Event-related dynamics of glutamate and BOLD signal at 3 T in a repetition suppression paradigm

Dace Apšvalka[1], Andrew Gadie[1], and Paul Gerald Mullins[1]
[1]*Psychology, Bangor University, Bangor, Gwynedd, United Kingdom*

Introduction. Current proton magnetic resonance spectroscopy (^{1}H-MRS) techniques have allowed several researchers to measure changes in glutamate (Glu) concentrations in studies of brain function [1,2,3,4]. Coupled with improved reliability for gamma-amino-butyric acid (GABA) [7] using ^{1}H-MRS to measure changes as a result of brain activity provides a novel window on brain function [1] which should be of interest to cognitive and basic neuroscientists alike.
Most previous functional MRS (fMRS) studies have used long (5 min and more) stimulation and acquisition blocks to achieve sufficient signal-to-noise ratio of the metabolite spectrum. However, prolonged stimulation may lead to habituation, in addition, brain metabolites, especially Glu and GABA, are homeostatically controlled to prevent brain excitotoxicity [2] implying that averaged across a long activation block metabolic changes would be very small or not visible at all. To avoid these effects and improve temporal resolution, time-locking of MRS acquisitions in an event-related designs are recommended. To our knowledge only two studies have used event-related fMRS (ER-fMRS) to detect Glu changes upon brain activation: [3,4], and only two more ER-fMRS studies have been reported at all: [5,6].
Our current study's primary aim was to use ER-fMRS to measure Glu, and GABA dynamics at 3T in the lateral occipital cortex (LOC) in response to a repetition suppression paradigm. The secondary aim was to investigate the relationship of Glu, GABA, and Blood Oxygen Level Dependent (BOLD) responses through the novel approach of interleaving water-suppressed ER-fMRS with water-unsuppressed ER-fMRS to detect neurotransmitter and BOLD related water peak changes simultaneously. We hypothesized that fMRS measures will show lower Glu concentration and lower BOLD signal for repeated versus novel stimuli. We also tested the exploratory hypothesis that GABA would show alterations in response to the two different classes of stimuli.
Methods. Nine volunteers (average age 22.11 ± 1.61 years) where scanned in a 3 T Phillips Achieva MRI scanner (Philips Health Care, Eindhoven, Netherlands) fitted with a sensitivity-encoded eight channel phased-array head coil. A real-time fMRI localizer scan was used to guide placement of the fMRS voxel in the LOC. fMRS was acquired using a single voxel asymmetric PRESS sequence (TE = 105 ms, TE1 = 15 ms) [7] which has been reported to provide improved reliability for both Glu and GABA measures (voxel size = 20 x 20 x 20 mm^3, TR = 1.5 s, and 2048 data points). Water-suppressed (T-M, for metabolite peaks) and water-unsuppressed (T-W, for water peaks) MRS acquisitions were acquired in an interleaved fashion.
The experimental paradigm was a modified version of that used in Lally et al. [4] using simple line drawings of real world objects. Stimuli were presented in blocks of 12 trials. Each trial comprised a 700 ms stimulus presentation followed by fixation-cross presentation until the next trial. Each stimulus presentation was triggered from the previous T-M data acquisition randomly choosing between 2650- 2800 ms after the first excitation phase, resulting in inter-stimulus intervals (ISI) randomly varying between 2850 and 3150 ms. Individual T-M and T-W data were therefore acquired between 200-350 ms and 1700-1850 ms after stimulus onset respectively. Each stimulus block lasted 36 s and was presented as either a non-repetition block, B1 (16 blocks) with all novel stimuli, or a repetition block, B2 (4 blocks) or B3 (12 blocks), with 6 to 8 repeated stimuli in each. Rest blocks of 36 s duration separated all blocks.
Individual T-M and T-W free induction decay signals (FIDs) were binned by block type (B1 and B2B3, 192 FIDs each) and presentation type (novel presentations P1 (264 FIDs) and repeated presentations P2P3 (120 FIDs)), as well as across task and rest conditions (384 FIDs each). Binned T-M FIDs were averaged and processed using TARQUIN for spectral fitting using the corresponding binned T-W as an internal reference for each condition. Water-scaled Glu and GABA concentrations were calculated in institutional units (IU). Average water peak width and height for each block type, and the rest and task conditions was estimated using TARQUIN and an in-house MATLAB script.
Results and Discussion. GABA could not be reliably estimated and was not included in further analysis. Consistent with our hypothesis, Glu was significantly lower ($p < 0.05$, 16% – 18%) in repetition compared to non-repetition trials (Fig. 1.A), showing that the repetition suppression effect can also be seen in Glu dynamics. Interestingly there was no difference between task and rest trials (Fig. 1.A), however this may arise due the task trails including both B1 and B2B3 blocks, and so may show reduced Glu due to the repetition suppression effect. The detected amplitude of event-related changes in Glu was comparable with that reported in previous ER-fMRS studies [3,4], but much higher (up to 18%) than previously reported in prolonged stimulation block experiments [8–10]. This, along with the possible effects of repetition suppression on Glu concentration between task and rest blocks, suggests that habituation and homeostatic regulation may account for decreased Glu dynamics within long stimulation blocks.
The BOLD signal, as measured by water peak width and height changes, showed significant ($p < 0.01$) increase in task compared to rest trials, but no significant difference between novel and repeated trials (Fig. 1.B and Fig. 1.C), the opposite of the effects observed for Glu. This result might be related to metabolic and haemodynamic timing differences, and requires further analysis to probe the relationship between BOLD and Glu dynamics.

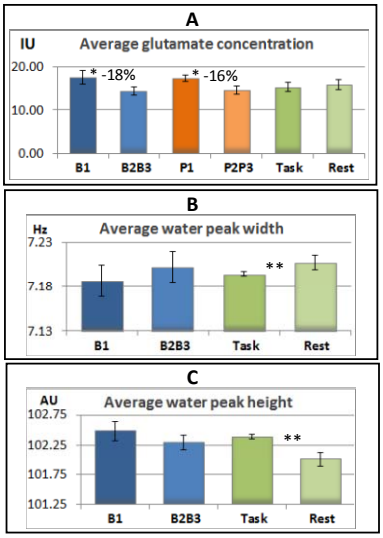

Fig. 1. Avg. estimated Glu **(A)** concentration in B1 and B2B3, P1 and P2P3, and task and rest conditions. Avg. water peak width **(B)** and height **(C)** in B1 and B2B3, and task and rest conditions. Error bars: 95% CI,* $p < 0.05$, ** $p < 0.01$.

Conclusion. Our results closely match previously reported results of event-related Glu dynamics and support the validity and importance of event-related designs in fMRS studies. We demonstrate that event-related changes in Glu can be detected at 3 T. We also propose a novel approach of water-suppressed-unsuppressed fMRS to acquire metabolic and haemodynamic changes simultaneously. The method and design used in the current study can be further developed to investigate glutamatergic neurotransmission and provide new insights into physiological processes underlying healthy and unhealthy brain function.

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