GABA concentration in Sensorimotor cortex following high-intensity exercise and relationship to lactate levels

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Key points

- Magnetic resonance spectroscopy before and after high-intensity interval exercise
- Sensorimotor cortex gamma-aminobutyric acid concentration increased by 20%
- Increase was positively correlated with the increase in blood lactate
- No change in dorsolateral prefrontal cortex
- No changes in glutamate-glutamine-glutathione peak

Abstract

High-intensity exercise increases the concentration of circulating lactate. Cortical uptake of blood borne lactate increases during and following exercise, however the potential relationship with changes in the concentration of neurometabolites remains unclear. While changes in neurometabolite concentration have previously been demonstrated in primary visual cortex following exercise, it remains unknown whether these changes extend to regions such as sensorimotor cortex (SM) or executive regions such as dorsolateral prefrontal cortex (DLPFC). Here we explored the acute aftereffects of high-intensity interval training (HIIT) on the concentration of gamma-amino butyric acid (GABA), a combined glutamate-glutamine-glutathione spectral peak (Glx), and their balance in SM and DLPFC, as well as the relationship to blood lactate levels. Following HIIT, there was a robust increase in GABA concentration in sensorimotor cortex, evident across the majority of participants. This change was not observed in DLPFC. Furthermore, the increase in sensorimotor cortex GABA was positively correlated with an increase in blood lactate. There were no changes in Glx concentration in either region. The observed increase in sensorimotor cortex GABA concentration implies functional relevance while the correlation with lactate levels may relate to the metabolic fate of exercise-derived lactate that crosses the blood-brain barrier.

Abbreviations: SM sensorimotor cortex; DLPFC dorsolateral prefrontal cortex; HIIT high-intensity interval exercise; GABA gamma-amino butyric acid; Glx glutamate-glutamine-glutathione; MRS ^{1}H proton magnetic resonance spectroscopy; TMS transcranial magnetic stimulation; MEGA-PRESS Meshcher-Garwood Point Resolved Spectroscopy; HRR heart rate reserve

Introduction

Cardiovascular exercise has been shown to benefit the brain, protect against cognitive decline, and to have efficacy as an adjunct treatment for neuropsychiatric conditions (Pedersen & Saltin, 2015; Prakash *et al.*, 2015; Rector *et al.*, 2015; Brellenthin & Koltyn, 2016). How this occurs remains unclear, but is likely related to the effects of exercise on brain plasticity and metabolism (Johansen-Berg & Duzel, 2016).

One candidate mechanism involves exercise-induced increases in lactate. When high power output is required during exercise, there is an accumulation of systemic lactate due to the glycolytic rate increasing in excess of lactate oxidation (Brooks *et al.*, 2011). Substantial lactate accumulation occurs during high-intensity interval exercise (HIIT) which involves alternating epochs of high and low intensity (a feature of sports played worldwide, e.g. football). It is now known that lactate crosses the blood-brain barrier (Bergersen, 2015; Machler *et al.*, 2016), that cortical concentrations of lactate increase during and following exercise (Kemppainen *et al.*, 2005; van Hall *et al.*, 2009; Rasmussen *et al.*, 2011), and that lactate may subsequently enter metabolic pathways involved in the synthesis of neurotransmitters such as glutamate and GABA (Maddock *et al.*, 2016). Nonetheless, the functional relevance of this increase in brain lactate is unclear. Thus, lactate is a focus of research to potentially explain the benefits of HIIT exercise relative to low intensity exercise (see e.g. (Thomas *et al.*, 2016).

There are only a handful of studies that have used ^{1}H proton magnetic resonance spectroscopy (MRS) to investigate neurometabolites during the acute post-exercise state (Maddock *et al.*, 2011; Dennis *et al.*, 2015; Maddock *et al.*, 2016). Typically, MRS spectra are acquired from a small region of the brain (i.e, voxel), both before and after exercise. Two studies have shown that lactate concentration in visual cortex increased following exercise in direct correlation with the peripheral increases in blood lactate (Maddock *et al.*, 2011; Dennis *et al.*, 2015). Additionally, increases in GABA and Glx, the glutamate-glutamine-glutathione composite signal, have been reported in visual cortex and anterior cingulate cortex, in some (Maddock *et al.*, 2011; Maddock *et al.*, 2016), but not all (Dennis *et al.*, 2015) studies. Thus, some of the lactate produced during exercise may be channeled into *de novo* synthesis of neurotransmitters via tricarboxylic cycle intermediates such as alpha ketoglutarate (Maddock *et al.*, 2011).

It has been suggested that this influence of post exercise lactate on neurometabolite concentrations might be global, reflecting a widespread effect across the brain (Maddock *et al.*, 2011; Maddock *et al.*, 2016). This remains largely untested as most measurements have been obtained from primary visual cortex. Also, the observed increase in GABA concentration in visual cortex (Maddock *et al.*, 2016) appears potentially at odds with findings from sensorimotor cortex examined using transcranial magnetic stimulation (TMS). Several TMS studies have reported reduced synaptic GABA inhibition in motor cortex following exercise (Singh *et al.*, 2014; Smith *et al.*, 2014; Mooney *et al.*, 2016) including one study where HIIT exercise was utilized (Stavrinos & Coxon, 2017). These TMS studies propose that the reduction in GABA is a permissive factor for plasticity processes in the motor system. Such findings potentially challenge the notion that all cortical regions are influenced in the same way by high-intensity exercise. Alternatively, it could be that TMS and MRS are providing measures of different aspects of inhibitory function (Stagg *et al.*, 2011c; Tremblay *et al.*, 2013; Dyke *et al.*,

2017). Interestingly, acute high-intensity exercise is also known to have benefits for executive function (Chang *et al.*, 2012), but the influence of HIIT on MRS measures of GABA and Glx in prefrontal regions such as the dorsolateral prefrontal cortex also remains unknown.

The aim of the present study was therefore to explore the effects of HIIT exercise on MRS-derived GABA and Glx neurometabolite concentrations in sensorimotor (SM) cortex and dorsolateral prefrontal cortex (DLPFC), and their correlation to exercise-induced changes in lactate. The results provide fundamental new information regarding the effects of exercise on the concentration of excitatory and inhibitory neurometabolites in the brain, including an initial exploration into the possible regional specificity of the effects.

Methods

Ethical approval

The Monash University Human Research Ethics Committee approved the study and all participants gave their written informed consent. The study conformed to the standards set by the Declaration of Helsinki, except for registration in a database.

