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RESEARCH REPORT

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A preliminary study of dynamic neurochemical changes in the dorsolateral prefrontal cortex during working memory

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Abstract

Working memory (WM) is one of the fundamental cognitive functions associated with the dorsolateral prefrontal cortex (DLPFC). However, the neurochemical mechanisms of WM, including the dynamic changes in neurometabolites such as glutamate and GABA in the DLPFC, remain unclear. Here, we investigated WM-related glutamate and GABA changes, alongside hemodynamic responses in the DLPFC, using a combination of functional magnetic resonance spectroscopy (fMRS) and functional magnetic resonance imaging (fMRI). During a WM task, we measured Glx (glutamate + glutamine) and GABA levels using GABA editing MEscher-GArwood Point REsolved Spectroscopy (MEGA-PRESS) sequence and blood-oxygen-level-dependent (BOLD) signal changes. In the DLPFC, we observed elevated Glx levels and increased BOLD signal changes during a 2-back task. Specifically, the Glx levels in the DLPFC were significantly higher during the 2-back task compared with fixation, although this difference was not significant when compared with a 0-back task. However, Glx levels during the 0-back task were higher than during fixation. Furthermore, there was a positive correlation between Glx levels in the DLPFC during the 2-back task and the corresponding BOLD signal changes. Notably, higher Glx increases were associated with increased DLPFC activation and lower WM task performance in individuals. No notable changes in DLPFC GABA levels were observed during WM processing. These findings suggest that the modulation of glutamatergic activity in the DLPFC may play a crucial role in both working memory processing and its associated performance outcomes.

KEYWORDS
DLPFC, fMRI, functional magnetic resonance spectroscopy, GABA, glutamate, working memory

Abbreviations: BOLD, blood-oxygen-level-dependent; DLPFC, dorsolateral prefrontal cortex; fMRI, functional magnetic resonance imaging; fMRS, functional magnetic resonance spectroscopy; Glx, glutamate + glutamine; WM, working memory.

1 | INTRODUCTION

The dorsolateral prefrontal cortex (DLPFC) plays a pivotal role in the domain of working memory (WM), a cognitive ability that briefly retains received information and manipulates it to facilitate other cognitive functions (Baddeley, 1992). It plays an important role in reasoning, comprehension, planning, problem-solving and the guidance of decision-making (Linden, 2007; Salazar et al., 2012). The DLPFC is directly linked to these executive functions, all of which are fundamental for the effective functioning of WM (Barbey et al., 2013; D'Esposito & Postle, 2015). Functional neuroimaging studies have consistently shown increased DLPFC activity during working memory tasks (Curtis & D'Esposito, 2003) and the degree of DLPFC activation is proportional to the relative working memory load (Rypma & D'Esposito, 1999). Although the involvement of the DLPFC in WM is well-established, only a few studies have investigated the underlying neurochemical mechanisms of DLPFC in WM (Woodcock et al., 2018, 2019).

Electrophysiological studies with primates have demonstrated that WM originates through the recurrent excitation of pyramidal cell microcircuits in the cortical layer III of the DLPFC (for a review, see Goldman-Rakic, 1995). Pharmacological studies have reported the significance of glutamate binding post-synaptic N-methyl-d-aspartate (NMDA) receptors and $GABA_A$ receptors in the DLPFC for WM in both animals and humans (Auger & Floresco, 2015; Honey et al., 2004; Krystal et al., 2005; Moghaddam & Adams, 1998; Rao et al., 2000; Sawaguchi et al., 1989; Wang et al., 2013). The evidence from these studies suggests the involvement of glutamatergic and GABAergic activities within the DLPFC. Given that glutamate is the primary excitatory neurotransmitter in the brain, whereas GABA is the main inhibitory neurotransmitter, research has shown their crucial role in various cognitive processing. Importantly, they are associated with neural activity measured by functional magnetic resonance imaging (fMRI): glutamate and GABA exhibit significant correlations with stimulus-induced hemodynamic responses across various brain regions including the occipital, sensorimotor and frontal cortex (for a review, see Duncan et al., 2014). Recent neuroimaging studies combining functional magnetic resonance spectroscopy (fMRS) and fMRI have demonstrated that stimulus-induced glutamate increases in visual cortex were positively correlated with stimulus-induced blood-oxygen-level-dependent (BOLD) responses in the visual cortex (Betina Ip et al., 2017, 2019). Other studies have reported a negative relationship between task-evoked BOLD activity and the baseline GABA levels in the anterior cingulate cortex (Northoff et al., 2007) and temporal lobe (Jung et al., 2017). Here, we aim to investigate glutamate and GABA dynamics in the DLPFC during working memory processing in relation to fMRI BOLD signal changes by combining fMRS and fMRI.

MRS is non-invasive, in vivo technique to measure neurometabolites such as glutamate and GABA (Harris et al., 2017). To date, three fMRS studies in healthy individuals have investigated dynamic changes in glutamate and GABA in the DLPFC during WM processing. These studies reported glutamate increases between 2.7% and 3.9% compared with baseline (e.g. passive viewing a fixation) in the DLPFC (voxel size = $15 \times 20 \times 15$ mm^3, 4.5 cm^3) with Point REsolved Spectroscopy (PRESS) sequence at 3 T (Woodcock et al., 2018, 2019). They employed a 2-back WM task (seven task blocks, 64 s each) interleaved with fixation (30 s), totaling approximately 11 min. Conversely, the only GABA-edited (MEGA-PRESS) study in the DLPFC (voxel size = $25 \times 40 \times 30$ mm^3, 30 cm^3) (Michels et al., 2012) failed to show Glx changes in the DLPFC. They had a 10-min fMRS session for resting as the baseline and four fMRS sessions with a delayed match-to-sample WM task (total 40 min). They demonstrated a transient DLPFC GABA increase during the first session relative to the baseline, followed by subsequent GABA decreases in the following sessions. Although these findings provide some clues for the role of neurometabolites in WM processing, the association with task performance and hemodynamic BOLD changes remains poorly understood. Additionally, these studies employed non-task conditions such as fixation and resting as their baselines to detect WM task-induced changes in glutamate and GABA. However, these non-task conditions can modulate the glutamate levels in the DLPFC (Lynn et al., 2018). They demonstrated that the glutamate levels in the DLPFC were less variable and lower during passive visual fixation than other conditions such as relaxed eyes closed or flashing checkerboard. In fMRI studies, it is well-established that an appropriate 'control' task condition is essential, as an uncontrolled baseline (resting or fixation) is known to be inadequate to assess task-specific modulations in BOLD signal changes (Amaro & Barker, 2006). Typically, a 0-back task is used as a control task condition for a 2-back task, as a 0-back requires attention but no WM demand (Miller et al., 2009). Accordingly, in this study, we tested three conditions: 2-back task, 0-back task (control) and baseline (fixation). This was aimed to evaluate task-specific modulations in neurometabolites and BOLD signal changes within the DLPFC.

Here, we combined fMRS with fMRI to evaluate dynamics in neurochemicals, fMRI BOLD signal changes in the DLPFC and task performance during a 2-back WM task. We hypothesised that a 2-back task would increase

Glx levels in the DLPFC compared with the fixation and control conditions in this preliminary study. Furthermore, we hypothesised that these Glx increases would be positively correlated with task-induced BOLD signal changes in the DLPFC during a 2-back task. Simultaneously, we expected that GABA levels in the DLPFC would be decreased during the 2-back task relative to the 0-back and baseline. Finally, we explored the relationship connecting changes in Glx and GABA levels in the DLPFC with individual WM task performance.

