Impact of Frequency Drift on Gamma-Aminobutyric Acid-Edited MR Spectroscopy

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INTRODUCTION

Edited MR spectroscopy (MRS) is being increasingly used to quantify metabolites that have previously been difficult to resolve in the in vivo spectrum. γ-Aminobutyric acid (GABA), the primary inhibitory neurotransmitter, is widely measured using edited MRS (1,2) in studies of healthy brain function [combining GABA measurements with behavioral tasks (3–6) and functional neuroimaging (7–12)] and a range of clinical conditions (13–19).

Edited MRS separates signals of interest from other overlapping signals by exploiting known couplings. In the case of GABA, a frequency-selective pulse can be applied to GABA spins at 1.9 ppm to modify the evolution of GABA spins at 3.01 ppm. Two subspectra are acquired, one with the 1.9 ppm editing pulse (“ON”) and one without the editing pulse (“OFF”). The difference between these subspectra contains a GABA signal at 3.01 ppm, while overlapping signals [in particular from creatine (Cr)] are removed (as in Figure 1a). While this method is conceptually simple, accurate subtraction of the larger Cr signal is required (20,21). One major limitation of this method is that insufficiently selective editing pulses result in co-editing of macromolecular (MM) signal at 3 ppm (due to a coupling to a signal at 1.7 ppm that is partially inverted by the editing pulses) as well as other metabolite species such as homocarnosine; the edited GABA signal is therefore widely referred to as GABA+.

One source of error is $B_0$ field drift during the experiment. This has two effects on edited spectra: (i) subtraction artifacts resulting from misalignment of the Cr signal in the ON-OFF subspectra (Fig. 1b) and (ii) changes in editing efficiency of GABA and MM as the frequency of the editing target resonance drifts relative to the constant frequency at which the editing pulse is applied (Fig. 1c).

The $B_0$ field is generally extremely stable. However, the application of field gradients during scanning deposits power, heating various scanner components, in particular the passive shim elements (22–24). This heating, and associated cooling, results in changes in the $B_0$ field. These “gradient-induced field drifts” are problematic for MRS studies (25), and may persist for hours (22,24,25).

The level of gradient-induced field drift depends on the quantity and placement of ferrous shim elements in an individual scanner (24,25) and the gradient duty-cycle causing the power deposition. While passive shim elements are limited in some modern systems, there may be
multiple factors that contribute to gradient-induced field drifts (22). The combination of MRS with other imaging, such as diffusion and functional MRI (fMRI), makes characterizing, understanding, and correcting these frequency drifts important.

Postprocessing correction methods to address frequency instability in GABA+-edited MRS have been proposed elsewhere (20,21,26), but often without differentiating between instabilities due to field drift or subject motion. Improved linewidths and/or SNR can be achieved in nonedited MRS by applying frequency correction either prospectively or retrospectively (23,25,27–29). Difference-edited MRS requires substantially greater stability because frequency instability may introduce subtraction and other artifacts (1,2,20,21,26).

The purpose of this manuscript is to quantify the field drifts caused by a single typical fMRI scan, to determine whether drifts of this size can impact subsequent GABA+ quantification, to investigate potential mechanisms causing this effect, and to evaluate a postprocessing field-drift correction scheme. This was accomplished by acquiring repeated in vivo GABA+-edited MRS data, both under stable conditions as well as following an 8-min fMRI acquisition, and by performing simulations to investigate the independent impact of frequency drift on subtraction artifacts and editing efficiency of GABA and the co-edited MM signal.

METHODS

Data were acquired at 3 Tesla (T). The main experimental data were acquired with a 32-channel head coil Philips Achieva system. Supplemental data, which are available online, were collected on a GE HDx system. The local Institution Review Boards (Johns Hopkins University School of Medicine, the ethics committee of the Ruhr – University Bochum and the ethics committee of the School of Psychology, Cardiff University) approved study protocols and all participants provided written informed consent.