Participants

The sample size was determined from the only previous study investigating the effects of exercise on GABA using MRS, for which an effect size of d = 1.35 was reported (Maddock *et al.*, 2016). For this effect size and a desired power of 90%, a sample size of N=9 was required. Thus we conservatively performed the experiment on ten right-handed individuals (8 male, 2

female). Participants were screened for contraindications to exercise (Physical Activity Readiness Questionnaire, PAR-Q) and magnetic resonance imaging, and were asked to refrain from strenuous physical activity for 24 hours prior.

General procedure

Repeated measures of GABA were obtained from magnetic resonance spectroscopy (MRS) before and after 20-minutes of HIIT exercise (Figure 1A). The exercise protocol was designed to ensure high levels of blood lactate concentration (>10 mmol/L) while limiting fatigue.

Magnetic resonance imaging

GABA-edited MRS data were acquired from two regions of cortex with a Siemens Skyra 3T MRI scanner (32-channel head coil for receive, body coil for transmit). Spectra were acquired from 2 x 2 x 2 cm voxels placed over sensorimotor (SM) cortex spanning the hand knob region of the central sulcus in the dominant (left) hemisphere (Figure 1B) and the right dorsolateral prefrontal cortex (DLPFC) (Figure 1C). GABA concentrations do not typically show hemispheric differences in healthy individuals (Grewal *et al.*, 2016). The SM hand knob region was chosen, as opposed to leg motor cortex, as we were interested in the general effects of exercise on the brain beyond the region driving the exercise. For both the pre and post exercise scans, a 1 x 1 x 1 mm isotropic T1-weighted image (MP-RAGE) was first acquired (TR = 1.54 s, TE = 2.55 ms, flip angle = 9°) for voxel localization. During voxel positioning, a pulsed arterial spin labeling sequence with a 3D GRASE readout was obtained (data not reported here). GABA-edited Meshcher-Garwood Point Resolved Spectroscopy (MEGA-PRESS) data was then acquired with the following parameters: TE = 68 ms, editing pulses at 1.9 ppm and 7.5 ppm, TR = 1.5 s, edit pulse bandwidth 45 Hz, 96 ON-OFF averages, 4:54 min per acquisition. Unsuppressed water

sequences (8 ON-OFF averages) with the same parameters and location were also acquired following each MRS acquisition.

Before exercise, two spectra were obtained from the SM voxel and one spectrum from the DLPFC voxel. Two SM spectra were obtained in order to assess the stability of MRS measures prior to exercise (sequence order: T1, pASL, SM1, DLPFC, SM2). After exercise, the participant was immediately repositioned in the scanner and three spectra were obtained from the SM voxel, along with one spectrum from the DLPFC voxel. The sequence order and time post exercise cessation was: T1 at 10 ± 2:46 min, pASL at 15± 3:10 min, SM1 at 24 ± 3:28 min, DLPFC at 31 ± 3:35 min, SM2 at 38 ± 3:48 min, SM3 at 45 ± 3:31 min). Participants were instructed to lay at rest with their eyes open viewing a fixation cross during the MRI scans.

Please insert Figure 1 about here

High-intensity interval (HIIT) exercise protocol

The HIIT exercise session was performed on a stationary cycle ergometer (Wattbike, Geelong, Australia) with the participant wearing a Polar H7 heart rate monitor (Polar Electro, Finland). Resting heart rate (RHR) was obtained whilst sitting and exercise intensity was tailored to each individual based on heart rate reserve (HRR):

$$HRR = \left(HR_{age\ predicted\ max} - RHR\right)$$

where $HR_{age\ predicted\ max} = 220 - \text{age}$.

Participants exercised for 20 minutes, alternating between periods of low-intensity cycling for 3 minutes at approximately 50% HRR (HRR*0.5 + RHR), and high-intensity cycling for 2 minutes

with a target HR of 90% HRR (HRR*0.9 + RHR) by the end of the protocol. The periods of lower intensity active recovery are required as by definition, high-intensity exercise cannot be sustained for prolonged periods of time. This exercise protocol is known to increase lactate levels above 10mmol/L (Roig *et al.*, 2012; Mang *et al.*, 2014; Stavrinos & Coxon, 2016). Fluid loss was minimized by having exercise occur in a temperature controlled environment, requesting that participants arrived well hydrated, and through the provision of water *ad libitum* both during and immediately after exercise. At the end of the protocol, participants then continued to cycle at low intensity for 2-3 minutes as heart rate recovered. During exercise, the following measures were recorded: Heart rate (beats per minute, bpm), Cadence (revolutions per minute, rpm), Power output (Watts), and Borg's 6–20 scale for rating of perceived exertion (RPE). For each measure the average was determined over the last minute of each low- and high-intensity epoch.

Blood lactate was quantified using an automated portable lactate analyzer and test strips (Lactate Pro2; Arkray, Kyoto, Japan). Following standard procedure, a spring-loaded lancet was used to obtain capillary blood samples (approximately 0.3 μL) from the tip of the left index finger. Baseline lactate was measured twice at rest, along with measurements immediately following the third and fourth high-intensity exercise epochs (i.e. at 15 minutes, and twice at 20 minutes, Figure 1A).

Processing of magnetic resonance spectroscopy data

Gannet 2.0 (Edden *et al.*, 2014; Mullins *et al.*, 2014) was used for analysis of the MRS spectra. Both GABA (3.0ppm) and Glx (3.75 ppm) concentrations were calculated relative to the unsuppressed water signal from the same region, obtained immediately after each sequence. Automated processing involved phased-array channel combination of the raw k-space data

(Siemens "twix" files), frequency- and phase-correction in the time domain with spectral registration (Near *et al.*, 2015), and filtering with 3-Hz exponential line broadening. GABA concentration was estimated with a single Gaussian peak superimposed on a linear baseline. The model for Glx incorporated a double Gaussian. To acknowledge a potential macromolecule contribution to the signal, we refer to GABA+ in figures and tables. Model fits are shown in red in Figure 1D.

The metabolites of interest (GABA, Glx) were quantified relative to both the unsuppressed water signal (fit with a Gaussian-Lorentzian model), and to the creatine (Cr) peak (integral of a two-Lorentzian model of Cr and choline in the OFF spectrum). The GABA:H_2O and Glx:H_2O ratios are expressed in institutional units (iu) and the formula used within Gannet takes into account the editing efficiency and approximate macromolecular contributions to the GABA+ peak.