2 | MATERIALS AND METHODS

2.1 | Participants

Twelve healthy young participants were recruited (nine females, mean age: 25 ± 2 years). All participants had normal or corrected-to-normal vision. All gave informed consent using a written form, approved by the University of Nottingham ethics committee.

2.2 | Magnetic resonance image (MRI) acquisition

All images and spectra were acquired using General Electric (GE) 3.0T MR scanner (Discovery MR750, GE Healthcare, Milwaukee, Wisconsin) with a 32-channel head coil. Anatomical images were acquired using a T1-weighted inversion recovery spoiled gradient-echo sequence (BRAVO on the GE platform) with 1 mm isotropic voxel size (repetition time [TR] = 7.3 ms, echo time [TE] = 3.0 ms, in-plane resolution 1×1 mm^2, slice thickness = 1 mm, field of view [FOV] = 256×256 mm^2, matrix = 256×256, flip angle = 12°). For the fMRS scan, a $40 \times 25 \times 30$ mm^3 (30 cm^3) voxel of interest (VOI) was positioned in the left DLPFC to cover the Brodmann (BA) area 9 and 46 (Brodmann, 1908). Chemical shift selective saturation (CHESS) was used for water suppression, and non-edited 16 water unsuppressed reference acquisitions were acquired. MEGA-PRESS (Mescher et al., 1998) editing for GABA is a spectral-difference method to isolate GABA and spectra were acquired with an editing pulse applied at 1.9 ppm to detect GABA signal for about 12 min (TR/TE = 2000/68 ms, 160 edited spectra and 160 non-edited spectra, phase cycling = 8). The detailed information of fMRS acquisition can be found in Table S3, following the Minimum Reporting Standards in Magnetic Resonance Spectroscopy checklist, recommendations of experts' consensus (Choi et al., 2021). Functional images were acquired using an echo planar imaging (EPI) sequence (TR/TE = 2000/20 ms, in-plane resolution 3×3 mm^2, slice thickness = 3 mm, FOV = 192×192 mm^2, matrix = 64×64, 40 slices, flip angle = 77°). In total, 240 imaging volumes were acquired.

2.3 | Task and procedure

An *n*-back working memory task was used to activate the DLPFC, where the MRS VOI was placed (Figure 1a). There were three task conditions in fMRS: resting (fixation), 0-back and 2-back (Figure 1b). Participants were asked to stare at a fixation in the first session. In the 0-back task, participants were asked to press the given button when the letter 'X' was presented. During the 2-back task, participants were instructed to press the given button if the letter matched the letter presented two trials before. For each task, the fMRS scan consisted of seven blocks, each interleaved with 8 s of fixation. Each block had 46 trials with each letter displayed for 1500 ms followed by a 500 ms blank screen (12 min per condition, 92 s per block). When the first spectra of fMRS was acquired, the task was manually started. Thus, the task was not synchronised with fMRS acquisition, leaving a 1–2 s gap between the acquisition of the first spectra and the task. In the fMRI session, a total of six blocks of the 0-back task and six blocks of the 2-back task were interleaved. Between task conditions, there was a 4 s fixation block. Within a task block, there were 18 trials for each task condition (0-back and 2-back). A trial started with a 500 ms fixation followed by the presentation of a letter for 1500 ms (36 s per block in fMRI). PsychoPy software (Peirce et al., 2019) was used to display stimuli and to record responses. In the 2-back fMRS session, the total targeted letters were 139, and for the 0-back fMRS session, it was 137. In the fMRI 2-back session, there were 41 target letters, while the fMRI 0-back session had 43 target letters.

2.4 | N-back performance

We quantified working memory performance on the 2-back task using *d* Prime (d') scores. d' is calculated using the formula: d' = norminv (hits/total target trials) − (false alarm/total non-target trials) (Macmillan & Creelman, 1990). Norminv represents the inverse of the standard normal cumulative distribution, false alarm represents the number of non-target trials with a button response. Reaction time (RT) to hits was also calculated. Two participants were excluded from the analyses involving working memory behavioural performance, as a result of a software malfunction that occurred during the data acquisition process.

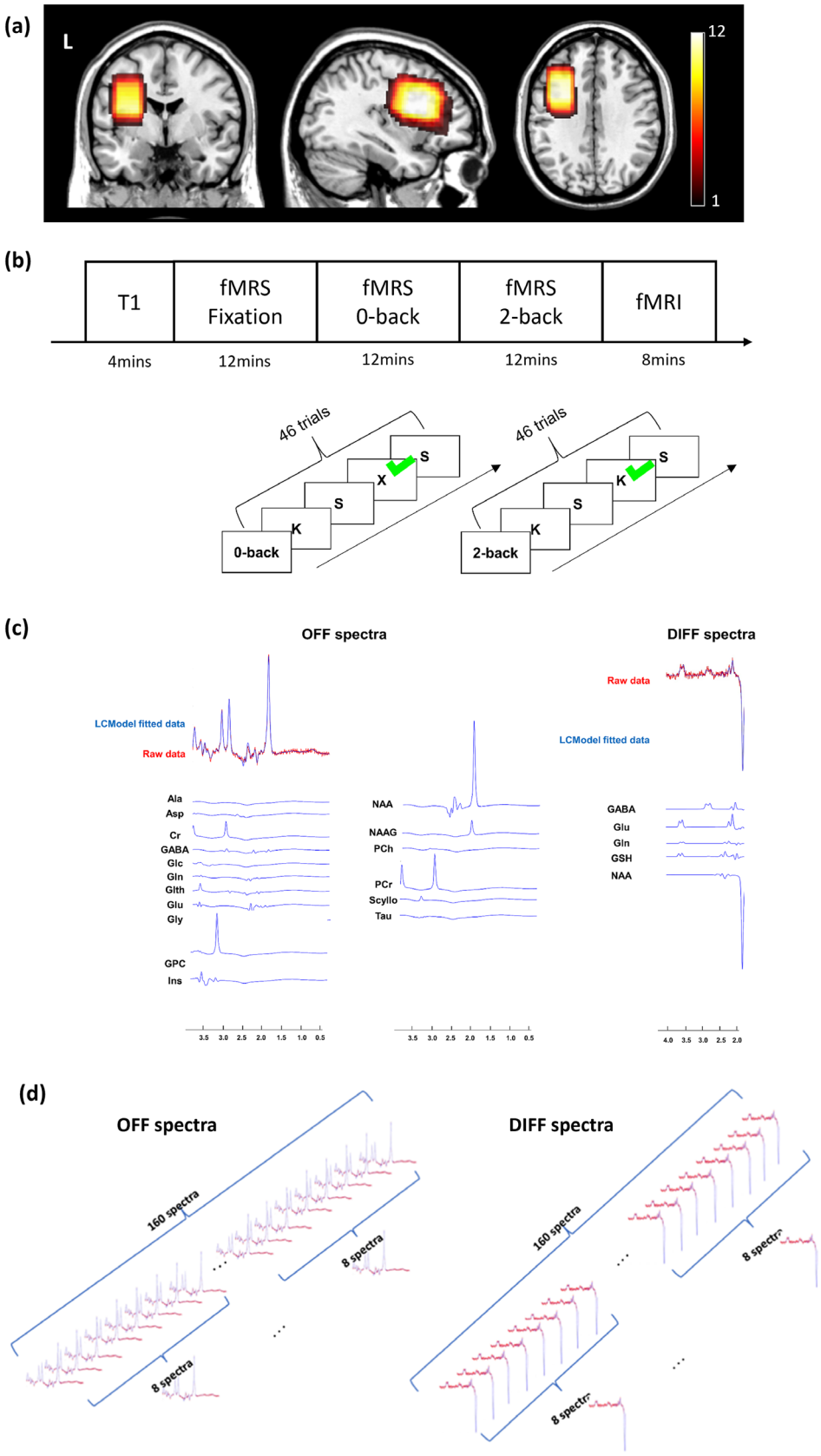

FIGURE 1 (a) Magnetic resonance spectroscopy voxel of interest (MRS VOI) in the left dorsolateral prefrontal cortex (DLPFC). Colour bar represents the overlapping DLPFC VOIs across the participants. (b) Experimental procedure and task. (c) An example MRS spectrum and fitted spectra for each metabolite from DLPFC. Raw data is represented in red colour. Fitted spectra by LCModel are shown in blue colour. (d) A diagram illustrating how eight spectra were averaged in 160 OFF and 160 DIFF spectra.

