although our primary goal was to investigate any regional difference in GABA under condition of the same tissue composition in the OCC and MPFC voxels all significant results remained statistically significant even after correction for multiple comparisons.

DISCUSSION

Few studies have investigated any regional differences in GABA levels (8,9,11,16,23) and most values are reported as a GABA to creatine ratio and more lately as a ratio to water. The correlation of the GABA to creatine ratio with gray matter fraction was previously tested and found significant in the parietal lobe (14) and in the frontal region (15). The ratio to water is potentially more accurate but only if corrections are made for differences in tissue water and CSF (15). Using chemical shift imaging of GABA in the parietal lobe, Choi and colleagues (16) found with their double quantum sequence a significant regional differences in GABA concentrations, and a strong correlation between GABA and tissue composition; this suggested that, within the parietal lobe, variation in GABA levels could be largely attributed to gray and white matter content. Zhu and colleagues (23) find a weaker positive correlation between GABA and gray matter using a two step csi editing sequence. Geramita and colleagues (17) studied the correlation between GABA levels in the anterior cingulate cortex (ACC) and tissue composition placing one voxel in mostly white and one voxel in mostly gray matter and found a significant but weak positive correlation between the GABA to creatine ratio and white matter fraction. In that study, the average value of the white matter fraction for the mostly gray and mostly white matter voxel was 0.22 and 0.73 respectively and of the gray matter fraction for the mostly gray and the mostly white matter voxel was 0.60 and 0.25 respectively. Because the range of the tissue type variation in our

MPFC voxel was much smaller than that used in the study by Geramita (17) and Zhu (23), we do not expect that the slight variation in tissue composition in our MPFC voxel to significantly affect our results, also we do not expect the slight bias towards gray matter in the segmentation in figure 1 to be of any influence given the small tissue variations in the voxels of this study and any bias would equally affect the two regions and therefore cancelling its effects on our regional comparison. Bhagwagar and colleagues (8) investigated GABA levels in the OCC and ACC of healthy adults and found that the GABA to creatine ratio was 19% higher in the OCC. Price and colleagues (11) found that the GABA to water ratio was 33% higher in the OCC than in the ACC. Neither study reported the tissue composition of the spectroscopy voxels. Evans (24) and colleagues found a 7.2% higher GABA to water ratio between a sensorimotor and the occipital area, their voxel composition had a much higher white matter fraction (about 55%) than this study. Puts (25) and colleagues also find a higher overall value for GABA in the occipital area. To avoid complications associated with tissue composition, we chose to place the voxels in areas with essentially the same tissue composition in order to measure differences in the GABA to creatine ratio in the MPFC and OCC. Towards this end, the OCC voxel was placed at the posterior edge of the ventricles and the MPFC voxel at the anterior edge of the ventricles, the same location as in (10).

GABA is widely distributed in the human brain, and works to inhibit nearly all neurons. Neurochemical data suggest that the distribution of GABA is heterogeneous, and depends on both brain regions and tissue composition (26). A growing body of evidence suggests that regional differences in GABA levels reflect the specific actions of GABAergic neurons in each region (27). This study shows that despite the same tissue composition, GABA concentration differs between the two regions investigated. Our results therefore underline the importance of assessing regional differences in GABA concentrations. Our results are also in agreement with recent findings of region-specific changes in brain GABA concentration in response to external stimuli or due to mental tasks or mental disorders (for example, Hasler et al (28), O’Gorman et al (29), and Gaetz et al (30)). Furthermore, by controlling tissue composition our results highlights that the MRS measure of GABA reflects underlying neurochemical processes that are not necessarily related to tissue composition. In particular, the results reported here should also facilitate the establishment of a baseline for our subsequent MRS studies of GABA in psychiatric disorders that may use the OCC as an internal control.

