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Long-term reproducibility of GABA magnetic resonance spectroscopy

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ABSTRACT

Recent findings suggest that cortical gamma aminobutyric acid (GABA) levels may provide a surrogate marker for a number of psychiatric and neurological conditions, as well as behavioural traits. However, the natural variability of GABA levels in the human brain over long periods of time (>8 days) has not yet been studied. The purpose of this work was to investigate the long-term variability of GABA concentrations in the human occipital cortex. Nineteen healthy male participants were recruited and underwent two sessions of magnetic resonance spectroscopy (MRS) to determine occipital GABA levels with an average between-session interval of 7 months. We assessed between-session variability, as well as the correlation between session 1 and session 2 GABA measurements. The mean coefficient of variation between sessions was 4.3% (bootstrap 95% confidence interval: 2.5, 6.4), which is comparable to reported GABA variability measurements over much shorter time intervals (<8 days). A significant positive correlation was observed between session 1 and session 2 GABA measurements ($r = 0.53$, $p = 0.014$), and the intra-class correlation coefficient was calculated to be 0.52 which was also statistically significant ($p = 0.012$). These findings establish experimentally that GABA concentrations in the occipital cortex as measured by MRS are relatively stable over periods as long as 7 months. The findings have significant implications for the internal validity of longitudinal studies of GABA levels in the human brain, and they lend foundational support to studies relating GABA levels to behavioural traits in healthy individuals.

Introduction

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain and plays an important role in regulating neuronal activity (McCormick, 1989). Abnormal GABA levels are implicated in various neurological and psychiatric conditions including stroke (Lei et al., 2009), epilepsy (Petroff et al., 1996), motor neuron disease (Foerster et al., 2012), ADHD (Edden et al., 2012a), schizophrenia (Kegeles et al., 2012; Rowland et al., 2013) and depression (Bhagwagar et al., 2007). GABA levels are also correlated with functional measures such as cerebral blood flow and the blood oxygen level dependent functional magnetic resonance imaging contrast (Donahue et al., 2010; Muthukumaraswamy et al., 2009). A growing body of new evidence suggests that in addition to its involvement in diseases and functional metrics, GABA also acts as a surrogate marker for a number of behavioural measures such as rash impulsivity (Boy et al., 2011), subconscious motor control (Boy et al., 2010), motor decision speed (Sumner et al., 2010), and tendency for cognitive failures (Sandberg et al., 2013) among others (Jocham et al., 2012). As the full relationship between GABA levels and behaviour continues to be uncovered, questions arise regarding the long-term stability of GABA levels; whether or not GABA levels remain stable over long periods of time will have important implications in the types of behaviours (trait vs. state) that GABA levels can be hypothesized to predict.

Measures of brain GABA levels are most commonly obtained using magnetic resonance spectroscopy (MRS), which currently provides the only non-invasive means to detect GABA levels in vivo. Using MRS, the short-term variability of cerebral GABA levels has been well characterized. Specifically, when GABA measurements are repeated in separate sessions up to 8 days apart in healthy male participants, the coefficient of variation (CV) ranges from 3.5 to 21% (Evans et al., 2010; Stephenson et al., 2011; Wijtenburg et al., 2013), which falls roughly within the same range as the within-session CV of the measurement technique (7–13%) (Bogner et al., 2010; Near et al., 2013; O'Gorman et al., 2011). Therefore over time intervals of 8 days or less, individual GABA levels are believed to be stable, and most of the variability observed in repeated GABA measurements on these time intervals can likely be attributed to measurement error.

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In the longer-term (>8 days), one study found that GABA levels in plasma are stable over a four year interval in subjects with depression (Petty et al., 1995), however investigations of the long-term stability of GABA levels in the brain have yet to be performed. The purpose of this study was, therefore, to investigate the long-term variability of brain GABA levels using repeated MRS measurements in occipital cortex. Nineteen participants were each scanned twice with a between-scan interval of approximately seven months, and we determined the average CV of the repeated GABA measurements, as well as the correlation between repeated measurements. Furthermore, we investigated the effect of voxel repositioning error on between-session variability.