2.5 | MRS processing and quantification

Prior to fitting, MRS data were pre-processed using an in-house pipeline written in MATLAB (The MathWorks Inc., Natick, MA, USA). Raw data (in GE .p file format) underwent coil-combination and eddy current correction using the unsuppressed water reference. Frequency and phase correction were performed using spectral registration (Near et al., 2015), aligning individual ON and OFF spectra to the mean OFF spectrum. To remove corrupted transients from subject motion, individual spectra were examined for outliers, with individual spectra discarded if the mean square error over the total choline (including phosphocholine, glycerophosphocholine and choline) exceeded ±3 standard deviations from the mean OFF spectrum (Mikkelsen et al., 2017; Waddell et al., 2007). Subsequent to the frequency, phase correction and outlier removal, the aligned spectra were averaged and subjected to subtraction, yielding difference (DIFF) spectra. Line broadening was not applied to the acquired MEGA-PRESS data. Eight individual spectra [32 s] were averaged over blocks for both dynamic DIFF and OFF spectra so that Glx and GABA were measured in 20 time points. The rationale for this approach was to perform an exploratory analysis of dynamic changes in each metabolite during the scanning session, consistent with prior studies (Michels et al., 2012; Woodcock et al., 2018). Spectral quality characteristics are summarised in Table S1. The processed spectra were quantified by LCModel (Provencher, 1993). GABA was measured in DIFF spectra (ON–OFF), and Glx, total N-acetylaspartate (tNAA) and total creatine (tCr, the summation of phosphocreatine plus creatine) were measured in non-edited (OFF) spectra. Metabolites were quantified by referencing to unsuppressed water signal. Glx and GABA measurements less than 50% in Cramer–Rao lower bound (CRLB) were included. The lenient CRLB criterion was applied to avoid biasing low-concentration estimation (Kreis, 2016).

Tissue segmentation was performed to examine partial volume effects over the MRS VOI. T1-weighted images were segmented into grey matter (GM), white matter and cerebrospinal fluid (CSF) using Statistical Parametric Mapping 12 (SPM12). The DLPFC VOI consisted of 34 ± 6% (mean ± standard deviation) of GM, 62 ± 7% of white matter and 4 ± 2% of CSF on average. As neurochemical levels including Glx and GABA are substantially higher in the GM compared with white matter (Jensen et al., 2005; Petroff et al., 1989), we used GM volume as a covariate in the following analyses.

2.6 | fMRI pre-processing and analysis

All anatomical and functional images were pre-processed by the Biomedical Research Centre (BRC pipeline (version 1.5.5) (Mohammadi-Nejad et al., 2019). The pre-processing included slice timing correction, brain extraction, motion correction, normalisation and spatial smoothing with 8 mm full width at half maximum (FWHM). Linear registration using FMRIB's (Oxford Centre for Functional Magnetic Resonance Imaging of the Brain) Linear Image Registration Tool (FLIRT) was employed to the T1 anatomical image for boundary-based registration and to Montreal Neurological Institute (MNI) standard space. Motion correction was performed based on FLIRT and six motion parameters were generated. The segmentation of white matter and CSF was computed by FMRIB's Automated Segmentation Tool (FAST) from T1 anatomical images, and time series data were measured from white matter and CSF to control physiological signal noise. One participant was excluded because of errors in the file.

General linear model (GLM) analysis was performed using SPM12. For individuals, a design matrix was created by modelling 2-back, 0-back and fixation with six motion parameters as regressors. T-contrast images were generated between the 2-back and 0-back (2-back- > 0-back). Second-level analysis was conducted using a random effect model (one-sample *t*-test). A statistical threshold was set at $p < 0.001$ at a voxel level and $p < 0.05$ at a cluster level with at least 50 contiguous voxels after family-wise error (FWE) correction.

Region of interest (ROI) analysis was performed by Marsbar toolbox (http://marsbar.sourceforge.net/). The DLPFC ROI was defined by combining the left Brodmann area (BA9 and BA46) and the averaged MRS VOI across the participants. The mean BOLD signal changes from the DLPFC ROI were extracted for each condition (fixation, 0-back and 2-back).

2.7 | Statistical analysis

The performance (accuracy and RT) of each task was computed and compared through a paired *t*-test.

To explore the dynamic changes of Glx and GABA, we performed a repeated measures ANOVA with condition (fixation, 0-back and 2-back) and time (20 time points) as within-subject factors, accounting for GM volume, the order of the session, sex and age. Because of data quality control, we excluded 5 time points during the fixation condition, 10 during the 0-back condition and 7 during the 2-back condition from the Glx level

analysis. The missing data was replaced with mean Glx values corresponding to the respective time points. There was no missing data on GABA levels across all task conditions.

To examine neurochemical changes in the DLPFC across task conditions (fixation, 0-back and 2-back), we conducted a linear mixed model analysis with the condition as the main factor as well as GM volume, the order of the session, sex and age as covariates in Glx and GABA *Post-hoc* paired *t*-tests were performed for the comparisons between task conditions. False-discovery rate (FDR) correction was applied for multiple comparisons. We reported the results thresholded at $p_{\text{FDR-corrected}} < 0.05$.

Partial correlation analysis was used to examine the relationship between task-induced neurochemical changes found in the linear mixed model, fMRI BOLD signal changes and working memory task performance. GM volume in the voxel, sex and age were included as covariates. FDR correction was applied for multiple comparisons. We reported the results thresholded at $p_{\text{FDR-corrected}} < 0.05$.

3 | RESULTS

3.1 | Behavioural results

Participants' performance on the WM task was compared between 0-back and 2-back conditions during fMRS. The planned paired *t*-test revealed that participants performed better at the 0-back task condition than the 2-back task condition in both accuracy (0-back: 99.69% ± 0.30, 2-back: 89.91% ± 6.40, $t = 4.773$, $p = 0.001$) and RT (0-back: 0.41 s ± 0.04, 2-back: 0.60s ± 0.06, $t = -9.785$, $p < 0.001$). The average of d' was 3.01 ± 0.63. In the fMRI sessions, participants performed better in the 0-back task compared with the 2-back in accuracy (0-back: 99.54% ± 0.65, 2-back: 95.46% ± 5.56, $t = 2.502$, $p = 0.034$) and RT (0-back: 0.45 s ± 0.04, 2-back: 0.53 s ± 0.07, $t = -3.55$, $p = 0.006$).

3.2 | Task modulated neurochemical changes in DLPFC

To examine the task condition and time-related changes in Glx and GABA levels, ANOVA with the task condition (fixation, 0-back and 2-back) and time (20 time points) as within-subject factors revealed a significant main effect of the task condition in Glx ($F_{1,10} = 4.995$, $p = 0.049$) only (Figure 2a). There was no significant effect of the time and the interaction between time and condition in Glx. In addition, there was a significant effect of age ($F_{1,8} = 33.866$, $p < 0.001$) and sex ($F_{1,8} = 7.321$, $p = 0.027$). GABA did not show any significant effects on the task condition and time (Figure 2b). However, age was a significant covariate ($F_{1,8} = 16.338$, $p < 0.001$) and sex was not significant ($F_{1,8} = 1.571$, $p = 0.21$).