Frequency Drift Quantification

FIG. 1. Difference editing of GABA+ in the presence of B0 field drift. a: ON and OFF subspectra and the difference spectrum in which there is minimal frequency drift and the 3.0 ppm GABA+ peak is well resolved. Voxel placement is shown in the inset. b: ON and OFF subspectra and the difference spectrum with frequency drift of −1.32 Hz/min across the acquisition. Comparing (a) and (b) shows the effects of frequency drift on the linewidth of the subspectra and the introduction of a subtraction artifact (marked by an arrow) in the difference spectrum. Note that the difference spectra for both (a) and (b) are scaled by a factor of 5 compared with the ON and OFF subspectra. c: Schematic of the inversion envelope of the editing pulse moving 20 Hz off resonance from the 1.9 ppm GABA peak, which will reduce the efficiency of inversion at 1.9 ppm and therefore also reduce the size of the edited signal.

Three sequential edited MRS acquisitions were performed in each of 15 sessions. For 10 of these sessions (5M/5F), an fMRI acquisition [repetition time/echo time (TR/TE) = 2500 ms/35 ms, 200 repetitions, field of view: 224 × 232 mm², 112 × 110 matrix, 39 3-mm slices, SENSE acceleration factor of 3, scan duration 8.3 min, maximum gradient amplitude = 80 mT m⁻¹, slew rate = 100 mT m⁻¹ ms⁻¹] was performed before MRS to generate gradient-induced frequency drift. This is intended as a standard fMRI scan, using default parameters for detecting BOLD activation. The remaining five control studies (2M/3F) were without fMRI (see Figure 2a for the protocol). Four subjects participated in both sessions (average age of 11 subjects: 27 ± 2.5 years). GABA+-edited MEGA-PRESS (30) was acquired using 14-ms sinc-Gaussian editing pulses (full-width half-maximum inversion bandwidth 86.6 Hz) applied at 1.9 ppm (ON scans) and 7.46 ppm (OFF scans). The 3×3×3 cm³ voxel was located in the precuneus (as seen in Figure 1a). Other scanning parameters included: TR/TE = 2 s/68 ms; 320 transients acquired in 20 dynamic scans, each composed of a 16-scan phase cycle, with editing pulse frequency (OFF/ON) alternating with each dynamic scan; 2048 data points sampled at a spectral width of 2 kHz, VAPOR water suppression. We use the term a dynamic to mean one phase cycle, for example 16 scans that are acquired in a consecutive block with the same editing frequency; editing frequency is updated with alternating dynamics. In PRESS experiments, phase-cycling is used...
Frequency Drift in GABA-edited MRS

Changes in GABA and MM as a function of frequency drift were first examined by simulating the offset-dependence of the editing efficiency, and second, by averaging across offsets to investigate the drift dependence. The 3.0 ppm GABA peak and the co-edited MM peak were independently simulated for editing pulse offsets from 0 Hz to -80 Hz in increments of 1.25 Hz (i.e., simulating the editing pulse applied at 1.0 to 1.275 ppm). Simulations were performed as described previously (38), whereby the density matrix formalism was used to generate simulated MRS data, using ideal instantaneous excitation and refocusing pulses. Simulations were performed for the GABA spin system (38) at a simulated field of 3T with 14 ms sinc-Gaussian editing pulses (as used in experiments). Prior Bloch equation simulations of the shaped editing pulses were used to determine the flip angle experienced by each of the GABA spins; editing pulses were incorporated into the MEGA-PRESS simulation as instantaneous rotations of these calculated flip angles. To account for the fact that the intensity of the 1.9 ppm GABA peak is spoiled in the ON-experiments, the excitation pulse was not applied to those spins in the ON-experiments. Similarly, the effects of signal offset on the MM signal contribution was investigated using the same formalism but using a 1.7 ppm resonance for MM to replace the 1.9 ppm GABA resonance (35). Frequency drift impact on editing efficiency for both GABA and MM across an experiment were simulated by averaging 64 ON-OFF pairs where the first pair had 0 Hz editing pulse offset and the last was shifted by a total drift of 0, -4, -8, -12, -16, and -20 Hz, with linear interpolation of editing offset for the intermediate dynamics. As the MM signal contribution to GABA+ (39,40) is likely to vary between sequences and brain regions, a range of relative signal contributions (40–60%) were examined.

