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Estimating glutamate and Glx from GABA-optimized MEGA-PRESS: Off-resonance but not difference spectra values correspond to PRESS values

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ABSTRACT

Proton magnetic resonance spectroscopy measurements of glutamate and GABA are important in neuropsychiatric research. Some study designs require simultaneous measurement of both metabolites. GABA measurement requires specialized pulse sequences, the most common approach being J-difference spectral editing with MEGA-PRESS. This method enables two different strategies for concurrently measuring glutamate - from either off-resonance or difference spectra. However, it is uncertain how either strategy compares to conventional glutamate measurements. Here we compared these approaches in 49 subjects (28 healthy volunteers and 21 first-episode psychosis patients), in whom both PRESS (TE 80) and MEGA-PRESS (TE 68) spectra were obtained from dorsolateral prefrontal cortex. Glutamate and glx estimates from MEGA-PRESS difference and off-resonance spectra were compared to glutamate and glx estimates from PRESS spectra using correlational analyses. In healthy volunteers, correlations between PRESS and MEGA-PRESS off-resonance values were $r \geq 0.88$ and were significantly higher than correlations between PRESS and MEGA-PRESS difference spectrum values ($r \leq 0.36$). Patients showed a similar pattern. Lower correlations with difference spectrum values may reflect a disproportionate impact of field instabilities on co-edited glutamate signals. The results suggest that MEGA-PRESS off-resonance spectra can substitute for separately-acquired PRESS spectra in studies requiring simultaneous glutamate and GABA measurements.

1. Introduction[1]

Proton magnetic resonance spectroscopy (1H-MRS) is a technique for the non-invasive measurement of neurometabolites in defined regions of the human brain. Using optimized acquisition sequences, 10 or more different brain metabolites may be present in sufficiently high concentration to be measurable with clinical scanners. Among these metabolites, glutamate and GABA are of particular interest, as their functions include serving as the principal excitatory and inhibitory neurotransmitters, respectively. Disruption of glutamatergic and GABAergic systems has been implicated in a variety of neuropsychiatric disorders, including psychotic disorders, seizure disorders, and mood disorders (Jun et al., 2014; Luykx et al., 2012; Maddock and Buonocore, 2012; Marsman et al., 2013; Schur et al., 2016; van Veenendaal et al., 2015). Aspects of brain metabolism or neurotransmission involving glutamate and GABA may be promising targets for the development of novel treatments for these disorders (Poels et al., 2014; Waschkies et al., 2014). Thus, 1H-MRS may have a key role in testing the engagement of targeted mechanisms by such novel treatments. While many clinical investigators may wish to measure glutamate and GABA simultaneously, it is not yet clear to what extent this can be adequately done using a single 1H-MRS acquisition sequence. Glutamate is most often measured using conventional PRESS or STEAM sequences, while measuring GABA on a clinical scanner requires use of a specialized acquisition sequence (Wijtenburg et al., 2015; Harris et al., 2017), the most widely used of which is the MEGA-PRESS sequence (Mescher et al., 1998). MEGA-PRESS sequences used to measure GABA can also provide nominal measures of glutamate (Mescher et al., 1998), but it is not yet known to what extent such glutamate measurements are comparable to those acquired using PRESS or STEAM. The goal of the

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[1] 1H-MRS: proton magnetic resonance spectroscopy; dlPFC: dorsolateral prefrontal cortex; CoV: coefficient of variation: CRLB: Cramer-Rao lower bounds; FoV: field of view; glx: glutamate + glutamine; MEGA-PRESS: Mescher-Garwood point-resolved spectroscopy; MP-Diff: MEGA-PRESS difference spectrum; MP-Off: MEGA-PRESS off-resonance spectrum; NAA: n-acetylaspartate; NAAG: n-acetylaspartylglutamate; NEX: number of excitations; PRESS: point-resolved spectroscopy; RF: radio frequency; STEAM: stimulated echo acquisition mode; TE: echo time; TR: repetition time.