To investigate task-modulated effects in Glx and GABA, we conducted a linear mixed model with the task condition (fixation, 0-back and 2-back) as a main factor, accounting for GM volume, the order of session, sex and age as covariates. Glx showed a significant condition effect ($F_{2,191} = 6.226$, $p = 0.002$) (Figure 2c). *Post-hoc* paired *t*-tests revealed that the 2-back task significantly increased Glx levels in the DLPFC compared with the staring fixation ($p = 0.001$). Glx levels during the 0-back task also significantly increased in the DLPFC relative to the fixation ($p = 0.037$). There was no significant difference in Glx level between the 0-back and the 2-back. The age and sex were not significant covariates (ps > 0.483). Unlike Glx, we did not observe the effect of condition in GABA ($F_{2,194} = 0.871$, $p = 0.420$) (Figure 2d). The age and sex were not significant covariates (ps > 0.509).

3.3 | Glx and fMRI BOLD signal change

2-back task-induced significant activation in the bilateral DLPFC, left inferior frontal gyrus, supplementary motor area, superior parietal cortex, intraparietal sulcus and left inferior temporal gyrus (Figure 3a, Table S2). ROI analysis revealed that the 2-back task significantly increased the BOLD signal in the DLPFC compared with the fixation ($t = -1.98$, $p = 0.038$) (Figure 3b).

To examine the relationship between task-modulated metabolites and DLPFC BOLD signal changes, we performed a partial correlation analysis accounting for GM volume, sex and age. This analysis showed that there was a significant linear relationship between individual mean Glx levels and BOLD responses during 2-back task ($r = 0.897$, $p_{FDR\text{-}corrected} = 0.031$) (Figure 3c). In addition, there were significant positive correlations between the fixation Glx levels and both fixation ($r = 0.912$, $p_{FDR\text{-}corrected} = 0.019$) and 2-back BOLD signal changes ($r = 0.885$, $p_{FDR\text{-}corrected} = 0.019$) (Figure S1). There were no significant correlations observed between Glx levels during the 0-back task, GABA and the changes in DLPFC BOLD signals.

3.4 | Glx, BOLD signal changes and working memory performance

A partial correlation analysis investigated the relationship between individual mean Glx levels and d' (2-back

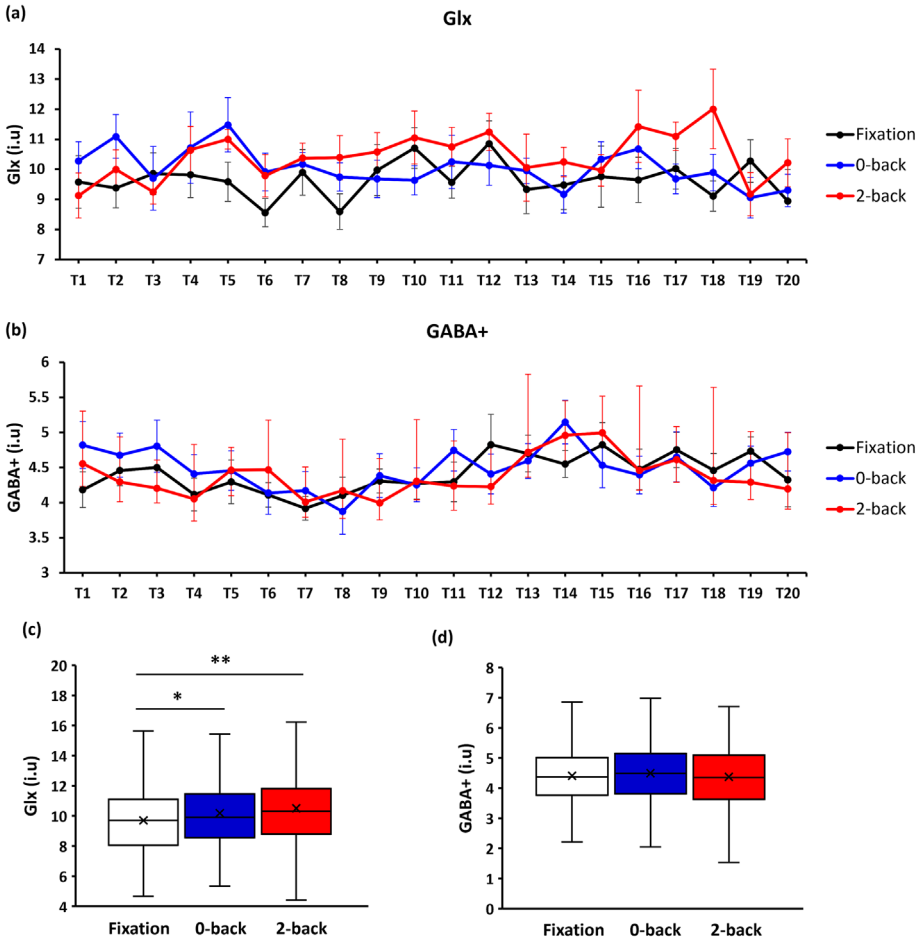

FIGURE 2 Task modulation effects in dorsolateral prefrontal cortex (DLPFC) Glx (glutamate + glutamine) and GABA. (a) The mean of all individual time courses of Glx changes. (b) The mean of all individual time courses of GABA changes. (c) Mean Glx levels for each task condition. (d) Mean GABA levels for each task condition. Error bars represent standard errors. i.u., institutional unit; T, time point. $^{*}p < 0.05$; $^{**}p < 0.01$.

task performance), regressing out GM volume, sex and age. There was a significant and negative correlation between Glx levels and d' ($r = -0.866$, $p_{FDR\text{-}corrected} = 0.031$) (Figure 3d). To investigate the relationship between task-induced BOLD signal changes and d', a partial correlation analysis was performed, accounting for GM volume, sex and age and demonstrated a significant correlation ($r = -0.859$, $p_{FDR\text{-}corrected} = 0.031$) (Figure 3e). GABA did not show any significant relationship with the task performance.

4 | DISCUSSION

Converging evidence has implicated the DLPFC contributions to working memory (Barbey et al., 2013; D'Esposito & Postle, 2015), but the underlying neurochemical mechanisms of the DLPFC are not fully understood. Here, we investigated task-modulated neurometabolite changes in the DLPFC in relation to BOLD signal changes and task performance during working memory processing. Our combined functional MRS with fMRI approach confirmed that the 2-back task increased Glx levels and BOLD signal changes in the DLPFC relative to crosshair. Task-modulated Glx changes were linked to task-induced regional haemodynamic response in the DLPFC. Importantly, the task-modulated Glx levels in the DLFPC were associated with individual task performance and BOLD activation during working memory processing. Our findings, while preliminary due to the small sample size and partially exploratory nature of our study, suggest that task modulation of DLPFC Glx levels may critically underpin working memory processing and performance and highlight that state-of-the-art fMRS at 3 T offers a robust non-invasive, neurometabolic window to brain function.