Subtraction Artifact Simulations

Creatine subtraction artifacts overlap with the edited GABA+ signal and potentially interfere with GABA+ quantification. These artifacts were simulated (independent from editing efficiency effects) by artificially adding a frequency shift to an in vivo dataset. This in vivo data set (TR/TE = 2 s/68 ms; 320 transients acquired in 40 dynamic scans of 8 phase-cycles; 14 ms editing pulses applied at 1.9 ppm; 2048 data points; spectral width = 2 kHz) was acquired at the beginning of the day. The small frequency drift that occurred was removed by aligning the residual water peak (based on the complex maximum in each spectrum). Different magnitudes of linear frequency drift were applied to generate total frequency drifts of -5 Hz, -10 Hz, -15 Hz and -20 Hz across the dataset. GABA+ concentration was then quantified as described above.

First, the acquired data were reordered to mimic an acquisition protocol of 20 dynamic scans of 16 phase cycles, so this simulation would be directly comparable to the main in vivo experimental data. In a secondary analysis investigating the impact of the frequency of alternating between ON and OFF scans, (i.e., the degree of interleaving), the same total simulated drifts were applied to the original (i.e., acquisition of 40 dynamics of eight-scan phase cycles) data to compare interleaving 8-scan blocks with 16-scan blocks.

Frequency Correction

Frequency correction (20) was applied to the main in vivo experimental data to evaluate its efficacy. Briefly, the Cr peak of each ON and OFF subspectra was modeled as a Lorentzian and realigned. The choline peak was used to correct differences between the ON and OFF subspectra. After this frequency correction, GABA+ concentration was quantified as described above and a paired t-test was applied to compare GABA+ concentration with and without frequency correction.
RESULTS

Three consecutive GABA+ edited spectra were acquired in fourteen subjects. One (control) subject did not complete the third scan, but the first two scans were included.

Frequency Drift Quantification

When MRS is performed after fMRI, a substantial increase in frequency drift is observed and this frequency drift can persist for at least 30 min (as shown in Figure 2b). Frequency drift was quantified by a linear fit of frequency over time (as shown in Figure 2c). This linear fit represents the drift well, $R^2 = 0.85 \pm 0.25$ across all fits. The average frequency drift rates in first, second, and third control scans were $0.025 \pm 0.23$ Hz/min, $0.074 \pm 0.16$ Hz/min, and $0.098 \pm 0.19$ Hz/min, respectively, while after fMRI drift rates were $-1.22 \pm 0.32$ Hz/min, $-0.91 \pm 0.26$ Hz/min, and $-0.48 \pm 0.18$ Hz/min. Student's t-tests confirm the drift rate is significantly different between fMRI and control sessions ($P < 0.001$ for each of the three comparisons). The repeated-measures ANOVA indicates that group (control/fMRI) has a significant effect on quantified GABA+ ($P < 0.05$).

Measured GABA+ concentration is plotted against the drift rate in Figure 2d. By visual inspection, one outlier was identified and was not considered in further analyses. Positive frequency drift is poorly defined because in practice it occurs infrequently, therefore datasets with a positive drift of 1.5 Hz or greater over the acquisition were excluded from further analyses (excluded points are represented with open circles). GABA+ measurement is linearly correlated with frequency drift, ($R^2 = 0.27; P < 0.001$); for example, a $-10$ Hz frequency drift predicts a 16% decrease in GABA+.