Materials and methods

In vivo MRS experiments

19 healthy male subjects (mean age 24 ± 3 years) were recruited to participate in this study. To avoid the potential confound of cyclical variation in GABA levels with the menstrual cycle (Epperson et al., 2006; Harada et al., 2011) only male participants were used. All subjects provided informed, written consent and experiments were approved by the local ethics committee, De Videnskabsetiske Komitéer for Region Midtjylland. All participants were scanned twice, with an average between-scan interval of 229 ± 42 days (~7.5 months), on a 3 Tesla Magnetom Trio system (Siemens, Erlangen, Germany) with a body coil transmitter and a 32-channel head receiver array coil. In all scans, high resolution T1-weighed MPRAGE structural images were acquired (TR/TE = 2420/3.7 ms, 1 mm isotropic resolution, 5.5 minute scan) and used to guide placement of a 3 × 3 × 3 cm^3 MRS voxel in occipital cortex. GABA edited MRS was performed using MEGA-PRESS (Mescher et al., 1998) with the following scan parameters: TR/TE = 2500/68 ms, 2048 points, 2000 Hz spectral width, and 192 averages for a total scan time of 8 min. Dual banded Gaussian shaped editing pulses with a 20 ms duration were applied with a water suppression band at 4.7 ppm and an editing band that alternated between 1.9 ppm and 7.5 ppm in even (edit-on) and odd (edit-off) scans, respectively.

MRS data processing and analysis

Data were processed using semi-automated in-house MATLAB processing routines as described previously (Near et al., 2013). Specifically, a weighted array coil recombination was performed, followed by an automated procedure to remove averages corrupted by motion. Time-domain spectral registration of averages (Near et al., 2014) was then performed separately on both the edit-on and edit-off scans to correct frequency and phase drift errors, prior to summation. Finally, the averaged edit-on and edit-off spectra were manually aligned by frequency and phase adjustment to minimize the residual choline difference signal, and the edit-on and edit-off scans were then subtracted (edit-on − edit-off) to produce a difference spectrum, and combined (edit-on + edit off) to produce a sum spectrum. Fully processed difference and sum spectra were analysed by peak fitting using jMRUI (Naressi et al., 2001) as described previously (Near et al., 2011). GABA concentrations were referenced to total creatine (creatine plus phosphocreatine, Cr), which was measured from the 3.0 ppm creatine resonance in the sum spectrum, and all metabolite concentrations were corrected for T_2 relaxation during the echo time by assuming T_2 values of 88 and 116 ms for GABA and Cr, respectively (Edden et al., 2012b). GABA concentrations were also corrected for the editing efficiency of the MEGA-PRESS sequence, which was assumed to be 41% (Near et al., 2011).

Statistical analyses

As a measure of the variability of GABA levels between sessions, the coefficient of variation was determined for each subject. To test the bivariate relationship between session 1 and session 2 GABA measurements, the Pearson product-moment correlation coefficient (r) between sessions was calculated. Finally, as a measure of the likeness of repeated GABA measurements to each other, the intra-class correlation coefficient for absolute agreement of single measures (as opposed to average measures) was calculated using a two-way mixed effects model, ICC(3,1) (McGraw and Wong, 1996).

To assess the effect of voxel repositioning errors on the between-session reproducibility of GABA measurements, a voxel mask was first generated for each MRS acquisition and overlayed with the high-resolution anatomical image from the corresponding session. Using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/), image coregistration was then performed to align each subject's session 2 anatomical scan with their session 1 anatomical scan, and the same linear transformation was applied to each subject's session 2 voxel mask to enable determination of the between-session fraction of voxel overlap (FO, common voxel volume divided by the volume of a single voxel). Finally, the bivariate correlation between FO and log(CV) was tested.