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current study is to compare glutamate measurements obtained using a conventional PRESS sequence with those acquired using a widely available, GABA-optimized, MEGA-PRESS sequence.

A key challenge in measuring glutamate is distinguishing its resonances from nearby resonances arising from glutamine, GABA and glutathione. When using conventional pulse sequences at field strengths below 3T, spectral resolution is not sufficient for curve-fitting algorithms to adequately isolate the glutamate resonances. Under such conditions, the total signal near the glutamate resonances is referred to as glx, which indicates the combined signal from glutamate and some of these other resonances, in proportions that vary with different scanning parameters and basis sets. Even at field strengths of 3T or higher, separation from other metabolites (especially glutamine) is sometimes a problem for the measurement of glutamate with conventional pulse sequences, and the degree of overlap varies with echo time (Schubert et al., 2004). In addition, glutamate measurement may be hampered by overlap with macromolecules at short echo times and by the J-evolution of its complex multiplet resonances at longer echo times. In an effort to find an optimal echo time for measuring glutamate at 3T, one group (Schubert et al., 2004) showed that a PRESS sequence using TE = 80 ms produced both a strong signal for the 2.34 and 3.74 ppm glutamate resonances and good separation of the glutamate resonance at 2.34 ppm from macromolecules, glutamine, and other resonances. These investigators also showed good correspondence between glutamate values obtained with this method and those obtained using a specialized multiple quantum coherence filter sequence designed to isolate glutamate. Subsequently, this method has been used in a variety of clinical investigations, including two independent studies demonstrating elevated hippocampal glutamate in patients with schizophrenia (Gallinat et al., 2016; Kraguljac et al., 2013).

The 1H-MRS spectrum of GABA contains three multiplet resonances. When acquired with conventional acquisition methods, all three resonances are almost completely obscured by overlapping signals from more highly concentrated brain metabolites. Thus, special acquisition techniques are needed (Wijtenburg et al., 2015; Harris et al., 2017). The most widely used method for identifying and measuring GABA is J-difference editing, typically using a MEGA-PRESS sequence with a TE of ~68 ms (Mescher et al., 1998; Mullins et al., 2014). This method takes advantage of the fact that the C2 methylene resonance of GABA at 3.01 ppm is J-coupled to the C3 methylene resonance of GABA at 1.89 ppm (Govind et al. 2015). The J-evolution associated with this coupling causes inversion of the outer triplet peaks of GABA at 3.01 ppm at echo times near 68 ms. The on-resonance editing pulse selectively inverts the resonance at 1.89 ppm, which reverses the J-modulation of the coupled peak at 3 ppm, such that the magnetization of this signal fully refocuses at echo times near 68 ms. The GABA-optimized MEGA-PRESS sequence interleaves an on-resonance editing pulse with an off-resonance editing pulse. In post-processing, the off-resonance acquisition is subtracted from the on-resonance acquisition, yielding an upright GABA resonance at 3.0 ppm, while resonances that lack a coupling partner near 1.89 ppm are subtracted away (Mescher et al., 1998). Thus, the MEGA-PRESS difference spectrum contains a quantifiable GABA signal that is relatively isolated from most other resonances. In addition, resonances from glutamate, glutamine and glutathione have coupling partners near 2.1 ppm, and these signals often co-edit with GABA. Many MEGA-PRESS sequences use an editing pulse bandwidth that is sufficiently broad to at least partially refocus the J-evolution of these 2.1 ppm coupling partners. When this is the case, glutamate resonances at 3.74 and 2.34 ppm, glutamine resonances at 3.75 and 2.45 ppm, and glutathione resonances at 3.77 and 2.53 ppm co-edit with GABA and are retained in the difference spectrum. Many investigators have used co-edited signals in the difference spectra to quantify glutamate or glx (Kegeles et al., 2012; Milak et al., 2016; Nezhad et al. 2018; Yoon et al., 2010). Alternatively, the off-resonance spectrum from a GABA-optimized MEGA-PRESS sequence will be very similar to a conventional PRESS sequence when the frequency selectivity of the off-resonance editing pulse is outside the range of most metabolites (e.g. 7.5 ppm). Many investigators have used these off-resonance spectra to measure glutamate (Maddock et al., 2016; Ongur et al., 2011; Stan et al., 2015). Because of the similarity to a PRESS sequence, glutamate measurements from the off-resonance spectra acquired with a MEGA-PRESS sequence should correspond closely those from a PRESS sequence acquired with a similar echo time. In contrast, the difference spectra from a MEGA-PRESS sequence are quite different from PRESS spectra. Although glutamate signal is present in both types of spectra, it is not easy to predict how closely the glutamate values will correspond between the two acquisition strategies. This study is designed to directly compare these different approaches to measuring glutamate. The ability to measure glutamate and GABA simultaneously is particularly important when the time course of activity-dependent changes in these metabolites is the focus of study. If glutamate values measured from a MEGA-PRESS scan are found to be substantially equivalent to those measured from a conventional PRESS scan, then investigators can have confidence in using the MEGA-PRESS glutamate values as a proxy for glutamate measured from a separately acquired PRESS scan.