The T1 anatomical image was segmented within each voxel (using FSL's FAST). Metabolite ratios were corrected post hoc for voxel grey matter (GM) and white matter (WM) tissue fractions, according to the following equations:

$$\text{(GABA concentration ratio}/(GM\%+WM\%))\times 100$$

$$\text{(Glx concentration ratio}/(GM\%+WM\%))\times 100$$

Tissue concentrations therefore reflect CSF-corrected individual GABA+ and Glx values.

The full-width half maximum of the creatine linewidth (Cr FWHM), the standard deviation of the water frequency in Hz, and the GABA signal fit error ($E_{GABA\text{-}Water}$) were used as metrics of data quality. $E_{GABA\text{-}Water}$ is a combined measure of the standard deviation of the residuals after fitting

models to the water and GABA peaks, expressed as a percentage of peak height. Spectra were accepted if Cr FWHM < 10 Hz, standard deviation of water frequency < 1 Hz, and $E_{GABA\text{-}Water}$ < 15 %. For the DLPFC voxel, data from 2 participants did not meet these criteria, and were thus omitted from the DLPFC analysis.

A secondary analysis of the MRS spectra was performed using LCModel software (version 6.3-H), as reported in (Maddock *et al.*, 2016). The difference spectra were fit using a simulated MEGA-PRESS basis set, which included GABA, Glx (glutamate, glutamine, and glutathione), and NAA (*n*-acetylaspartate, *n*-acetylaspartyl-glutamate). From this, GABA+:NAA and Glx:NAA ratios were calculated for each of the acquired difference spectra. The off-resonance spectra were fit using a simulated PRESS basis set, which included NAA, Glx, Cr (creatine, phosphocreatine), Choline (phosphocholine, glycerophosphocholine), Ins (myo-inositol), scyllo-inositol, and taurine. From this, NAA:Cr, Glx:Cr, Cho:Cr, and Ins:Cr ratios were calculated.

Statistical analysis of magnetic resonance spectroscopy data

One-way repeated measures analysis of variance (rmANOVA) was performed for blood lactate, and for MRS variables obtained from the SM voxel (factor = Time with 5 levels). Greenhouse-Geisser adjusted p-values are reported for instances where sphericity was violated. Contingent upon a significant rmANOVA, planned contrasts interrogated i) the stability of the baseline measures prior to exercise (contrast vector [-1 1 0 0 0]) and ii) whether effects could be ascribed to exercise (contrast vector [-3 -3 2 2 2]). DLPFC MRS variables were subjected to paired *t*-tests. A Pearson correlation tested for a positive relationship between percentage change in GABA concentration after exercise and change in blood lactate. Grubbs' test was applied to both variables and identified one significant outlier. This data point was omitted from the analysis to satisfy the assumption of normality. This participant demonstrated an

abnormally low lactate reading in response to the exercise protocol and may have been due to a procedural error when obtaining the blood lactate measure (sweat contamination), or their status as a highly trained endurance cyclist, which is known to enhance lactate utilization within muscle (Billat *et al.*, 2003). Data is reported as mean ± standard deviation (SD) within text and tables, and as mean ± standard error (SE) for figures.

Results

On average (mean ± S.D), participants were 29.40 ± 10.72 years of age, 1.76 ± 0.05 meters tall, weighed 74.40 ± 9.37 kg, and had a body mass index (BMI) of 23.91 ± 2.80 kg/m^2. Resting heart rate while seated was 63.30 ± 4.32 beats per minute (bpm), age-predicted maximum heart rate was 190.60 ± 10.72 bpm, and heart rate reserve (HRR) was 127.30 ± 10.99 bpm. A detailed description of the HIIT exercise session is provided in Table 1. By the end of the protocol, participants were exercising at 91 ± 8.2 % of heart rate reserve (182 ± 8.2 beats per minute). Importantly, blood lactate measures (Figure 2) confirm that the protocol was successful in achieving high-intensity exercise. The rmANOVA main effect for blood lactate was significant ($F_{4,36}$ = 66.08, p<.001, η^2_p = .88), with planned contrasts confirming that blood lactate was stable at baseline ($F_{1,9}$ = 0.61, p = .46, η^2_p = .06), and elevated during exercise ($F_{1,9}$ = 102.7, p < .001, η^2_p = .92). Peak blood lactate during exercise was 12.3 ± 3.5 mmol/L.

Please insert Figure 2 about here

MRS voxel localization and tissue composition

The overlap in voxel position for pre and post scans for the SM voxel was 86.3% ± 12.33% and for the DLPFC voxel 81.2% ± 16.03%. Within each MRS voxel, paired t-tests established that there were no significant differences across pre- and post-exercise scans in the proportion of

grey matter (SM pre 0.33 ± 0.06, post 0.33 ± 0.06; DLPFC pre 0.36 ± 0.03, post 0.37 ± 0.03), white matter (SM pre 0.56 ± 0.06, post 0.55 ± 0.07; DLPFC pre 0.55 ± 0.04, post 0.54 ± 0.03), or cerebrospinal fluid (SM pre 0.11 ± 0.04, post 0.11 ± 0.05; DLPFC pre 0.08 ± 0.02, post 0.08 ± 0.01), all $p > .17$.

Sensorimotor cortex (SM).

There was a significant main effect of Time for GABA in the SM voxel, expressed relative to both water and creatine (Table 2). Planned contrasts revealed that GABA ratios were stable at baseline, but significantly elevated post exercise. Averaging across pre and post acquisitions, HIIT exercise was associated with a 29% increase in GABA:H_2O (Figure 3A) and a 24% increase in GABA:Cr (Figure 3C). In contrast, Glx ratios did not show significant modulation as a function of Time (Table 2 and Figure 3B and 3C). The rmANOVA model applied to data quality metrics indicated that measures were stable over Time (Table 2). The increase in GABA may be related to the accumulation of lactate during exercise as there was a significant positive correlation ($r = .63$, $p = .034$) between the increase in blood lactate due to exercise and percentage increase in GABA in the SM voxel (Figure 4).

Please insert Figures 3 and 4 about here

Dorsolateral prefrontal cortex (DLPFC).

Paired t-tests revealed no significant differences pre to post exercise in the DLPFC voxel for either GABA ratio (GABA:H_2O: pre 2.03 ± 0.67, post 2.07 ± 0.32, $t_7 = 0.12$, $p = .91$; GABA:Cr: pre 0.123 ± 0.033, post 0.124 ± 0.026, $t_7 = 0.12$, $p = .91$), or Glx ratio (Glx:H_2O: pre 1.54 ± 0.50, post

1.65 ± 0.07, t_7 = 0.62, p = .56; Glx:Cr: pre 0.093 ± 0.027, post 0.097 ± 0.010, t_7 = 0.46, p = .66), nor for any of the data quality metrics (all p > .13).