Data from two of the nineteen participants were excluded from the final analysis; the first due to severe unsuppressed water signal contamination in one MRS session, and the second due to a large voxel repositioning error (FO = 0.59) which was determined to be an outlier. Thus, the remaining seventeen participants were included in final analyses. For GABA measurements at sessions 1 and 2 as well as FO, Shapiro–Wilk tests and histogram inspection did not refute the assumption of normality ($W > 0.92$, $p > 0.15$ for all variables), and Cook–Weisberg tests did not refute the assumption of homoscedasticity ($chi^2(1) < 1.50$, $p > 0.12$ for all variables). For this reason, the relationship between session 1 and session 2 GABA levels was tested using the parametric Pearson product-moment correlation (r). However, for CV measurements, Shapiro–Wilk test and histogram did refute the assumption of normality ($W < 0.84$, $p < 0.01$). Therefore, confidence intervals on mean CV values were obtained via bootstrap resampling. Specifically, data were resampled 10,000 times (with replacement) and the 95% confidence interval was determined to be the middle 95% of the resampled means. Furthermore, for correlational analyses, CV values were log transformed. Then, for log(CV) values, Shapiro–Wilk tests did not refute the assumption of normality ($W > 0.92$, $p > 0.19$) and Cook–Weisberg tests did not refute the assumption of homoscedasticity ($chi^2 < 2.4$, $p > 0.12$). All relationships were linear (see Results).

To enable evaluation of the null hypothesis that the measured long term CVs for GABA were not significantly greater than previously reported CVs for GABA over shorter time intervals (<8 days), the distribution of likelihood ratios for log(CV) was calculated based on the sample characteristics (mean and standard error of log(CV)), and the assumption of approximate normality. From this distribution, the credibility interval, the interval corresponding to the 1/32nd amplitudes of the likelihood ratio distribution, was calculated.

The relationship between FO and log(CV) was tested in the following two ways. Firstly, the parametric Pearson product-moment correlation (r) was calculated. Secondly, a distribution of the posterior probability of the strength of the correlation (r) between FO and log(CV) was generated using a Markov Chain Monte Carlo (MCMC) simulation, as implemented using R (The R Project for Statistical Computing, www.r-project.org) and JAGS (Just Another Gibbs Sampler, mcmc-jags.sourceforge.net). MCMC simulation was performed using a bivariate normal distribution model with parameters r, μ_{FO}, $\mu_{log(CV)}$, σ_{FO}, and $\sigma_{log(CV)}$, where μ and σ are the estimated population mean and standard deviation, respectively. The following prior probability distributions were specified for each of the five model parameters:

$$r \sim unif[-1, 0]$$
$$\mu_{FO} \sim unif[0.5, 1]$$
$$\sigma_{FO} \sim unif[0, 0.5]$$
$$\mu_{log(CV)} \sim unif[-2.3, 3]$$
$$\sigma_{log(CV)} \sim unif[0, 3]$$

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where unif[A,B] represents a uniform distribution from A to B. Notably, the prior probability distribution of r included only values less than or equal to zero, since a positive correlation between FO and log(CV) corresponds to the impossible scenario that poorer voxel repositioning leads to lower CV's.

Finally, GABA levels in this study were presented as a ratio with total creatine because at least one previous study showed that creatine referencing results in optimal reproducibility (Bogner et al., 2010). Nonetheless, to rule out the possibility that variability of GABA concentrations could be masked by covariability with creatine, GABA/NAA ratios and NAA/Cr ratios were also determined by measuring the residual NAA peak in difference spectra, and the CV for long-term repeated measures of each of these quantities was also calculated.

Results

Fig. 1 shows pairs of occipital GABA MRS difference spectra, obtained with an average between-scan interval of ~7 months, from all 17 included participants. The edited GABA resonance appears at 3 ppm. For display purposes, the amplitude of each spectrum in Fig. 1 was scaled in proportion the measured amplitude of the creatine peak in the corresponding sum spectrum. Very good visual correspondence was observed between the repeated measurements.

Fig. 2 shows the measured GABA/Cr concentrations for both sessions in each subject. Across the 17 subjects, the between-session CV ranged from 0.2% to 12.3%, with a mean of 4.3% and a bootstrapped 95% confidence interval (CI) of [2.5, 6.4]%. The mean CV is similar in magnitude to previously reported measurements of GABA variability over much shorter time intervals (<8 days). The ratios of GABA/NAA and NAA/Cr also displayed similar reproducibility between sessions, with mean CV values of 4.9% and 5.1%, respectively, and bootstrapped 95% CIs of [3.5, 6.4]% and [3.6, 6.7]%, respectively.