Our analysis identified NAA to creatine ratios of 1.42 and 1.78 for the MPFC and OCC, respectively (see Table 1), which closely matched values found by Bhagwagar and colleagues (8) in both regions, and by Hasler and colleagues (10) in the MPFC. Our NAA- and choline- to creatine ratios were also consistent with values reported by Pouwels and Frahm (22) for both regions, and for NAA to creatine ratios in the MPFC observed by Geramita and colleagues (17) when taking into account the gray and white matter fraction. Taken together with regional differences in GABA found in this study these results indicate the importance of region-specific quantification of metabolites.

In conclusion, and to the best of our knowledge, this study is the first to compare the regional differences in GABA concentrations by selecting two brain regions with essentially the same tissue composition. We found that the GABA to creatine ratio in the OCC voxel was significantly higher than in the MPFC voxel by ~16%. When normalized to tissue water, the GABA concentration in the OCC was 14% higher than that in the MPFC.

Acknowledgments

Financial disclosures: This study was supported by the Intramural Research Program of the National Institute of Mental Health, National Institutes of Health (IRP-NIMH-NIH).

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Figure 1. Location of spectroscopy voxels in the medial prefrontal cortex (MPFC) and occipital cortex (OCC). The lower two images show the segmentation of the anatomical images, Gray=white matter, Dark gray=gray matter, and Blue=cerebrospinal fluid (CSF) space.

Figure 2.

A representative GABA editing scan on the MPFC is shown in the left panels, the GABA editing scan on the OCC on the same volunteer is shown in the right panels. Top panels: the un-edited spectra and their respective metabolite fits. Bottom panels: the difference spectrum containing the co-edited Glx (glutamate+glutamine) and gamma-aminobutyric acid (GABA) peaks, and the fits.

Figure 3.

Left panel, the paired values of the GABA to creatine ratios for the 18 subjects. The ratio for the medial prefrontal cortex (MPFC) was 0.0953 ± 0.0041 and 0.1103 ± 0.0050 for the occipital cortex (OCC) ($p=0.0001$). The right panel displays the intra-subject regional correlation of the GABA to creatine ratio; the best linear fit and 95% confidence intervals are shown. The correlation is statistically insignificant with a Pearson's correlation coefficient of 0.356 ($p = 0.2$).

Table 1

Tissue composition and metabolite ratios for the MPFC and OCC voxels.

	MPFC	OCC	p value
Gray matter fraction	0.535 ± 0.042	0.522 ± 0.056	0.47
White matter fraction	0.372 ± 0.051	0.386 ± 0.064	0.50
CSF fraction	0.089 ± 0.022	0.092 ± 0.036	0.76
NAA/water	$2.07 \times 10^{-3} \pm 7.9 \times 10^{-5}$	$2.53 \times 10^{-3} \pm 1.2 \times 10^{-4}$	6.0×10^{-7}
creatine/water	$1.48 \times 10^{-3} \pm 6.6 \times 10^{-5}$	$1.42 \times 10^{-3} \pm 6.4 \times 10^{-5}$	0.22
choline/water	$1.18 \times 10^{-3} \pm 7.5 \times 10^{-5}$	$0.82 \times 10^{-3} \pm 5.7 \times 10^{-5}$	1.9×10^{-8}
GABA/water	$1.38 \times 10^{-4} \pm 4.6 \times 10^{-6}$	$1.57 \times 10^{-4} \pm 4.2 \times 10^{-6}$	7.4×10^{-7}
co-edited Glx/water	$1.18 \times 10^{-4} \pm 4.9 \times 10^{-6}$	$1.14 \times 10^{-4} \pm 4.8 \times 10^{-6}$	0.22
NAA/creatine	1.4160 ± 0.040	1.7763 ± 0.064	1.6×10^{-9}
choline/creatine	0.8012 ± 0.038	0.5761 ± 0.038	8.7×10^{-10}
GABA/creatine	0.0953 ± 0.0041	0.1103 ± 0.0050	1.0×10^{-4}
co-edited Glx/creatine	0.0812 ± 0.0035	0.0802 ± 0.0044	0.74