Editing Efficiency

In Figure 3a, the 3 ppm GABA peak changes appearance as the editing pulse moves off-resonance, resulting in a reduced integral (as shown in Figure 3b). These simulations are consistent with the phantom data reproduced from (41). The GABA signal decreases and the co-edited MM signal initially increases as the editing pulse is offset (as shown in Figure 3b). Figure 3c shows the drift-dependence (rather than offset-dependence) of the editing efficiency for both MM and GABA. For a $-10$ Hz frequency drift, GABA signal loss on the order of a 1.5% whereas the co-edited MM signal shows a 10% increase. The net effect on GABA+MM signal depends on the relative contributions of GABA and MM to the GABA+ signal (as shown by the gray area in Figure 3c representing 40:60 to 60:40 relative contributions of GABA:MM). Assuming
Frequency Drift in GABA-edited MRS

FIG. 3. Editing efficiency simulations. a: Simulated difference spectra for discrete editing frequency offsets. As the 1.9 ppm peak is shifted off resonance from the inversion pulse, the shape of 3.0 ppm GABA peak is altered. b: Relative integrals of the simulated peaks for both GABA (solid line) and MM (dashed line), for a range of editing pulse offsets. GABA phantom data from a previous study (41) is shown in grey circles to demonstrate agreement between the simulations and experimental data. c: Simulated integral of the 3.0 ppm GABA peak (solid line) and the MM peak (dashed line) as a function of frequency drift occurring throughout the experiment, normalized to the signals at 0 Hz offset. The net impact of frequency drift on the GABA and MM peaks for quantified GABA+ is shown as a thick line assuming 50:50 signal contributions for GABA and MM and as a shaded area for the range of 40:60 to 60:40 signal contributions for GABA and MM at zero drift.

Initial signal contributions of 50:50, a -10 Hz frequency drift will result in +4% GABA+ signal change and the relative contributions of GABA:MM will change to 47:53 as shown in Figure 3c. A 60% initial MM contribution would change to 63% after -10 Hz drift.

Subtraction Artifacts

Figure 4a shows the GABA+ peak reduces with drift due to imperfect subtraction of the Cr signal. The zero-drift spectrum appears approximately Gaussian, the intermediate spectra more triangular and the -20 Hz-drift spectrum appears to have “pseudo-doublet” character. The effects on quantified GABA+ concentration are shown in Figure 4b, a -10 Hz drift over an acquisition predicts an 11% reduction in GABA+ measurement.

The degree of interleaving ON-OFF cycles impacts the observed subtraction artifact. Doubling the rate of interleaving (while maintaining the same total number of transients) approximately halves the relative loss in measured GABA+ (a -10 Hz drift over the more interleaved acquisition predicts only in a 5.9% reduction in GABA). The 3 ppm GABA resonance is qualitatively similar in appearance, although consistent with greater subtraction artifacts at slower rates of interleaving.

Frequency Correction

Losses in the GABA+ measurement due to the subtraction artifact appear to be largely corrected after applying frequency correction. Postcorrection datapoints (filled) are almost all higher than precorrection (open) datapoints (as shown in Figure 5a). The correlation between GABA+ concentration and frequency drift was largely removed after frequency correction ($R^2 = 0.11$; Fig. 5b). The linear fit of GABA+ concentration as a function of frequency drift, with the intercept constrained to match that in Figure 2e, was $-0.0038$ i.u./Hz. There is a significant increase in GABA+ concentration with frequency correction ($P < 0.001$), with an average increase of 21 ± 16% and the coefficient of variation reduces from 26% before correction to 18% with frequency correction.

DISCUSSION

Frequency drift increases linewidth and measurement uncertainty in PRESS spectroscopy (25). Implementing post-processing frequency correction has been previously advocated for GABA+-edited MEGA-PRESS (21), and improves measurement repeatability (20). The quantitative impact of frequency drift and its subsequent correction on in vivo GABA+ measurements have not previously been shown.