To our best knowledge, this is the first study to demonstrate that task-modulated Glx changes in the DLPFC were associated with haemodynamic responses to DLPFC activation. This is well in line with cumulative evidence from ultra-high field MRS/MRI studies establishing tight dynamic coupling of glutamate and BOLD increase in visual and motor activation (Bednařík et al., 2015; Betina Ip et al., 2017; Koush et al., 2021; Kurcyus et al., 2018; Martínez-Maestro et al., 2019; Schaller et al., 2014). Glutamate is the major excitatory neurotransmitter in the brain, but MRS-detectable glutamate can be more closely linked to energy metabolism as

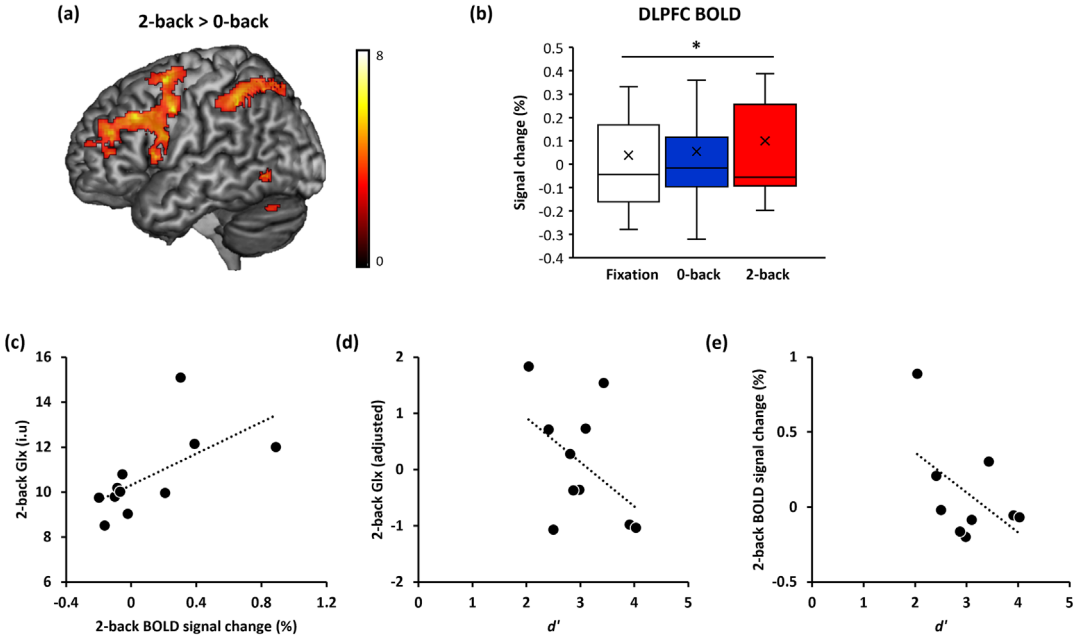

FIGURE 3 (a) Functional magnetic resonance imaging (fMRI) results of the contrast of interest (2-back > 0-back). Colour bar represents Z score. (b) Blood-oxygen-level-dependent (BOLD) signal changes (relative to the baseline) in the dorsolateral prefrontal cortex (DLPFC) across task conditions. (c) Scatterplot showing the positive correlation between Glx (glutamate + glutamine) levels and fMRI BOLD signal changes in the DLPFC during 2-back task condition. (d) Scatterplot showing the negative correlation between DLPFC Glx levels and d' during 2-back task condition. The plotted individual Glx values were accounted for grey matter (GM) value, sex and age. (e) Scatterplot showing the negative correlation between DLPFC BOLD signal changes and d' during a 2-back task condition. Error bars indicate the standard errors. *$p < 0.05$.

glutamate is a key metabolite in the tricarboxylic acid (TCA) cycle and the metabolic Glu pool is substantially larger than the neurotransmitter pool (Chhina et al., 2001; Hyder et al., 2006; Rothman et al., 2003). In the healthy brain, metabolism and neuronal processes are tightly coupled, evidenced by the upregulation of glucose consumption and glutamate-glutamine cycling during task-driven neuronal activation (Rothman et al., 2003; Sibson et al., 1998). Glutamine can be converted to glutamate in the glutamate-glutamine cycling process. Glutamate can be transformed into α-ketoglutarate, a metabolite in the TCA cycle, which is integral to glucose energy metabolism. The connection between hemodynamic responses and TCA activity further supports the idea that the observed changes in coupled Glx/BOLD signals reflect the coordination of task-modulated regional energy metabolism and vasodilation (for a review, see Sonnay et al., 2017). Therefore, the increased Glx levels measured by functional MRS reflect increased glucose metabolism while the extent of possible contribution from excitatory neurotransmission remains unclear.

Glutamate is present in neuronal, glial, and metabolic pools in the brain (Rae, 2014). As MRS measured glutamate is the overall tissue content of glutamate, it is challenging to distinguish whether dynamic changes in glutamate reflect neurotransmitter change or metabolic processes. Previous studies have shown that the glutamate changes related to the metabolic process are slow, about approximately 18 min (Maddock et al., 2016), whereas glutamatergic neuronal transmissions occur in milliseconds and can be measured about a few seconds at 7 T functional MRS (Betina Ip et al., 2017, 2019). Our paradigm is more compatible with the metabolic processes—glucose consumption and glutamate–glutamine cycling (Hyder et al., 2006; Rothman et al., 2003). However, primate studies have repeatedly demonstrated that spatial working memory is associated with increased neural spiking activity in the DLPFC (for a review, see Arnsten, 2009). Our results may reflect an increase in excitatory neural activity along with energy metabolism in the DLPFC during working memory processing (Lea-Carnall et al., 2023). Future studies will be needed to elucidate this issue with event-related functional MRS design at 7 T.

Interestingly, we observed an inverse correlation between working memory performance and 2-back task modulated Glx levels as well as BOLD signal changes during the 2-back task. Individuals with lower Glx levels along with less task-induced BOLD responses during

working memory processing showed better task performance (Figure 3d,e). These results seem to be contrasted with the involvement of the DLPFC in working memory such that DLPFC activation increases are associated with performance improvements (for a review, Just & Carpenter, 1992). However, Rypma and D'Esposito (1999) demonstrated the inverse relationship between DLPFC activation and working memory task performance, showing that the increased DLFPC activity was related to poorer task performance (slower RT). They explained their results with a model of neural efficiency—individuals with better processing efficiency show lower brain activation (Neubauer & Fink, 2009). Haier et al. (1992) have reported that individuals with higher scores on Raven's Advanced Progressive Matrices showed reduced glucose metabolic rate in the DLPFC compared with individuals with lower scores. Consistent with these findings, our results provide a better understanding of the individual variability in task performance and their neurochemistry in the DLPFC during working memory processing, supporting the neural efficiency hypothesis (Neubauer & Fink, 2009; Nussbaumer et al., 2015). Subjects with lower working memory efficiency could require more resources in the DLPFC leading to an increase in Glx levels along with BOLD signal changes.

Although we observed task-related Glx increase during the 2-back task relative to the baseline, by replicating previous findings (Woodcock et al., 2018, 2019), we did not find a significant increase of Glx during the 2-back task compared with the 0-back task. However, we observed a significant increase of Glx during the 0-back task relative to fixation. Lynn et al. (2018) examined the glutamate levels in the DLFPC during different 'task-active' conditions such as passive visual fixation, flashing checkerboard and finger tapping in comparison to a 'non-task-active' condition—eyes closed. They reported that visual fixation generated less variability and lower Glx levels in the DLPFC compared with other task active conditions including flashing checkerboard and finger tapping. In line with these findings, our study found that Glx levels in the DLPFC were elevated during the 0-back condition when contrasted with the fixation. Considering the DLPFC's pivotal role in task-related processes, the extent of attention or executive control appears to influence its engagement (Duncan, 2010). Thus, the elevated Glx levels observed during the 0-back task might be linked to direct attentional processing. Importantly, we showed a progressive increase in Glx levels in the DLPFC corresponding to task conditions, moving from fixation to 0-back and reaching the highest increase during the 2-back condition.

