GABA measured by ^{1}H-MRS is not affected by Tiagabine.

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Target Audience: Researchers interested in pharmacological action of tiagabine or GABA-edited MRS.

Purpose: Uncertainty remains regarding the exact nature of the GABA signal measured by ^{1}H-MRS. GABA acts both as a neurotransmitter and a metabolite; it is thought that the GABA pool associated with neurotransmission is concentrated near the synaptic terminals (both intra- and extracellular), and the metabolic GABA distributed throughout the neuron (i.e. intracellular). Pharmacological manipulations have demonstrated that the GABA concentration detected by ^{1}H-MRS is sensitive to a number of epileptic and affective disorder medications[1], but since many of these have a non-specific mode of action it is difficult to infer the source of the GABA signal. The antiepileptic drug tiagabine has been shown to inhibit the uptake of GABA from the synaptic cleft by glia and neurons, thus affecting the extracellular GABA concentration. The purpose of this work is to determine whether a change in the concentration of extracellular GABA caused by tiagabine administration can be measured by *J*-difference edited ^{1}H-MRS.

Figure 1: Voxel Positions

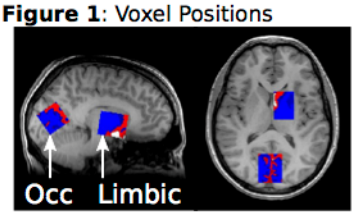


Figure 2: GABA Spectra

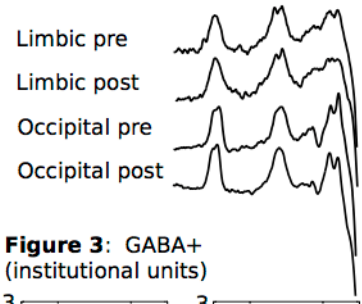
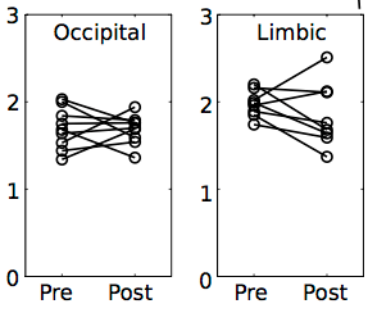


Figure 3: GABA+ (institutional units)



Methods: Ten participants (all male, mean±SD: 33±10 years) took part in the study which involved two scans, on the same day, before and after a 15 mg oral dose of tiagabine. All participants gave informed consent for the study, which was approved by a local Ethics Committee. The physiological effects of tiagabine were evaluated using the participants self-report of "sleepiness" on a visual analogue scale. Using a 3.0 T GE HDx system, GABA-edited spectra were acquired using MEGA-PRESS[2] with the following parameters; TR/TE = 1800/68 ms, 16ms editing pulses applied at 1.9ppm or 7.5ppm. Data were acquired from occipital ($(3cm)^3$, 332 averages), and left limbic voxels (35x25x30mm APxSIxLR, 384 averages). A T_1-weighted structural scan was acquired to evaluate the voxel tissue composition. Fig 1 shows typical positioning of occipital and limbic voxels and tissue segmentation (blue-white matter, red-grey matter, white-CSF). All analyses were performed with *Gannet* (http://gabamrs.blogspot.co.uk/). Participants with spectra of insufficient quality were discarded (1 occipital, 2 limbic). GABA+ values (GABA+macromolecules) were evaluated using water as a concentration reference, correcting for tissue composition.

Results: There was a significant increase in participants' self-report of "sleepiness" following tiagabine administration (mean±SD: 2.0±4.2 to 30.5±15.3, $p < 0.0001$). Fig. 2 shows representative spectra from the limbic and occipital voxels from one participant pre- and post-tiagabine administration. There was no detectable change in GABA+ concentration following tiagabine administration, either in the occipital (p=0.44, df=8, one-tailed t-test) or the limbic region (p=0.16, df=8, one-tailed t-test). The mean GABA+ concentration in institutional units, was (mean±SEM): Occipital; pre=1.69±0.08; post=1.68±0.09, Limbic pre=1.97±0.06; post=1.85±0.14. The data quality in the limbic region was systematically worse than that of the occipital region, as reflected by both 43%-reduced SNR ($p<0.0001$) and 54%-increased linewidth ($p<0.0001$).

Discussion: The mechanism of tiagabine and the physiological effects reported by participants indicate that extracellular GABA concentration would have been increased during this study. However, no detectable change in GABA+ was detected with ^{1}H-MRS. Changes in the mean concentration were -0.9% and -6.7% in occipital and limbic regions respectively, which are less than the typical repeatability of ^{1}H-MRS using MEGA-PRESS. Given that tiagabine acts by interfering with transport of GABA between compartments, it would not be immediately expected to impact total GABA concentration (which is what is measured by MRS). Furthermore, the majority of the GABA-MRS signal is likely to be intracellular, consistent with animal literature suggesting the concentration of intracellular GABA is ~750 times higher than that of extracellular GABA[3].

Conclusions: Tiagabine has a GABAergic action, but does not have a significant impact on total GABA concentration.

References: 1. Puts & Edden, In vivo magnetic resonance spectroscopy of GABA: a methodological review. Progress NMR Spectroscopy, 60:29-41, 2012. 2. Mescher *et al*, Simultaneous in vivo spectral editing and water suppression, NMR Biomed, 1998,11:266. 3. Zaleska & Erecinska, Role of sialic acid in synaptosomal transport of amino acid transmitters, PNAS 84:1709-12,1987