Secondary analysis using LCModel

As reported above for the SM voxel (primary GANNET analysis), the significant main effect of Time for GABA, but not Glx, was confirmed using the LCModel software package, with NAA as the denominator (Table 3). A *t*-test indicated that GABA:NAA was significantly elevated at the first Post timepoint compared to the average of Pre (t_9 = 3.75, p = .007). The percent increase in GABA:NAA was also positively correlated with change in blood lactate (r = .57, p = .042). The signal-to-noise ratio (SNR) and line width (full-width at half maximum) values were stable (Table 3) and similar to those reported by (Maddock *et al.*, 2016). The mean Cramer–Rao lower bound (CRLB) for GABA was 5.5 (range, 4–8) indicating the reliability of the values obtained.

Analysis of the off-resonance spectra revealed no significant main effects for NAA:Cr, Glx:Cr, Ins:Cr, or Cho:Cr (Table 3), again with similar data quality as reported by (Maddock *et al.*, 2016). The mean CRLB for Glx was 7.06 (range 6-10), and for was ≤ 8 for the other metabolite resonances reported in Table 3.

For DLPFC, paired t-tests revealed no significant differences for any of the metabolite ratios or data quality metrics (all t < 1.83, p > .11).

Discussion

This study investigated the effects of HIIT-exercise on systemic lactate accumulation and on the concentration of the neurometabolite GABA, the brain's primary inhibitory neurotransmitter. We report novel evidence of a large 20% increase in GABA concentration in upper-limb sensorimotor cortex in the first hour after lower-limb cycling exercise. This result complements a previous study (Maddock *et al.*, 2016) that reported a 7% GABA increase in visual cortex. Here we show that the increase in GABA is of a greater magnitude and persists for a longer duration in sensorimotor cortex compared to what has been reported previously in visual cortex. We did not observe any change in GABA in a prefrontal cortex voxel (DLPFC), providing some preliminary evidence that increased GABA following exercise may be regionally specific as opposed to a global phenomenon. We also report novel evidence of a positive correlation between greater increases in systemic lactate and the increase in sensorimotor cortex GABA.

Cortical changes in neurometabolite concentrations evoked by HIIT

To our knowledge, this is the first study to investigate the effects of high-intensity exercise on GABA and Glx concentrations in sensorimotor cortex and DLPFC. Previous studies demonstrated the modulation of neurometabolite concentrations following exercise in visual and anterior cingulate cortex (ACC) in samples of 8 to 11 participants (Maddock *et al.*, 2011; Dennis *et al.*, 2015; Maddock *et al.*, 2016). More specifically, in agreement with the increase in sensorimotor cortex in the present study, GABA levels have been reported to be increased in visual cortex (Maddock *et al.*, 2016). In contrast, markers of glutamatergic neurometabolite concentration have been reported to be increased in visual cortex and ACC (Maddock *et al.*, 2016) or remain unchanged in visual cortex (Dennis *et al.*, 2015). It remains unclear to what extent such regions might be functionally involved in high-intensity exercise or represent more

generalized and global influences of exercise on neurometabolite levels. While it has been noted that the ACC plays a functional role in executive function (Maddock 2016), it is also involved in a variety of autonomic functions (e.g. regulation of blood pressure and heart rate) and tasks requiring focused mental effort (for review see (Allman *et al.*, 2001). In the present study, we sampled the DLPFC which is consistently implicated in executive function and saw no changes in GABA and Glx levels. This is perhaps to be expected given relatively automatic nature of exercise on a stationary cycle ergometer with relatively low cognitive demands. Nonetheless, these results indicate a complex picture in which neurometabolite changes are neither global, nor fully explained by the functional relevance of a cortical region.

Interestingly, the increase in GABA concentration in sensorimotor cortex was strongly correlated with blood lactate levels. One plausible candidate mechanism for the observed increase in GABA is the cortical uptake of lactate and its non-oxidative metabolism and conversion to GABA via α-ketoglutarate transamination (Maddock *et al.*, 2016). This result may be partially mediated by the neuronal populations that are active during exercise – visual processing and sensorimotor cortex activity both occur during exercise. Active cortical regions receive more blood flow during tasks as evidenced in blood oxygen level dependent (BOLD) functional MRI studies (Logothetis, 2003), and may therefore receive more peripheral lactate and then process this metabolically. This may provide a degree of regional specificity in terms of the increase in lactate and neurometabolite concentrations. Future studies could investigate this notion by determining whether functional activation of cortical regions during or following exercise, such as the activation of DLPFC by a cognitive task, would similarly increase local blood flow, lactate, and consequently neurometabolite levels in the activated regions.

The exercise-induced increase in sensorimotor cortex GABA concentration was supported by

two analyses using different processing pipelines. The effects were stronger and more enduring for our primary analysis using Gannet than our secondary analysis using LCModel. The Gannet pipeline was chosen for our primary analysis as this analysis package is specifically designed and optimised for the detection of GABA using the MEGA-PRESS sequence (Edden *et al.*, 2014; Mullins *et al.*, 2014). Additionally, one advantage of Gannet is that outliers (frames exhibiting excessive frequency shift e.g. due to subject movement) are identified and rejected during preprocessing to maximise signal:noise of the averaged spectrum, which may improve measurement reliability. The use of a larger voxel size and longer scanning acquisition (e.g. 160 averages) also increases the reliability of GABA concentration measurement (Brix *et al.*, 2017). Our relatively short acquisition duration (96 averages per timepoint) and small voxel (8 cm^3), were chosen to maximise the temporal and spatial resolution of our results, however this came at the expense of a higher coefficient of variation (16% at baseline) compared to that reported for larger voxels and longer acquisition durations (Mullins *et al.*, 2014; Maddock *et al.*, 2016; Brix *et al.*, 2017). Our use of repeated measures ANOVA assists in mitigating the reduced signal:noise ratio of each individual measure.