2. Methods

2.1. Participants

Participants were 28 healthy volunteers (24 male, aged 19 to 37, mean age 26) and 21 patients receiving treatment for first-episode psychosis (15 male, aged 18 to 32, mean age 23), all of whom were recruited as part of a larger study of cognition and brain function in first-episode psychosis. All participants were medically and psychiatrically assessed prior to brain imaging, and were free of significant medical problems. Healthy volunteers were free of current or past psychiatric diagnoses. All participants provided informed consent following a protocol approved by the IRB of the University of California, Davis and were screened for magnetic resonance imaging contraindications.

2.2. Magnetic resonance imaging and spectroscopy acquisitions

MR data were acquired using a 3 Tesla Siemens TIM/trio scanner (Berlin/Munich, Germany) with a 32-channel radiofrequency head coil. The single scanning session began with a T1-weighted structural scan (MPRAGE, TR/TE = 2500/4 ms, 1100 ms TI, flip angle = 7°, FoV 256 * 256, 0.95 mm^3 voxel size, acceleration factor of two) that was used to guide voxel placement. A 30 * 15 * 35 mm voxel was centered on the left middle frontal gyrus (dlPFC), with the voxel orientation rotated to maximize the amount of cortical grey matter, while accommodating each individual participant's anatomy. The outer surface of the voxel was positioned a few millimeters inside the cortical surface to avoid inclusion of meninges in the measurements. Fig. 1 demonstrates typical voxel placement. A combination of advanced automated and manual voxel shimming was used to minimize line width. A series of four MEGA-PRESS subscans were then acquired from the dlPFC voxel. MEGA-PRESS scanning parameters were TR/TE = 1500/68 ms, edit pulse frequencies = 1.9 ppm (on) and 7.5 ppm (off), Gaussian edit pulse bandwidth = 45 Hz, delta frequency = −1.7 ppm relative to water (optimized for signal detection at 3.0 ppm), water suppression bandwidth = 50 Hz, NEX = 72 each for on- and off-resonance acquisitions, duration = 3.6 min). Dividing the acquisition into four short subscans allowed for a quick updating and re-centering of the water frequency between scans. This was intended to reduce the effects of frequency offset (drift) on the editing pulse and required only a few seconds. Thus, the four subscans were acquired in rapid succession. The subscans were later combined off-line for analysis. Total data acquisition time for all four MEGA-PRESS scans was 14.4 min and included 288 excitations each for the on- and off-resonance acquisitions. Next, a single PRESS scan was acquired from the same dlPFC voxel. PRESS