Based on the sample characteristics and the assumption of an approximately normal distribution on log(CV), Fig. 3 shows the calculated distribution of likelihood ratios for log(CV). The credibility interval on log(CV), or the interval corresponding to the 1/32nd amplitudes of the likelihood ratio distribution is [−0.09, 1.75], which, by inverse log transformation, corresponds to a credibility interval on CV of [0.9, 5.8]%.

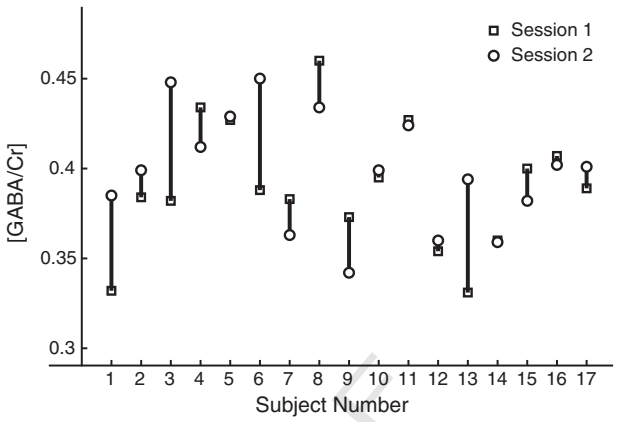

Fig. 2. The session 1 and session 2 occipital GABA/Cr measurements in 17 healthy participants. The average coefficient of variation between sessions was 4.3 ± 4.2% across all subjects.

The correlation between session 1 and session 2 GABA measurements was r(15) = 0.53, p = 0.014 (Fig. 4), indicating a significant positive correlation, and the intra-class correlation coefficient was r = 0.52, p = 0.012, indicating statistically significant absolute agreement between GABA levels at seven month intervals.

Fig. 5a shows an example of voxel positions for the two subjects who had the lowest (76%, left) and highest (93%, right) FO values, respectively. The average FO across subjects was 84.5% ± 5.8%. No significant correlation was observed between log(CV) and FO (rho(15) = 0.05, p = 0.84, Fig. 5b). Furthermore, Fig. 5c shows the estimated Bayesian posterior distribution of r obtained by MCMC simulation. Based on this distribution, the maximum-likelihood estimate (MLE) of r