Contrary to our hypothesis, we found no evidence of GABA changes in the DLPFC during working memory processing. Few functional MRS studies have reported task-modulated GABA changes in the motor cortex at 7 T (Chen et al., 2017; Kolasinski et al., 2019) and the DLPFC at 3 T (Michels et al., 2012). These studies showed a reduction of GABA over 20 min during cognitive processing (Kolasinski et al., 2019; Michels et al., 2012). In this study, GABA levels were measured for 12 min, which might not be sufficient to detect GABA changes in a cortical region. A recent study failed to observe GABA changes in the motor cortex with a 6-min motor learning task (Maruyama et al., 2021). Further studies to detect GABA changes during a cognitive condition may require a relatively longer functional MRS session or several repetitive sessions with a task.

This study has several limitations. First, our sample size was relatively and considerably small. Due to COVID, there were many barriers in recruiting participants and then we replaced the scanner after re-opening the MRI centre. Therefore, there might be a risk of overinterpreting the results especially the relationship between metabolic/functional responses and working memory task performance. However, we have replicated previous findings by demonstrating the task-modulated Glx changes in the DLPFC (Woodcock et al., 2018, 2019) and a significant relationship between the Glx changes and BOLD signal changes during a task and cognitive processing (Bednařík et al., 2015; Betina Ip et al., 2017, 2019; Koush et al., 2021; Kurcyus et al., 2018; Martínez-Maestro et al., 2019; Schaller et al., 2014). Second, the order of tasks was fixed in functional MRS sessions. Although we included the order of tasks as a covariate in the analysis, we could not exclude the possibility that they might affect our findings. Third, the different task block durations in fMRS (92 s) and fMRI (36 s) influenced the 2-back task performance (fMRS: 90% accuracy and 0.6 s, fMRI: 95% accuracy and 0.5 s). Despite a positive correlation in the 2-back task accuracy between fMRS and fMRI was positively correlated ($r = 0.85$, $p = 0.002$), this discrepancy might have impacted results. Future studies may explore the utilization of simultaneous fMRI-MRS (Betina Ip et al., 2017) to capture synchronised neuromatabolites and BOLD signal changes during cognitive processing. Fourth, we employed the GABA-edited MEGA-PRESS sequence to measure GABA changes. Although the editing is crucial for the GABA measurements, long echo times make the quantification of metabolite levels susceptible to low signal-to-noise ratio (SNR) and confounds different relaxation times (Choi et al., 2021; Ramadan et al., 2013). Finally, it should be noted that the large size of MRS VOI contained a substantial portion of white matter. This characteristic raises the possibility that metabolite signals originating from the white matter could potentially influence the measurement of Glx in this study.

5 | CONCLUSION

This study presents preliminary findings that offer insight into a potential neurometabolic mechanism related to the DLPFC. We confirm that a prolonged block-design working memory task increases Glx in the DLPFC. Furthermore, we revealed a positive relationship between the neurochemical responses and hemodynamic responses, as evidenced by regional BOLD increases. Notably, the extent of both Glx and BOLD signal increases was inversely associated with working memory performance. Our findings suggest that modulation of glutamate in the DLPFC might hold significance in the context of working memory processing and its performance.

AUTHOR CONTRIBUTIONS

The original design was co-created by JeYoung Jung, Henryk Faas, Ben Babourina-Brooks and Hyerin Oh. Adam Berrington and Ben Babourina-Brooks contributed to MRS analysis. Henryk Faas, JeYoung Jung and Dorothee P Auer contributed to advice on analysis design/plan and data interpretation. The draft was written by Hyerin Oh and JeYoung Jung. All authors reviewed the final version of the draft.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author, J.J.

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REFERENCES

Amaro, E., & Barker, G. J. (2006). Study design in fMRI: Basic principles. *Brain and Cognition*, *60*(3), 220–232. https://doi.org/10.1016/j.bandc.2005.11.009

Arnsten, A. F. T. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. *Nature Reviews Neuroscience*, *10*(6), 410–422. https://doi.org/10.1038/nrn2648

Auger, M. L., & Floresco, S. B. (2015). Prefrontal cortical GABA modulation of spatial reference and working memory. *International Journal of Neuropsychopharmacology*, *18*(2), 1–11. https://doi.org/10.1093/ijnp/pyu013

Baddeley, A. (1992). Working memory. *Science*, *255*(5044), 556–559. https://doi.org/10.1126/science.1736359

Barbey, A. K., Koenigs, M., & Grafman, J. (2013). Dorsolateral prefrontal contributions to human working memory. *Cortex*, *49*(5), 1195–1205. https://doi.org/10.1016/j.cortex.2012.05.022

Bednařík, P., Tkáč, I., Giove, F., DiNuzzo, M., Deelchand, D. K., Emir, U. E., Eberly, L. E., & Mangia, S. (2015). Neurochemical and BOLD responses during neuronal activation measured in the human visual cortex at 7 Tesla. *Journal of Cerebral Blood Flow & Metabolism*, *35*(4), 601–610. https://doi.org/10.1038/jcbfm.2014.233

Betina Ip, I., Berrington, A., Hess, A. T., Parker, A. J., Emir, U. E., & Bridge, H. (2017). Combined fMRI-MRS acquires simultaneous glutamate and BOLD-fMRI signals in the human brain. *NeuroImage*, *155*, 113–119. https://doi.org/10.1016/J.NEUROIMAGE.2017.04.030

Betina Ip, I., Emir, U. E., Parker, A. J., Campbell, J., & Bridge, H. (2019). Comparison of neurochemical and BOLD signal contrast response functions in the human visual cortex. *Journal of Neuroscience*, *39*(40), 7968–7975. https://doi.org/10.1523/JNEUROSCI.3021-18.2019

Brodmann, K. (1908). BeiträgezurhistologischenLokalisationder Grosshirnrinde. VI. Mitteilung: Die Cortexgliederung des Menschen. *Journal of Psychology and Neurology (Leipzig)*, *10*, 231–246.

Chen, C., Sigurdsson, H. P., Pépés, S. E., Auer, D. P., Morris, P. G., Morgan, P. S., Gowland, P. A., & Jackson, S. R. (2017). Activation induced changes in GABA: Functional MRS at 7 T with MEGA-sLASER. *NeuroImage*, *156*, 207–213. https://doi.org/10.1016/J.NEUROIMAGE.2017.05.044

Chhina, N., Kuestermann, E., Halliday, J., Simpson, L. J., Macdonald, I. A., Bachelard, H. S., & Morris, P. G. (2001). Measurement of human tricarboxylic acid cycle rates during visual activation by13C magnetic resonance spectroscopy. *Journal of Neuroscience Research*, *66*(5), 737–746. https://doi.org/10.1002/jnr.10053

Choi, I., Andronesi, O. C., Barker, P., Bogner, W., Edden, R. A. E., Kaiser, L. G., Lee, P., Marjańska, M., Terpstra, M., & Graaf, R. A. (2021). Spectral editing in ^{1}H magnetic resonance spectroscopy: Experts' consensus recommendations. *NMR in Biomedicine*, *34*(5), e4411. https://doi.org/10.1002/nbm.4411

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences*, *7*(9), 415–423. https://doi.org/10.1016/s1364-6613(03)00197-9

D'Esposito, M., & Postle, B. R. (2015). The cognitive neuroscience of working memory. *Annual Review of Psychology*, *66*(1), 115–142. https://doi.org/10.1146/annurev-psych-010814-015031

