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Technical note

Use of quantitative brain water imaging as concentration reference for J-edited MR spectroscopy of GABA☆

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ABSTRACT

Purpose: To compare two different methods of obtaining the water reference for determination of quantitative water-scaled in vivo concentration estimates of γ-aminobutyric acid (GABA).
Methods: Water-scaled GABA estimates from localized J-difference edited MR spectroscopy experiments can be computed using standard values for tissue-specific water content and relaxation times. Water content and relaxation may, however, be altered in pathology. This work re-analyzed data from a recent study in healthy controls and patients with minimal (mHE) or grade I (HE 1) hepatic encephalopathy, a disease associated with slight elevation of brain water content. J-difference edited MR spectroscopy data were combined with quantitative brain water measures, which provided individual water density references and T_1 relaxation times. Resulting GABA estimates were compared to concentration values obtained using standard tissue-specific water content and relaxation values.
Results: Occipital GABA concentration values obtained from individual water and T_1 maps were 1.64 ± 0.35 mM in controls, and significantly higher ($P < 0.01$) than in mHE (1.15 ± 0.28 mM) and HE 1 patients (1.18 ± 0.09 mM). Results from the tissue-dependent approach (1.58 ± 0.30 mM (controls), 1.10 ± 0.27 mM (mHE) and 1.12 ± 0.12 mM (HE 1)) were slightly lower ($P < 0.05$ in each group).
Conclusion: Water-scaled in vivo GABA estimates can be obtained with individual water density and T_1 relaxation mapping. This approach may be useful for studying GABA levels in pathologies with substantial brain water content or relaxation changes.

1. Introduction

γ-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the human brain. Magnetic resonance spectroscopy (MRS) is the only technique to non-invasively measure cerebral GABA in vivo and has therefore gained a lot of research interest [1–3]. In single-voxel proton magnetic resonance spectroscopy (^{1}H-MRS) at field strengths of 1.5 to 3 T, J-resolved spectral editing sequences are required to isolate the GABA resonance that is otherwise obstructed by peaks like creatine. MEGA-PRESS is one of the frequently used editing schemes amongst others [4,5].

GABA concentration estimates from MRS are currently almost exclusively reported in two ways: either normalized to other metabolites such as N-acetylaspartate (NAA) or creatine (Cr), or scaled to a water-unsuppressed spectrum and then provided in absolute measures (mM), based on assumptions of tissue specific molar water concentrations [1].

Particularly for water-scaled concentration estimation, data comparison across research sites, scanner platforms, and sequence implementations can be difficult, as the quantification routines are not uniform. Reported water-scaled GABA concentration for the healthy brain may range from 1.1 mM [6] to 2.5 mM [7], depending on the assumptions made. More importantly, the concentration estimates may be biased in pathologies where the water concentration in brain tissue might deviate from the assumptions, such as hepatic encephalopathy [8].

Both MEGA-PRESS spectra and brain water content data have been acquired from healthy controls and patients with hepatic encephalopathy (HE) in the course of a recent study [9]. HE

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comprises impairment of cerebral functions as a consequence of liver damage. Its severity can be classified from grade I to IV, complemented by the term *minimal HE* (*mHE*) to describe patients with subtle symptoms only measurable with psychometric testing [10]. HE is believed to be associated with a low-grade cerebral oedema due to disturbed cell volume regulation [11]. Previous investigations in HE patients showed mildly increased MR brain water content measures in white matter [8] and decreased T_1 values in certain regions within the basal ganglia [12].

HE is therefore a suitable model to examine to what extent such alterations might affect water-scaled MR spectroscopic GABA concentrations. Hence, the goal of the present work was the employment of individual brain water content data to serve as subject-specific concentration reference for water-scaling, including individual T_1 relaxation correction [13,14]. A similar approach has previously been suggested by Gasparovic et al. for metabolite quantification in chemical shift imaging experiments [15,16]. To examine the impact of putative brain water and T_1 alterations in pathology, the obtained values were compared to GABA concentration estimates calculated using standard tissue-specific water density and relaxation values.

2. Material and methods

2.1. Determination of GABA concentrations

For water-scaled spectroscopy experiments, the concentration of a metabolite [*M*] can be calculated according to

$$[M] = \frac{S_M}{S_{H_2O}} \cdot [H_2O] \cdot \frac{2}{H_M} \cdot C_{ref} \tag{1.1}$$

S_M and S_{H2O} are the peak areas of the metabolite and water (including accounting for the averaging over the acquisitions). $[H_2O]$ denotes the concentration of MR visible water (55.5 mol/L for pure water). H_M is the number of signal giving metabolite protons (2 in the γ methylene group of GABA at 3 ppm), and C_{ref} is a term accounting for the water densities used for referencing, their relaxation properties and the relaxation behavior of the target metabolite.

2.1.1. Water-scaling and relaxation correction

Treatment of the water reference determination varies largely across studies. In its general form

$$C_{ref} = \frac{f_{H_2O} \times R_{H_2O}}{R_M} \tag{1.2}$$

f_{H2O} denotes the assumed or measured tissue water density (with 1 being pure water). R_{H2O} and R_M contain the relaxation, according to $R_y = e^{-TE/T_{2,y}} \cdot (1 - e^{-TR/T_{1,y}})$.