Drifts of -10 Hz over a 10-min acquisition were common and impacted GABA+ measurements. An 8-min fMRI run can cause significant frequency drifts up to 30 min later (as shown in Figure 2c). Of interest, the control study and two fMRI studies with the largest negative drifts (Fig. 2c and d) were performed after an MR exam that included multiple fMRI/diffusion imaging runs, providing evidence that frequency drift may persist between MR exams. In supplementary data, we present drift examples from three other 3T scanners (two Philips Achieva, one GE Signa HDx). On both Philips scanners, the drift after an 8-min fMRI run is appreciable (as shown in Supplemental Figure Sa, which is available online). By contrast, drift appears minimal after a 5-min fMRI run on the GE system (shown in Supplemental Figure Sb). Clearly, field drift differs between scanners, and this manuscript provides a template to quantify drift on individual systems. Drift will be influenced by gradient strength, system design (i.e., the quantity of iron shim elements) and system stability. As inherent magnet homogeneity improves, fewer shim elements are required; nevertheless, passive shimming is used to extend the field-of-view. Superconducting shims used as an alternative to iron shims and are expected to reduce frequency drift. When comparing frequency drift
between scanners both in this manuscript (refer to Supp. Fig. Sa) and in Lange et al (25), greater drift was observed in the system with more shim iron installed. MRS acquisitions are less gradient-intensive than imaging acquisitions, therefore, cooling (negative frequency drift) is most relevant to mixed MRI/MRS protocols. The impact of positive frequency drift is not well sampled by this in vivo dataset because the gradient duty cycle during MRS was insufficient to cause substantial gradient heating. Therefore, only data showing frequency drifts of less than 1.5 Hz (zero-drift datasets included) over the scan were used to examine the relationship between frequency drift and GABA$^+$ concentration.

Negative frequency drifts reduce the editing efficiency of GABA and increase the editing of MM (as the degree of inversion of the MM signal at 1.7 ppm increases). The MM signal fraction of GABA$^+$ is at least 40% (39,40), but likely varies with sequence parameters (TR and editing pulse bandwidth), brain region and individual differences. As seen in Figure 3c, the total GABA$^+$ signal changes modestly due to editing efficiency effects because the changes in GABA and MM have opposite sign. Although GABA$^+$ changes due to editing efficiency effects are modest, it is important to recognize that the relative contributions of GABA and MM to the GABA$^+$ signal changes with frequency drift. For example, assuming equal signal contributions of GABA and MM (50:50) at 0 Hz drift, the relative signal contributions will change to 47:53 with 10 Hz drift. This has implications for studies examining GABA differences between groups/conditions by making GABA$^+$ measurements as changes in GABA:MM complicate the interpretation of data.

As long as the frequency drift is small compared with the bandwidth of the editing pulses, efficiency effects will remain relatively small. Within a 68 ms TE, editing pulse duration is generally limited to ~14 ms and the editing selectivity of GABA+edited MRS is broadly similar (although some 3T scanners can achieve B$_1$ fields of approximately 20 μT, so permit more selective editing pulses of over 20 ms (42), because the slice-selective pulses are shorter). It is possible to suppress the MM contribution (39), by placing editing pulses in OFF and ON scans symmetrically about the MM resonance at 1.7 ppm (i.e., ON 1.9 ppm and OFF 1.5 ppm). This removes the confound of MM that is present in GABA+ experiments and would remove any overestimation of GABA+ due to MM; however, frequency drifts will interrupt the symmetry of this arrangement and result in a gradual return of MM contributions.

Subtraction artifact due to misalignment of the Cr spectra is the dominant source of GABA+ underestimation; a simulated ~10 Hz drift results in an 11% signal loss, which is on the order of the total losses observed (16%). Other sources of signal loss may explain the discrepancy, such as order effects and subject compliance. The effect of frequency drift on signal localization is expected to be minimal as even a 20 Hz drift is minor compared with the ~1.4 kHz refocusing pulse bandwidth. This results in a linear shift in voxel location of the order of 1% of the voxel size, in each direction defined by a refocusing pulse. This shift is small and for most brain regions is unlikely to include new tissue with no GABA, so the impact on measurements will also be small. The residual water signal, which will gradually increase as drift worsens the water suppression, will also cause drift-dependent subtraction artifacts in edited spectra, as seen in Figure 1b. This may result in substantial disturbances to the baseline, and negatively impact quantification of GABA+ unless appropriate analysis methods are used to deal with such baseline distortions.