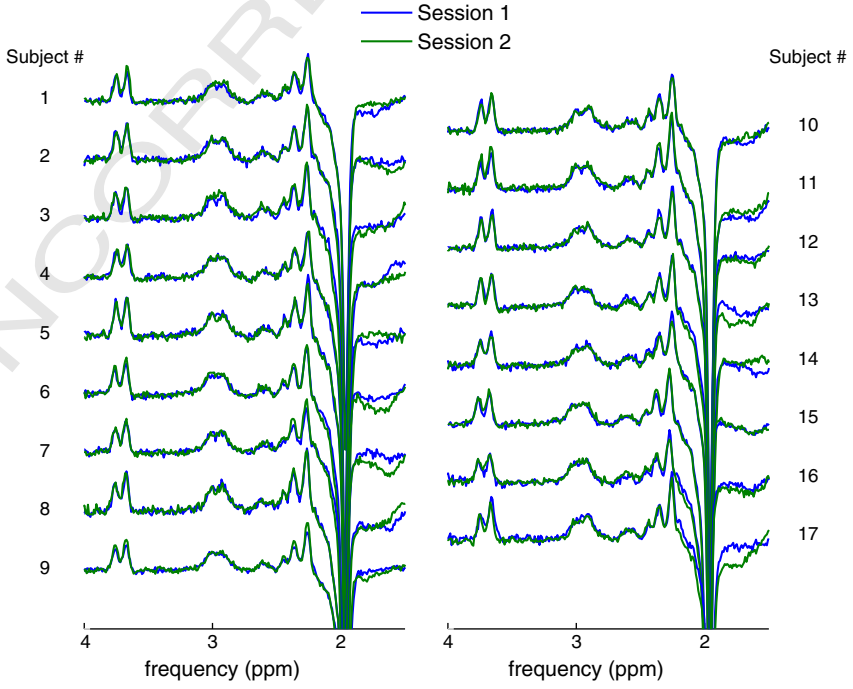

Fig. 1. Pairs of occipital GABA MRS difference spectra (TR/TE = 2500/68 ms, 192 averages, 8 minute scan), obtained with an average between-scan interval of ~7 months, from 17 healthy male participants. The edited GABA resonance appears at 3 ppm. For display purposes, the amplitude of each spectrum in Fig. 1 was scaled in proportion the measured amplitude of the creatine peak in the corresponding sum spectrum. No filtering was applied. Very good visual correspondence was observed between the repeated measurements.

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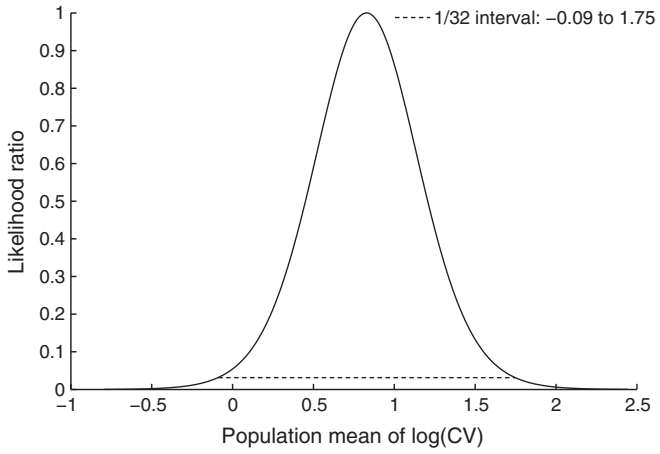

Fig. 3. Distribution of likelihood ratios for log(CV), based on the sample characteristics and assuming a normal distribution. The credibility interval, or the 1/32nd amplitudes of the distribution, is [−0.09, 1.75], which corresponds to an interval on CV of [0.9, 5.8]% following inverse log transformation.

(corresponding to the maximum amplitude of the posterior distribution) is −0.01, and the Bayes estimate (BE) of r (corresponding to the mean value of the distribution) is −0.19.

Discussion

Taken together, the results of this study establish experimentally that GABA concentrations in the occipital cortex as measured by MRS are relatively stable over periods as long as 7 months. In repeated measurements using edited MRS at 3 T with a between-scan interval of 7 months, the mean observed variability of GABA levels was 4.3%, which is comparable to those reported over short time intervals (<8 days) using similar methodology (Bogner et al., 2010; Near et al., 2013; O'Gorman et al., 2011; Wijtenburg et al., 2013). The similarly low variability in the ratios of GABA/NAA (4.9%) and NAA/Cr (5.1%) effectively rules out the possibility that larger between-session variability in GABA levels was masked by correlated variability in Cr levels. Based on the likelihood distribution of log(CV), the upper estimate of the variability of GABA levels over long time intervals was 5.8%, which was still not greater than a majority of previously published short term GABA variability estimates, suggesting that the dominant source of variability in repeated GABA measurements, even over intervals as long as seven months, is likely due to measurement error.

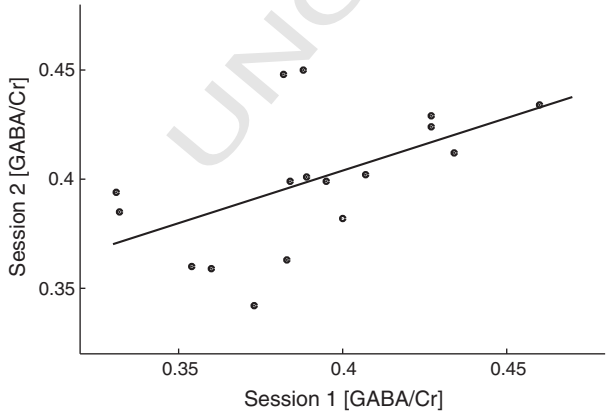

Fig. 4. Scatter plot of session 1 versus session 2 GABA measurements. A significant positive correlation ($r(15) = 0.53$, $p = 0.014$) and a significant intraclass correlation ($r = 0.52$, $p = 0.012$) between the two sessions was observed.