2.1.2. Spectral editing specific modifications

In case of spectral editing, Eq. (1.1) needs to be modified by an additional factor C_{edit}. It contains acquisition specific corrections treating (i) macromolecular contamination and (ii) editing efficiency, and is calculated by $C_{edit} = \frac{MM_{cor}}{eff}$.

Regarding (i), editing techniques suffer from GABA peak contamination with co-edited resonances from other compounds such as macromolecules and homocarnosine. Different approaches have been introduced to work around the MM problem (MM nulling [17,18] or MM-symmetric editing [4]). In many cases, the presence of contamination is simply accepted and explicitly acknowledged, with the corresponding peak area often being termed "GABA+" (for GABA + MM + homocarnosine).

In the present study, the macromolecular contribution to the GABA+ peak was assumed to be 55% since the classic editing scheme (pulses at 1.9 and 7.5 ppm) was used [1].

MM_{cor} was therefore set to 0.45 in this work.

Regarding (ii), the editing efficiency indicates how much of the signal intensity of the 3 ppm GABA resonance is conserved in the difference spectrum. Ideally, the normalized peak intensities within the triplet are 1–2-1 (with editing, ON resonance) and (−1)-2-(−1) (without editing, OFF resonance). Hence, they follow a 2–0-2 pattern in the ideal difference spectrum, conserving 100% of the peak area of the 1–2-1 pattern. As ON and OFF are subtracted and not averaged, accounting for the number of acquisitions (ON and OFF = 2, DIFF = 1) results in the ideal value of 0.5 for *eff*. In practice, imperfect editing leads to contribution of the central peak [19], altering *eff*. In the present work, *eff* was measured as described previously [17,20,21], by comparing PRESS and MEGA-PRESS spectra from a phantom containing GABA and glycine (pH = 7.0, concentration = 100 mM/L each) according to $eff = (\frac{I_{GABA,MEGA\text{-}PRESS,(ON\text{-}OFF)}}{I_{Gly,MEGA\text{-}PRESS,(ON+OFF)}}) / (\frac{I_{GABA,PRESS}}{I_{Gly,PRESS}})$, containing the intensities of the GABA multiplet and the glycine singlet from the respective scans. The experimental value for *eff* was determined to be 0.63, exceeding the ideal value of 0.5 due to presence of the residual central peak [21].

2.1.3. Methods of GABA quantification

We designed two different quantification routines: segmentation and watermap.

The segmentation approach is based on tissue class segmentation of anatomical images into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). C_{ref} can be written as

$$C_{ref} = \frac{f_{GM} \times R_{H_2O,GM} + f_{WM} \times R_{H_2O,WM} + f_{CSF} \times R_{H_2O,CSF}}{R_{GABA} \cdot (1 - f_{vol\_CSF})} \tag{1.3}$$

f_i describes fractional water densities. C_{ref} is calculated pixel-wise using

$$f_i = \frac{f_{vol\_i} \cdot WD_i}{f_{vol\_GM} \cdot WD_{GM} + f_{vol\_WM} \cdot WD_{WM} + f_{vol\_CSF} \cdot WD_{CSF}} \tag{1.4}$$

where f_{vol_i} is the tissue class probability, and WD_i is its assumed relative water density [15]. Eq. (1.4) provides the tissue water densities, calculated from the tissue volume fractions, weighted by their water densities. Here, the term 'water density' describes the relative tissue water content with respect to 100% pure water (i.e. a water concentration of 55.5 mol/L). A similar approach has been described and used before [20,22,23]. In this work, GABA concentration estimates were calculated assuming the relative water densities in WM, GM, and CSF to be $WD_{WM} = 0.70$, $WD_{GM} = 0.80$ and $WD_{CSF} = 0.99$ [14,24]. Tissue specific values for water T_1 relaxation times were used: $T_{1,GM} = 1331$ ms, $T_{1,WM} = 832$ ms, $T_{2,GM} = 110$ ms, $T_{2,WM} = 79.6$ ms [25], $T_{1,CSF} = 4160$ ms and $T_{2,CSF} = 500$ ms [26]. As CSF contains negligible amounts of metabolites, partial volume correction was applied by dividing the complete term by the sum of non-CSF tissue fractions (GM + WM).

The watermap approach was originally suggested for chemical shift imaging [16]. Instead of assuming relative water densities for each tissue class (WD_i), it is based on the additional acquisition of several multi gradient echo and EPI images as previously proposed [14]. This procedure yields a quantitative water and T_1 map, providing individual tissue-specific water intensities and T_1 for each high-resolution pixel inside the spectroscopic volume. Eq. (1.4) thus becomes

$$f_y = \frac{\sum_i f_{vol,y}(i) \times WD_{Watermap}(i) \times R(i)}{\sum_i WD_{Watermap}(i)}.$$

already including the relaxation terms. In this term, $WD_{Watermap}$ denotes the water density as measured by the watermapping