Our data show no evidence for increases in neurometabolites involved in excitatory neurotransmission in sensorimotor cortex or DLPFC. The literature to date is mixed with respect to the effects of exercise on MRS derived measures of excitatory neurometabolites in different cortical regions with some studies reporting an increase (Maddock *et al.*, 2011; Maddock *et al.*, 2016), and others unable to replicate the effect (Dennis *et al.*, 2015). Lactate is linked to metabolic processes that can upregulate de novo synthesis of glutamate (Maddock *et al.*, 2011), so it appears surprising that no changes in Glx were observed in our study with high-intensity exercise and a previous study using moderate level exercise (Dennis *et al.*, 2015). This may relate to the fact that we used a sequence optimized for the detection of GABA, although we also did not observe any changes in Glx in a separate analysis of the 'off-resonance' PRESS

sequence. Alternatively, it could be due to only being able to resolve the composite glutamatergic signal Glx on our 3T scanner. It is possible that this composite signal could miss some effects that are specific to glutamate or glutamine. Interestingly, a 7T MRS study in which rats were exercised to exhaustion revealed greater increases in glutamine relative to glutamate (Swiatkiewicz *et al.*, 2017). Nonetheless, we note that Dennis and colleagues, who were able to resolve separate peaks for glutamate and glutamine at 7T in humans, reported no increase following exercise (Dennis *et al.*, 2015). Yet another possibility is that this may reflect regional specificity of HIIT effects. Further studies are required to better understand this discrepancy.

What might an exercise-induced change in GABA concentration represent?

One question that arises is whether the increase in GABA concentration observed here and previously, reflects synaptic neurotransmitter concentrations or, alternatively, represents other pools of GABA. GABA is utilized in synaptic neurotransmission, extrasynaptic neurotransmission, and in cell metabolism via the 'GABA shunt' (Martin & Rimvall, 1993). Although GABA concentrations have been associated with functions such as motor learning (Stagg *et al.*, 2011a; Kim *et al.*, 2014), it is thought that the majority of the GABA-MRS signal primarily reflects extrasynaptic and metabolic pools of GABA (Stagg *et al.*, 2011b). Indeed, most common TMS measures of inhibition are uncorrelated with GABA concentrations as derived by MRS (Stagg *et al.*, 2011c; Tremblay *et al.*, 2013; Dyke *et al.*, 2017). Therefore, the changes observed here, especially as they are being measured at rest during scanning, probably do not reflect an increase in synaptic neurotransmission, but rather changes at the metabolic or extrasynaptic level. Increases in GABA in the extrasynaptic space typically occur following large amounts of GABA release and subsequent pooling in the synaptic and extrasynaptic space (Brickley & Mody, 2012). However, TMS studies, which typically measure the strength of synaptic GABAergic neurotransmission (Kujirai *et al.*, 1993; Ziemann *et al.*, 2015), indicate that synaptic GABA function is *decreased* following exercise (Singh *et al.*, 2014; Smith *et al.*, 2014;

Mooney *et al.*, 2016; Stavrinos & Coxon, 2016). Although GABA pooling can result in synaptic disinhibition via extrasynaptic $GABA_B$ autoreceptors, extrasynaptic $GABA_B$ is typically cleared within hundreds of milliseconds (Cash *et al.,* 2010). GABA may also be found in the extracellular fluid, where it may impact on non-synaptic GABAergic tone, however the impact of this on synaptic transmission remains unclear (for discussion see (Stagg *et al.*, 2011c). Overall, these arguments suggest that the increase in the GABA-MRS signal is probably unlikely to reflect synaptic or extrasynaptic GABA content (Stagg *et al.*, 2011c; Tremblay *et al.*, 2013; Dyke *et al.*, 2017). Instead the increase in MRS GABA observed here may reflect an increase in intracellular GABA content following HIIT, whereby GABA might be preferentially utilized to support the energetic demands of mitochondria. The underlying processes, and implications of this for brain plasticity, require further investigation.

It is conceivable that brain-derived neurotrophic factor (BDNF), plays a role in this process alongside lactate given that this neurotrophic factor is released during high intensity exercise (Saucedo Marquez *et al.*, 2015), plays a regulatory role in mediating the balance between excitation and inhibition (Cash *et al.,* 2017), and enhances clearance of GABA from the synapse (Vaz *et al.*, 2011). Future studies could explore this interplay and how the balance between excitation and inhibition is restored over time following HIIT by obtaining, in the same participants, MRS and TMS measures as well as lactate and BDNF concentrations.

Limitations

There are some limitations in this study. Firstly, lactate concentration was measured peripherally from the blood, rather than centrally via MRS. However, previous studies have shown that cerebral increases in lactate following exercise co-occur with peripheral blood changes in lactate (Maddock *et al.*, 2011) and that these measures are correlated with one

another (Dennis *et al.*, 2015). Brain lactate levels increase during and following exercise, albeit to a lesser extent than the increases in peripheral lactate, presumably because this incoming lactate is rapidly metabolized by the brain (Dennis, 2015; Ide et al., 2000; Dalsgaard et al., 2004; van Hall et al., 2009; Volianitis et al., 2011; Maddock 2011). We anticipate that the strength of relationship between GABA and central lactate levels may, if anything, be potentially underestimated by measuring peripheral blood lactate levels. Secondly, it was not feasible to include a control study at rest without HIIT. However, Glx, NAA, Choline, and Myo-Inositol levels remained stable across all time points (Tables 2 and 3) and GABA levels were stable at baseline, before increasing following exercise in the sensorimotor cortex but not the DLPFC voxel (although this latter result may be driven by inter-subject variability in DLPFC concentrations observed at baseline). The relationship between GABA levels and lactate levels supports a functional relationship to exercise. Thirdly, it could be argued that GABA:H_20 and Glx:H_20 metrics would be influenced by dehydration during exercise. However, we took various steps to avoid dehydration (see methods), and also examined ratios using Creatine as the denominator which confirmed our results (see Figure 3, and secondary LCModel analysis reported in Table 3). Dehydration cannot explain that effects were observed in sensorimotor cortex but not DLPFC. Furthermore, if the results for GABA:H_20 were due to a change in water levels, then Glx:H_20 would not have remained stable as was the case here. Lastly, the present findings demonstrate a functional, but correlative, relationship between lactate levels and GABA neurometabolite concentration. Future studies could explore this relationship by testing whether neurometabolite concentrations change following injection of lactate peripherally, in the absence of HIIT.

Conclusion

Our study provides the first evidence of changes in GABA, but not Glx, neurometabolite concentrations following HIIT in human sensorimotor cortex using MRS. Our data indicates for

the first time a potential regional specificity of these changes, something that has not previously been recognized. The correlation between GABA and lactate concentration warrants investigation in future studies.