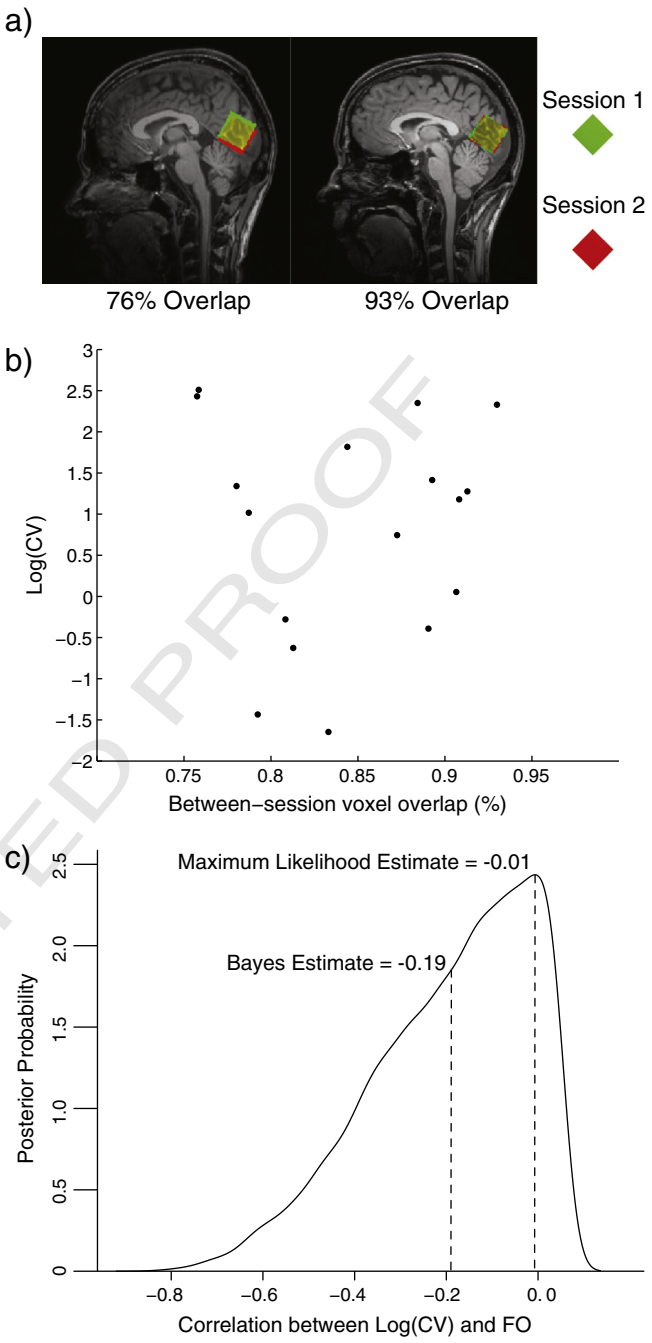

Fig. 5. Effect of between-session voxel repositioning error on between-session GABA measurement variability. a) Session 1 (green) and session 2 (red) voxel positions are shown for the subjects with the poorest voxel repositioning (76% voxel overlap, left) and the best voxel repositioning (93% voxel overlap, right). The average between-session voxel overlap was 84.5% ± 5.8%. b) Scatter plot of log(CV) versus between-session voxel overlap (FO). Voxel repositioning errors did not explain differences in GABA measurement reproducibility between individuals. c) Posterior probability distribution of the correlation, r, between log(CV) and FO, generated using a Markov Chain Monte Carlo simulation, and with a flat, one-sided prior on r ($-1 \le r \le 0$). The maximum likelihood estimate of r is −0.01 and the Bayes estimate is −0.19, suggesting a weak inverse relationship between log(CV) and FO.