Duncan, J. (2010). The multiple-demand (MD) system of the primate brain: Mental programs for intelligent behaviour. *Trends in Cognitive Sciences*, *14*(4), 172–179. https://doi.org/10.1016/j.tics.2010.01.004

Duncan, N. W., Wiebking, C., & Northoff, G. (2014). Associations of regional GABA and glutamate with intrinsic and extrinsic neural activity in humans—A review of multimodal imaging studies. *Neuroscience & Biobehavioral Reviews*, *47*, 36–52. https://doi.org/10.1016/j.neubiorev.2014.07.016

Goldman-Rakic, P. S. (1995). Cellular basis of working memory. *Neuron*, *14*(3), 477–485. https://doi.org/10.1016/0896-6273(95)90304-6

Haier, R. J., Siegel, B., Tang, C., Abel, L., & Buchsbaum, M. S. (1992). Intelligence and changes in regional cerebral glucose metabolic rate following learning. *Intelligence*, *16*(3–4), 415–426. https://doi.org/10.1016/0160-2896(92)90018-M

Harris, A. D., Saleh, M. G., & Edden, R. A. (2017). Edited ^{1}H magnetic resonance spectroscopy in vivo: Methods and metabolites. *Magnetic Resonance in Medicine*, *77*, 1377–1389. https://doi.org/10.1002/mrm.26619

Honey, R. A. E., Honey, G. D., O'Loughlin, C., Sharar, S. R., Kumaran, D., Bullmore, E. T., Menon, D. K., Donovan, T., Lupson, V. C., Bisbrown-Chippendale, R., & Fletcher, P. C. (2004). Acute ketamine administration alters the brain responses to executive demands in a verbal working memory task: An fMRI study. *Neuropsychopharmacology*, *29*(6), 1203–1214. https://doi.org/10.1038/sj.npp.1300438

Hyder, F., Patel, A. B., Gjedde, A., Rothman, D. L., Behar, K. L., & Shulman, R. G. (2006). Neuronal–glial glucose oxidation and glutamatergic–GABAergic function. *Journal of Cerebral Blood Flow & Metabolism*, *26*(7), 865–877. https://doi.org/10.1038/sj.jcbfm.9600263

Jensen, J. E., deB. Frederick, B., & Renshaw, P. F. (2005). Grey and white matter GABA level differences in the human brain using two-dimensional, J-resolved spectroscopic imaging. *NMR in Biomedicine*, *18*(8), 570–576. https://doi.org/10.1002/nbm.994

Jung, J., Williams, S. R., Sanaei Nezhad, F., & Lambon Ralph, M. A. (2017). GABA concentrations in the anterior temporal lobe predict human semantic processing. *Scientific Reports*, *7*, 15748. https://doi.org/10.1038/s41598-017-15981-7

Just, M. A., & Carpenter, P. A. (1992). A capacity theory of comprehension: Individual differences in working memory. *Psychological Review*, *99*(1), 122–149. https://doi.org/10.1037/0033-295X.99.1.122

Kolasinski, J., Hinson, E. L., Divanbeighi Zand, A. P., Rizov, A., Emir, U. E., & Stagg, C. J. (2019). The dynamics of cortical GABA in human motor learning. *The Journal of Physiology*, *597*(1), 271–282. https://doi.org/10.1113/JP276626

Koush, Y., de Graaf, R. A., Kupers, R., Dricot, L., Ptito, M., Behar, K. L., Rothman, D. L., & Hyder, F. (2021). Metabolic underpinnings of activated and deactivated cortical areas in human brain. *Journal of Cerebral Blood Flow & Metabolism*, *41*(5), 986–1000. https://doi.org/10.1177/0271678X21989186

Kreis, R. (2016). The trouble with quality filtering based on relative Cramér-Rao lower bounds. *Magnetic Resonance in Medicine*, *75*(1), 15–18. https://doi.org/10.1002/mrm.25568

Krystal, J. H., Abi-Saab, W., Perry, E., D'Souza, D. C., Liu, N., Gueorguieva, R., McDougall, L., Hunsberger, T., Belger, A., Levine, L., & Breier, A. (2005). Preliminary evidence of attenuation of the disruptive effects of the NMDA glutamate receptor antagonist, ketamine, on working memory by pretreatment with the group II metabotropic glutamate receptor agonist, LY354740, in healthy human subjects. *Psychopharmacology*, *179*(1), 303–309. https://doi.org/10.1007/s00213-004-1982-8

Kurcyus, K., Annac, E., Hanning, N. M., Harris, A. D., Oeltzschner, G., Edden, R., & Riedl, V. (2018). Opposite dynamics of GABA and glutamate levels in the occipital cortex during visual processing. *The Journal of Neuroscience*, *38*(46), 9967–9976. https://doi.org/10.1523/JNEUROSCI.1214-18.2018

Lea-Carnall, C. A., El-Deredy, W., Stagg, C. J., Williams, S. R., & Trujillo-Barreto, N. J. (2023). A mean-field model of glutamate and GABA synaptic dynamics for functional MRS. *NeuroImage*, *266*, 119813. https://doi.org/10.1016/j.neuroimage.2022.119813

Linden, D. E. J. (2007). The working memory networks of the human brain. *The Neuroscientist*, *13*(3), 257–267. https://doi.org/10.1177/1073858406298480

Lynn, J., Woodcock, E. A., Anand, C., Khatib, D., & Stanley, J. A. (2018). Differences in steady-state glutamate levels and variability between 'non-task-active' conditions: Evidence from ^{1}H fMRS of the prefrontal cortex. *NeuroImage*, *172*, 554–561. https://doi.org/10.1016/j.neuroimage.2018.01.069

Macmillan, N. A., & Creelman, C. D. (1990). Response bias: Characteristics of detection theory, threshold theory, and "nonparametric" indexes. *Psychological Bulletin*, *107*(3), 401–413. https://doi.org/10.1037/0033-2909.107.3.401

Maddock, R. J., Casazza, G. A., Fernandez, D. H., & Maddock, M. I. (2016). Acute modulation of cortical glutamate and GABA content by physical activity. *The Journal of Neuroscience*, *36*(8), 2449–2457. https://doi.org/10.1523/JNEUROSCI.3455-15.2016

Martínez-Maestro, M., Labadie, C., & Möller, H. E. (2019). Dynamic metabolic changes in human visual cortex in regions with positive and negative blood oxygenation level-dependent response. *Journal of Cerebral Blood Flow & Metabolism*, *39*(11), 2295–2307. https://doi.org/10.1177/0271678X18795426

Maruyama, S., Fukunaga, M., Sugawara, S. K., Hamano, Y. H., Yamamoto, T., & Sadato, N. (2021). Cognitive control affects motor learning through local variations in GABA within the primary motor cortex. *Scientific Reports*, *11*(1), 18566. https://doi.org/10.1038/s41598-021-97974-1

Mescher, M., Merkle, H., Kirsch, J., Garwood, M., & Gruetter, R. (1998). Simultaneousin vivo spectral editing and water suppression. *NMR in Biomedicine*, *11*(6), 266–272. https://doi.org/10.1002/(SICI)1099-1492(199810)11:6<266::AID-NBM530>3.0.CO;2-J

Michels, L., Martin, E., Klaver, P., Edden, R., Zelaya, F., Lythgoe, D., Lüchinger, R., Brandeis, D., & O'Gorman, R. (2012). Frontal GABA levels change during working memory. *PLoS ONE*, *7*(4), e31933. https://doi.org/10.1371/journal.pone.0031933

Mikkelsen, M., Saleh, M. G., Near, J., Chan, K. L., Gong, T., Harris, A. D., Oeltzschner, G., Puts, N., Cecil, K. M., Wilkinson, I. D., & Edden, R. (2017). Frequency and phase correction for multiplexed edited MRS of GABA and glutathione. *Magnetic Resonance in Medicine*, *80*(1), 21–28. https://doi.org/10.1002/mrm.27027

Miller, K. M., Price, C. C., Okun, M. S., Montijo, H., & Bowers, D. (2009). Is the *n*-back task a valid neuropsychological measure for assessing working memory? *Archives of Clinical Neuropsychology*, *24*(7), 711–717. https://doi.org/10.1093/arclin/acp063

Moghaddam, B., & Adams, B. W. (1998). Reversal of phencyclidine effects by a group II metabotropic glutamate receptor agonist in rats. *Science*, *281*(5381), 1349–1352. https://doi.org/10.1126/science.281.5381.1349

Mohammadi-Nejad, A.-R., Pszczolkowski, S., Auer, D., & Sotiropoulos, S. (2019). *Multi-modal neuroimaging pipelines for data preprocessing*. Zenodo.