Table 1. Exercise parameters. L = Low-intensity epoch, H = High-intensity epoch. *HRR heart rate reserve, RPE rating of perceived exertion.*

Time (minutes)	**0-3**	**3-5**	**5-8**	**8-10**	**10-13**	**13-15**	**15-18**	**18-20**
Mean ± S.D.	**L1**	**H1**	**L2**	**H2**	**L3**	**H3**	**L4**	**H4**
Cadence (rpm)	78.7 (7.1)	98.5 (6.2)	80.9 (7.1)	102.4 (7.8)	83.6 (8.1)	107.1 (6.5)	83.7 (8.3)	111.7 (8.3)
Power (Watts)	90 (13)	184 (60)	87 (17)	211 (92)	94 (27)	219 (80)	85 (19)	255 (78)
Power:Weight (Watt/kg)	1.21 (0.14)	2.47 (0.71)	1.17 (0.21)	2.81 (1.13)	1.27 (0.34)	2.91 (0.94)	1.14 (0.18)	3.40 (0.89)
Heart rate (bpm)	117 (13.0)	149 (10.9)	132 (13.3)	164 (9.6)	141 (13.0)	173 (8.6)	146 (12.3)	182 (8.3)
% HRR	39 (6.8)	65 (6.7)	51 (7.5)	77 (8.2)	58 (8.3)	84 (8.5)	63 (8.2)	91 (8.2)
Borg's RPE (scale 6-20)	10.0 (1.56)	13.4 (1.90)	10.6 (0.84)	14.6 (1.35)	11.2 (1.55)	16.0 (0.47)	11.3 (2.26)	18.1 (1.45)

Table 2. GABA+ and Glx ratios obtained from the primary analysis using GANNET for the sensorimotor cortex (SM) voxel, along with associated data quality metrics. Significant results are highlighted with bold text. Planned comparisons were only carried out if a main effect was present in the repeated measures ANOVA.

GANNET: MEGA-PRESS Difference Spectrum								
Mean ± S.D.	Pre 1	Pre 2	Post Ex 1 (24 min)	Post Ex 2 (38 min)	Post Ex 3 (46 min)	rmANOVA	Contrast 1 (Pre 1 vs. Pre 2)	Contrast 2 (Post vs. Pre)
GABA+ : H_2O	2.00 (0.33)	1.81 (0.29)	2.45 (0.53)	2.50 (0.54)	2.35 (0.37)	**$F_{(4,36)} = 5.24$, $p = .002$** **$\eta^2_p = .37$**	$F_{(1,9)} = 2.56$, $p = .14$ $\eta^2_p = .22$	**$F_{(1,9)} = 25.18$, $p = .001$** **$\eta^2_p = .74$**
GABA+ : Cr	0.121 (0.0160)	0.111 (0.0197)	0.144 (0.0353)	0.147 (0.0356)	0.138 (0.0168)	**$F_{(4,36)} = 3.93$, $p = .01$** **$\eta^2_p = .30$**	$F_{(1,9)} = 1.52$, $p = .25$ $\eta^2_p = .14$	**$F_{(1,9)} = 16.72$, $p = .003$** **$\eta^2_p = .65$**
Glx : H_2O	1.57 (0.25)	1.62 (0.38)	1.53 (0.40)	1.50 (0.43)	1.66 (0.36)	$F_{(4,36)} = 0.50$, $p = .74$ $\eta^2_p = .05$	-	-
Glx : Cr	0.094 (0.0180)	0.098 (0.0223)	0.088 (0.0214)	0.085 (0.0200)	0.095 (0.0179)	$F_{(4,36)} = 0.90$, $p = .47$ $\eta^2_p = .09$	-	-
Cr FWHM (Hz)	7.98 (0.60)	7.93 (0.65)	8.06 (0.56)	7.85 (0.46)	7.92 (0.40)	$F_{(4,36)} = 0.44$, $p = .78$ $\eta^2_p = .05$ $GG_\varepsilon = .28$	-	-
Water Frequency SD (Hz)	0.62 (0.23)	0.55 (0.19)	0.49 (0.10)	0.59 (0.13)	0.60 (0.14)	$F_{(4,36)} = 1.40$, $p = .25$ $\eta^2_p = .14$	-	-
Normalised fitting error $E_{GABA,Water}$	9.56 (2.57)	9.67 (2.01)	8.74 (2.16)	10.03 (2.71)	9.37 (1.99)	$F_{(4,36)} = 0.53$, $p = .71$ $\eta^2_p = .06$	-	-

Table 3. Secondary analysis using LCModel for the sensorimotor cortex (SM) voxel, along with associated data quality metrics. Significant results are highlighted with bold text. Planned comparisons were only carried out if a main effect was present in the repeated measures ANOVA.

LC-Model: MEGA-PRESS Difference Spectrum								
Mean ± S.D.	Pre 1	Pre 2	Post Ex 1 (24 min)	Post Ex 2 (38 min)	Post Ex 3 (46 min)	rmANOVA	Contrast 1 (Pre 1 vs. Pre 2)	Contrast 2 (Post vs. Pre)
GABA+ : NAA	0.34 (0.05)	0.34 (0.06)	0.38 (0.05)	0.35 (0.06)	0.36 (0.05)	**$F_{(4,36)} = 2.77$, $p = .042$** **$\eta^2_p = .24$**	$F_{(1,9)} = 0.06$, $p = .81$ $\eta^2_p = .01$	$F_{(1,9)} = 3.33$, $p = .10$ $\eta^2_p = .27$
Glx : NAA	0.99 (0.10)	1.01 (0.09)	1.02 (0.11)	1.01 (0.12)	0.99 (0.13)	$F_{(4,36)} = 0.42$, $p = .64$ $\eta^2_p = .05$	-	-
Line width (ppm)	0.037 (0.016)	0.037 (0.013)	0.034 (0.004)	0.034 (0.004)	0.033 (0.00)	$F_{(4,36)} = 0.83$, $p = .41$ $\eta^2_p = .09$ $GG_\varepsilon = .32$	-	-
SNR	26.7 (5.98)	26.8 (6.29)	25.9 (3.41)	26.0 (3.40)	25.9 (3.75)	$F_{(4,36)} = 0.21$, $p = .76$ $\eta^2_p = .02$	-	-
LC-Model: 'Off' resonance PRESS Spectrum								
Mean ± S.D.	Pre 1	Pre 2	Post Ex 1 (24 min)	Post Ex 2 (38 min)	Post Ex 3 (46 min)	rmANOVA	Contrast 1 (Pre 1 vs. Pre 2)	Contrast 2 (Post vs. Pre)
NAA : Cr	1.90 (0.12)	1.90 (0.13)	1.86 (0.14)	1.93 (0.28)	1.90 (0.16)	$F_{(4,36)} = 0.73$, $p = .046$ $\eta^2_p = .08$ $GG_\varepsilon = .35$	-	-