The observed intra-class correlation coefficient of 0.52 was statistically significant, meaning that repeated measurements acquired seven months apart strongly resemble each other (with absolute agreement) when between-subject variations are taken into account. Based on the conventions outlined in (Cicchetti and Sparrow, 1981), an ICC between 0.40 and 0.59 is considered 'fair'. It is important to note, however, that even in the hypothetical case that GABA levels are identical between

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sessions, the ICC would still never approach unity due to experimental test–retest variability, which, as mentioned above, has been shown in previous short-term reproducibility studies to result in CVs similar to those obtained in this study.

The observed variation in GABA levels between sessions was not explained by errors in voxel positioning. However, based on the posterior probability distribution of the correlation, r, between log(CV) and FO, and assuming a flat, one-sided prior distribution on r ($-1 \leq r \leq 0$), a weak inverse correlation between log(CV) and FO is predicted. This result agrees with what one might have expected intuitively if we assume that spatial variation of GABA levels in the occipital cortex is small. The above result is an important one, as it suggests that GABA levels are only weakly affected by voxel positioning in the occipital cortex, and therefore perfect voxel repositioning is not absolutely critical in longitudinal GABA studies in the occipital cortex.

The finding of relatively stable GABA concentrations over the long term suggests that GABA levels are a reflection of trait, rather than state. This finding provides foundational support for the growing body of research in which GABA levels are related to behavioural traits (Boy et al., 2010; Boy et al., 2011; Jocham et al., 2012; Sandberg et al., 2013; Sumner et al., 2010). Furthermore, the finding of stable GABA levels over long periods of time in healthy subjects suggests that GABA is an appropriate target for placebo-controlled longitudinal studies involving pharmacological agents, neuromodulative therapies (rTMS, etc.) or induction of plasticity changes, since longitudinal GABA measurements are not likely to be confounded by normal long-term (on the order of 7 months) GABA fluctuations. Over time intervals much longer than 7 months, GABA levels in adults are expected to decline slowly, based on the results of a cross-sectional study showing reduced GABA levels in older participants (Gao et al., 2013).

Due to the use of single voxel MRS in this study, the finding of long-term stability of GABA levels is specific to the occipital cortex. Future studies are required to assess the long-term stability of GABA levels in other cortical regions. It should be noted that the occipital cortex provides relatively favourable MRS data quality compared with some previously studied regions such as the anterior cingulate (Stephenson et al., 2011; Wijtenburg et al., 2013) or the dorsolateral prefrontal cortex (O'Gorman et al., 2011; Wijtenburg et al., 2013). Therefore, poorer measurement reproducibility might be expected in other brain regions due to increased measurement error.

It was noticed that the four subjects with the largest changes in GABA levels (subjects 1, 3, 6 and 13) all exhibited positive changes in GABA levels over the seven month interval, with CVs of 10.3, 11.4, 10.5 and 12.3% respectively. This fact resulted in a slight deviation from the diagonal in the slope of the relationship between session 1 and session 2 GABA levels, and we cannot rule out the possibility that some unexplained factor caused real increases in GABA levels in these four subjects. However, we judge that this is most likely a chance occurrence, and we also note that even the magnitudes of these four largest GABA changes were similar or smaller than what some authors have reported as the average CV of GABA levels over short time intervals (<8 days) (Bogner et al., 2010; Near et al., 2013; O'Gorman et al., 2011; Wijtenburg et al., 2013).

One well-known limitation of the MEGA-PRESS technique is that the acquired GABA signal is contaminated by overlapping macromolecule signals. As a result, the GABA quantities measured in this study do not represent pure GABA, but rather a combination of GABA + macromolecules. The results of this study therefore suggest that both GABA and macromolecular levels are likely relatively stable over long periods of time, thus further reinforcing the internal validity of longitudinal (interventional) and correlational studies of GABA levels using MEGA-PRESS.

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