Near, J., Edden, R., Evans, C. J., Paquin, R., Harris, A., & Jezzard, P. (2015). Frequency and phase drift correction of magnetic resonance spectroscopy data by spectral registration in the time domain. *Magnetic Resonance in Medicine*, *73*(1), 44–50. https://doi.org/10.1002/mrm.25094

Neubauer, A. C., & Fink, A. (2009). Intelligence and neural efficiency. *Neuroscience & Biobehavioral Reviews*, *33*(7), 1004–1023. https://doi.org/10.1016/j.neubiorev.2009.04.001

Northoff, G., Walter, M., Schulte, R. F., Beck, J., Dydak, U., Henning, A., Boeker, H., Grimm, S., & Boesiger, P. (2007). GABA concentrations in the human anterior cingulate cortex predict negative BOLD responses in fMRI. *Nature Neuroscience*, *10*, 1515–1517. https://doi.org/10.1038/nn2001

Nussbaumer, D., Grabner, R. H., & Stern, E. (2015). Neural efficiency in working memory tasks: The impact of task demand. *Intelligence*, *50*, 196–208. https://doi.org/10.1016/j.intell.2015.04.004

Peirce, J., Gray, J. R., Simpson, S., MacAskill, M., Höchenberger, R., Sogo, H., Kastman, E., & Lindeløv, J. K. (2019). PsychoPy2: Experiments in behavior made easy. *Behavior Research Methods*, *51*(1), 195–203. https://doi.org/10.3758/s13428-018-01193-y

Petroff, O. A. C., Spencer, D. D., Alger, J. R., & Prichard, J. W. (1989). High-field proton magnetic resonance spectroscopy of human cerebrum obtained during surgery for epilepsy. *Neurology*, *39*(9), 1197. https://doi.org/10.1212/WNL.39.9.1197

Provencher, S. W. (1993). Estimation of metabolite concentrations from localizedin vivo proton NMR spectra. *Magnetic Resonance in Medicine*, *30*(6), 672–679. https://doi.org/10.1002/mrm.1910300604

Rae, C. D. (2014). A guide to the metabolic pathways and function of metabolites observed in human brain ^{1}H magnetic resonance spectra. *Neurochemical Research*, *39*(1), 1–36. https://doi.org/10.1007/s11064-013-1199-5

Ramadan, S., Lin, A., & Stanwell, P. (2013). Glutamate and glutamine: A review of *in vivo* MRS in the human brain. *NMR in Biomedicine*, *26*(12), 1630–1646. https://doi.org/10.1002/nbm.3045

Rao, S. G., Williams, G. V., & Goldman-Rakic, P. S. (2000). Destruction and creation of spatial tuning by disinhibition: $GABA_A$ blockade of prefrontal cortical neurons engaged by working memory. *The Journal of Neuroscience*, *20*(1), 485–494. https://doi.org/10.1523/JNEUROSCI.20-01-00485.2000

Rothman, D. L., Behar, K. L., Hyder, F., & Shulman, R. G. (2003). In vivo NMR studies of the glutamate neurotransmitter flux and neuroenergetics: Implications for brain function. *Annual Review of Physiology*, *65*(1), 401–427. https://doi.org/10.1146/annurev.physiol.65.092101.142131

Rypma, B., & D'Esposito, M. (1999). The roles of prefrontal brain regions in components of working memory: Effects of memory load and individual differences. *Proceedings of the National Academy of Sciences*, *96*(11), 6558–6563. https://doi.org/10.1073/pnas.96.11.6558

Salazar, R. F., Dotson, N. M., Bressler, S. L., & Gray, C. M. (2012). Content-specific fronto-parietal synchronization during visual working memory. *Science*, *338*(6110), 1097–1100. https://doi.org/10.1126/science.1224000

Sawaguchi, T., Matsumura, M., & Kubota, K. (1989). Delayed response deficits produced by local injection of bicuculline into the dorsolateral prefrontal cortex in Japanese macaque monkeys. *Experimental Brain Research*, *75*(3), 457–469. https://doi.org/10.1007/BF00249897

Schaller, B., Xin, L., O'Brien, K., Magill, A. W., & Gruetter, R. (2014). Are glutamate and lactate increases ubiquitous to physiological activation? A ^{1}H functional MR spectroscopy study during motor activation in human brain at 7 Tesla. *NeuroImage*, *93*, 138–145. https://doi.org/10.1016/j.neuroimage.2014.02.016

Sibson, N. R., Dhankhar, A., Mason, G. F., Rothman, D. L., Behar, K. L., & Shulman, R. G. (1998). Stoichiometric coupling of brain glucose metabolism and glutamatergic neuronal activity. *Proceedings of the National Academy of Sciences*, *95*(1), 316–321. https://doi.org/10.1073/pnas.95.1.316

Sonnay, S., Gruetter, R., & Duarte, J. M. N. (2017). How energy metabolism supports cerebral function: Insights from 13C magnetic resonance studies in vivo. *Frontiers in Neuroscience*, *11*, 288. https://doi.org/10.3389/fnins.2017.00288

Waddell, K. W., Avison, M. J., Joers, J. M., & Gore, J. C. (2007). A practical guide to robust detection of GABA in human brain by J-difference spectroscopy at 3 T using a standard volume coil. *Magnetic Resonance Imaging*, *25*(7), 1032–1038. https://doi.org/10.1016/j.mri.2006.11.026

Wang, M., Yang, Y., Wang, C.-J., Gamo, N. J., Jin, L. E., Mazer, J. A., Morrison, J. H., Wang, X.-J., & Arnsten, A. F. T. (2013). NMDA receptors subserve persistent neuronal firing during working memory in dorsolateral prefrontal cortex. *Neuron*, *77*(4), 736–749. https://doi.org/10.1016/j.neuron.2012.12.032

Woodcock, E. A., Anand, C., Khatib, D., Diwadkar, V. A., & Stanley, J. A. (2018). Working memory modulates glutamate levels in the dorsolateral prefrontal cortex during ^{1}H fMRS. *Frontiers in Psychiatry*, *9*, 66. https://doi.org/10.3389/fpsyt.2018.00066

Woodcock, E. A., Greenwald, M. K., Khatib, D., Diwadkar, V. A., & Stanley, J. A. (2019). Pharmacological stress impairs working memory performance and attenuates dorsolateral prefrontal cortex glutamate modulation. *NeuroImage*, *186*, 437–445. https://doi.org/10.1016/j.neuroimage.2018.11.017

SUPPORTING INFORMATION

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