Glx : Cr	0.74 (0.11)	0.74 (0.11)	0.76 (0.10)	0.75 (0.11)	0.76 (0.13)	$F_{(4,36)} = 0.39$, $p = .81$ $\eta^2_p = .04$	-	-
Ins : Cr	0.91 (0.13)	0.91 (0.11)	0.89 (0.14)	0.92 (0.12)	0.91 (0.15)	$F_{(4,36)} = 0.53$, $p = .72$ $\eta^2_p = .05$	-	-
Cho : Cr	0.25 (0.04)	0.25 (0.05)	0.24 (0.04)	0.24 (0.04)	0.25 (0.41)	$F_{(4,36)} = 0.83$, $p = .43$ $\eta^2_p = .08$ $GG_\varepsilon = .41$	-	-
Line width (ppm)	0.037 (0.012)	0.036 (0.011)	0.033 (0.003)	0.034 (0.003)	0.035 (0.004)	$F_{(4,36)} = 0.67$, $p = .48$ $\eta^2_p = .07$ $GG_\varepsilon = .34$	-	-
SNR	34.4 (5.42)	35.3 (5.40)	34.2 (2.49)	33.2 (5.27)	34.5 (2.95)	$F_{(4,36)} = 0.43$, $p = .61$ $\eta^2_p = .05$ $GG_\varepsilon = .38$	-	-

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Author contributions:

This work was performed in the Movement and Exercise Neuroscience Laboratory, Monash Institute of Cognitive and Clinical Neurosciences. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed. Author contributions as follows: Conception or design of the work (JC, NR, MY), acquisition, analysis or interpretation of data for the work (JC, CS, RC, JH, ES), drafting the work (JC, RC) and revising it critically for important intellectual content (JC, RC, JH, CS, NR, MY).

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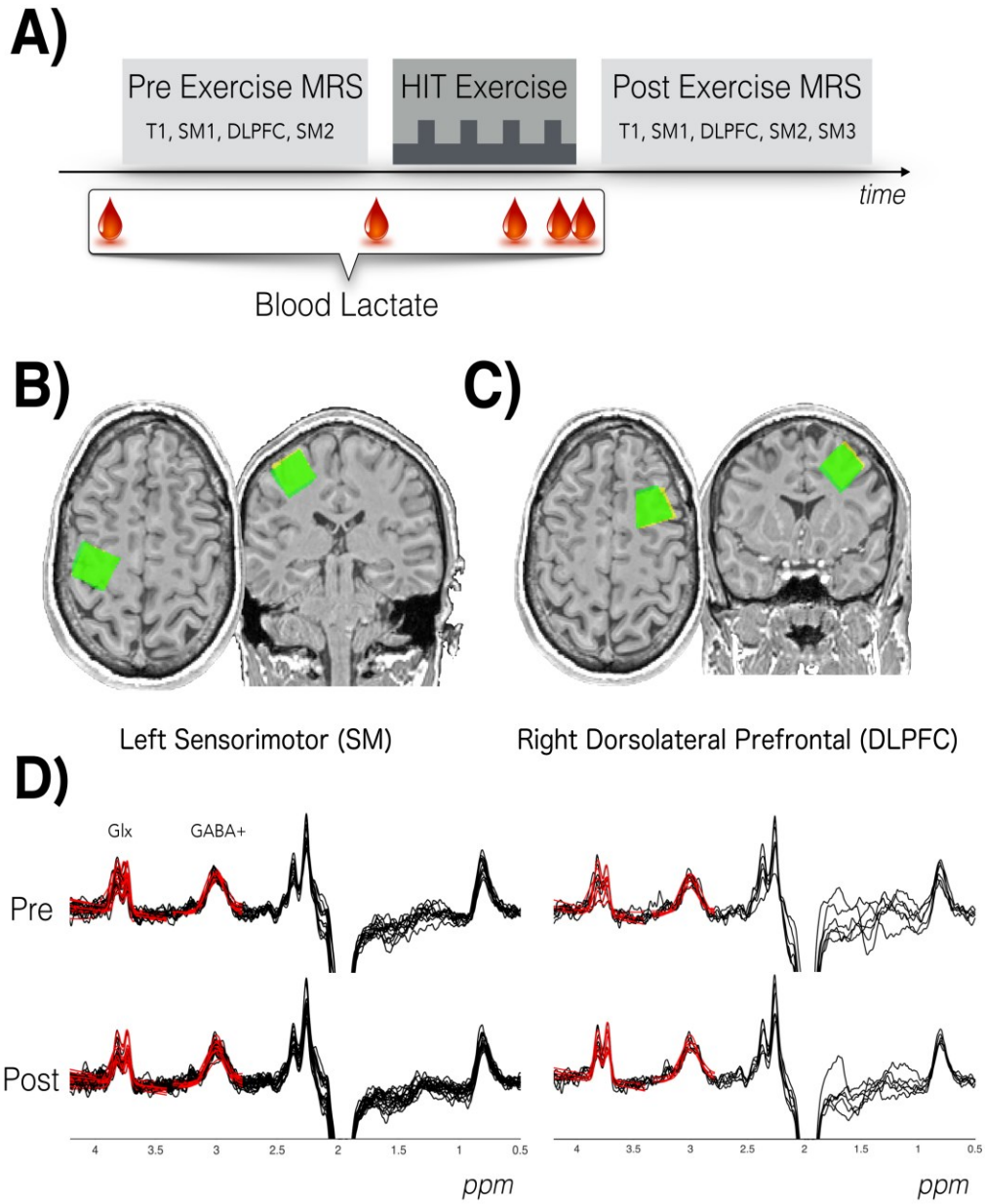

Figure 1. Experiment overview. Magnetic resonance spectroscopy (MRS) measures were obtained before and after high-intensity interval (HIIT) exercise using Meshcher-Garwood Point Resolved Spectroscopy tuned to detect gamma-aminobutyric acid (GABA). A) Following acquisition of an anatomical image (T1), MRS sequences were repeated for left sensorimotor cortex (SM) hand knob region and right dorsolateral prefrontal cortex (DLPFC) voxels. Lactate was measured from capillary blood at rest (x2 baseline measures), during HIIT, and at the cessation of exercise. B and C) Positioning of the SM and DLPFC voxels, respectively. The post exercise voxel (green) is overlaid upon the pre exercise voxel (yellow). D) Difference spectra for all participants and timepoints are shown for each voxel (black lines). Model fit for each acquired difference spectrum is superimposed (red lines) for the GABA peak at 3.0 parts per million (ppm) and the Glx peak at 3.75 ppm.