Crusher gradients are applied to dephase out-of-voxel signal contamination. However, due to TE limitations in
the MEGA-PRESS experiment, the duration of these
gradients is limited and therefore signal suppression by
gradients is imperfect. Phase cycling augments voxel
localization without additional averages and no impact
on TE (2), but is usually implemented at the expense of
rapid interleaving, resulting in proportional losses in
measured GABA+ concentration. One possible improve-
ment to the implementation used here is to allow phase
cycling across editing interleaves.

FIG. 5. Changes in measured GABA+ concentration as a result of
postprocessing frequency correction. a: Measured GABA+ concen-
tration for each MRS acquisition before (open circles) and after
frequency correction (closed circles). b: Frequency-corrected esti-
mates of GABA+ concentration as a function of frequency drift.
The linear fit of this data has a slope of $-0.0038 \text{i.u./Hz}$ indicating
that the apparent linear dependency between GABA+ concen-
tration and frequency drift is essentially removed after frequency
correction.

The frequency correction scheme (20) used here generally
increases GABA+ measurement (as shown in Figure 5) by
correcting subtraction artifacts, resulting in GABA+ mea-
surements closer to the expected no-drift condition. Although some consequences of gradient-induced fre-
quency drift may be corrected, substantial variance remains;
the coefficient of variation across all scans is reduced from
26% before frequency correction to 18% after, equivalent to
a 19% removal of independent variance. The remaining
variance may be due to imperfect frequency correction, the
uncorrected consequences of editing efficiency, varying sig-
nal contributions of GABA and MM, and residual water
artifacts. It is prudent to avoid drift errors where possible,
for example by ordering imaging protocols such that MRS
acquisitions occur before scans with high gradient duty
cycles, and by using MRS acquisitions with highly inter-
leaved ON and OFF subspectra.

Prospective frequency correction aims to correct the
drift at its source, removing both subtraction artifacts
and editing efficiency changes, including changes in the
GABA-MM signal contribution. A small flip-angle water
navigator can be used to acquire an unsuppressed water
signal as a metric for magnetic field instabilities, motion
artifacts and severely corrupted transients (29). This
method has been adapted to provide an index to reject
motion-corrupted data from MEGA-PRESS GABA+
acquisitions (26). To mitigate drift for PRESS in real-
time, the unsuppressed water signal can be used to
update the RF carrier frequency (25), using online recon-
struction and feedback of the water resonance frequency
to update the carrier frequency of the RF pulses and the
analog-to-digital converters. Further expansion of this
method to MEGA-PRESS could minimize the need for
post-hoc frequency correction. Similarly, on Philips sys-
tems a water-based field lock option exists and is
reported to maintain the carrier frequency to within 2 Hz
(21). It is important to stress that the general aim of
frequency-lock methods is to reduce the linewidth of
standard averaged spectra, and that the requirements for
difference editing are substantially different. The timing
and accuracy of the prospective frequency updates is
crucial to avoid causing, rather than removing, subtrac-
tion errors (43). Data presented in Supp. Fig. Sa show
that the Philips field lock (referred to as “Frequency
Stabilization”) largely removes the gross drift but at the
expense of increased field variability due to inaccuracies
in determining the field rapidly from a navigator scan.
Prospective frequency correction is clearly desirable, but
needs to be implemented with caution.

In conclusion, MRI scans with a high gradient duty
cycles, can negatively impact subsequent edited MRS
acquisitions. The primary effect of frequency drift on
GABA+-edited MEGA-PRESS is to cause spectral mis-
alignment resulting in subtraction artifacts. While these
errors can be remedied to some degree by postprocessing
frequency correction, it is best to avoid introduction of
these errors, for example by ordering MR protocols such
that MRS is performed before any fMRI scanning or
applying prospective frequency correction.

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![Diagram](image-url)