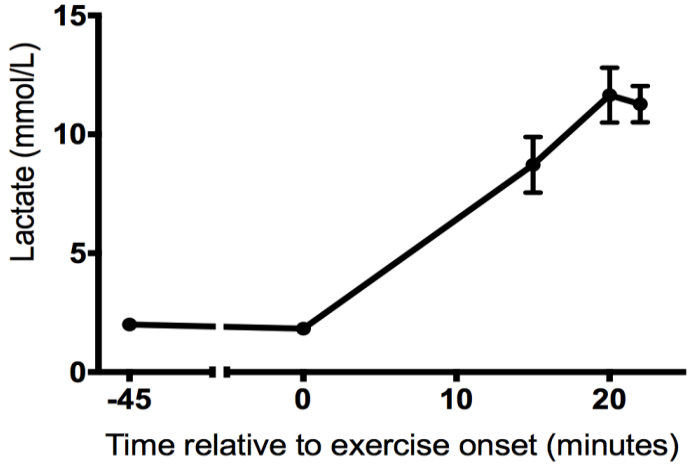

Figure 2. Blood lactate. Measures are displayed relative to exercise onset. The second baseline measure was obtained within the 5 minutes prior to exercise commencing. During exercise, measures were obtained at the end of the third and fourth high-intensity epochs.

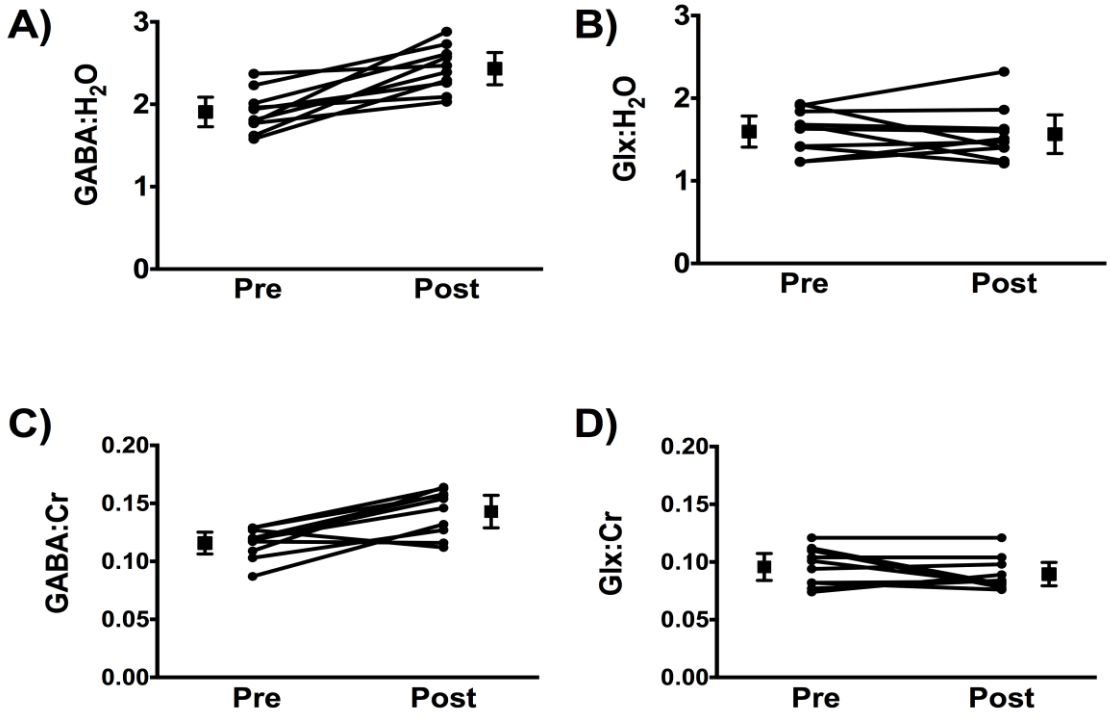

Figure 3. Sensorimotor (SM) voxel GABA and Glx ratios. Concentrations are shown for pre and post HIIT exercise, depicting the main contrast of interest. Metabolite concentrations are shown relative to water (A and B) and creatine (C and D). Squares depict the mean and 95% confidence interval. Circles show individual subject data.

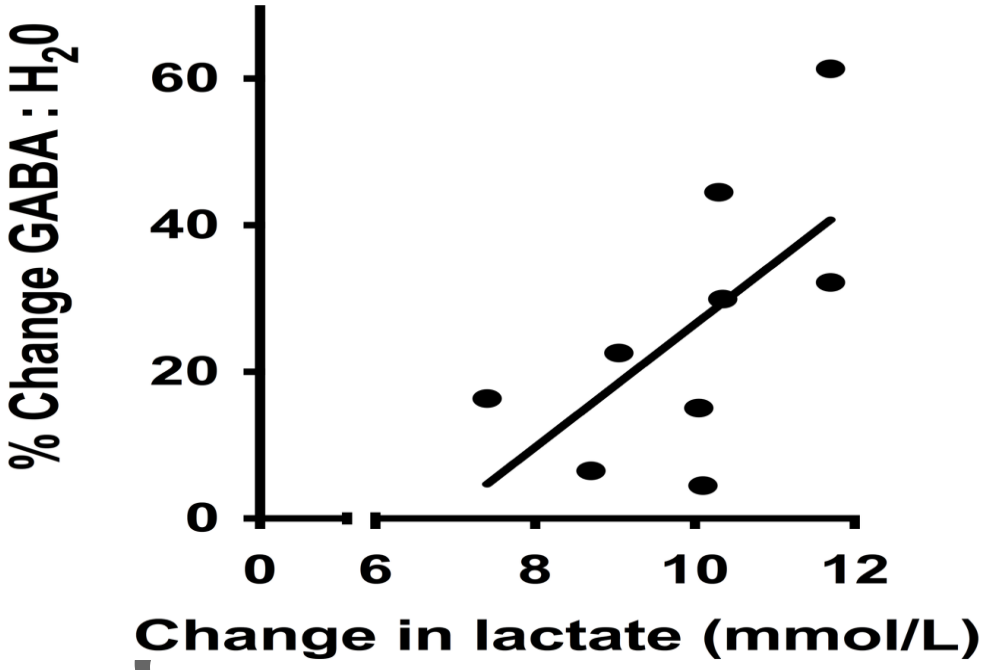

Figure 4. Correlation between increase in blood lactate and the percent increase in GABA concentration in the SM voxel following HIIT (r = .63, p = .034).

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