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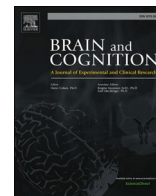
Frontal GABA levels associate with musical rhythm production in healthy aging adults

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ABSTRACT

Changes in neuronal inhibition have been implicated in age-related declines in sensorimotor performance. While indirect evidence suggests that inhibitory mechanisms are also involved in rhythm entrainment, this association has not been tested. Using magnetic resonance spectroscopy, we tested the association between dorsomedial frontal GABA+/H2O concentrations and musical rhythm production in healthy younger (n = 14; 18–35) and older (n = 12; 55–79) adults, hypothesizing that lower GABA+/H2O concentrations would be associated with increased timing error, particularly on more difficult exercises, and intra-individual variability (quantified via mean successive squared difference (MSSD)). Rhythm learning exercises were presented in order of complexity. Linear mixed effects modeling revealed GABA+/H2O-by-exercise number interaction (β = -0.59, p = 0.006) such that participants with lower GABA+/H2O showed greater performance decrement with increasing exercise difficulty. GABA+/H2O trended toward an inverse association with MSSD (β = -0.25, p = 0.089), such that higher GABA+/H2O was associated with lower variability in performance. Older age was associated with increased absolute timing error (β = 0.66, p < 0.001) and greater MSSD (β = 0.86, p = 0.012). However, there was no evidence for age group differences in GABA+/H2O−performance relationships. This finding suggests that GABAergic neuronal inhibition may be important in musical rhythm production across age groups.

1. Introduction

Participation in cognitively-stimulating activities contributes greatly to sustained cognitive and emotional health, as well as overall quality of life and well-being, in older adults (Hertzog et al., 2008; Weziak-Bialowolska et al., 2023). Increasing evidence indicates that music appreciation and practice may be beneficial for older adults: music practice is associated with decreased depressive symptoms, improvements in quality of life, and improvements in cognitive function, although the mechanism of action is not yet well understood (Seinfeld et al., 2013; Sutcliffe et al., 2020; Kim and Yoo, 2019). While music performance into older age is associated with many benefits, the ability to perceive and perform a musical rhythm accurately and consistently

may decline in normal aging. Performance on neuropsychological tests of rhythm perception and auditory attention declines with age (Moehle and Long, 1989), as does performance on behavioral tapping measures testing rhythm production (Thompson et al., 2015). Prior work supports the conclusion that increasing age decreases timing consistency and event tracking, attentional processing, time estimation and temporal predictability (McAuley et al., 2006; Missonnier et al., 2011; Baudouin et al., 2019; Sauvé et al., 2019; Schirmer et al., 2020; Brinkmann et al., 2021). Changes in the ability to learn and perform rhythms may reflect brain aging. However, the neural underpinnings of healthy age-related change in rhythm processing are not fully understood and require further investigation.

Gamma-aminobutyric acid (GABA) is the primary neurotransmitter

responsible for neuronal inhibition in the brain and is critical for motor learning and shaping neuroplastic responses throughout the brain. During normal aging, GABA concentrations throughout the brain decline (Gao et al., 2013; Porges et al., 2017; Cuypers et al., 2018; Simmonite et al., 2019; Chamberlain et al., 2021; Porges et al., 2021). Even when adjusting for age-related brain atrophy, GABA concentrations are associated with cognitive change in aging (Porges et al., 2017), likely due to reduced inhibitory tone and concomitant impairments in inhibition-dependent processes. Consistent with this model, age-related GABA declines have been linked to age-dependent reductions in performance across cognitive domains, including general sensorimotor performance (Maes et al., 2022); however, less is known about the association of age-related GABA changes with other putative inhibition-related sensorimotor processes such as musical rhythm production.

Indirect evidence, predominantly from EEG studies, strongly suggests that GABAergic activity plays a role in rhythm perception and production. GABAergic inhibition regulates spike timing synchronization, fine-tunes coincidence detection, and enhances signal discrimination from noise within the neuronal networks from which cortical network oscillations arise (Koh et al., 2023; Mann and Paulsen, 2007); it has been hypothesized that selective oscillatory activity at the frequency of a musical beat is critical to beat perception (Doelling et al., 2019). In older adults, oscillatory activity is less frequency-selective; this response dedifferentiation in aging may underlie age-related alterations in rhythm processing and loss of temporal precision (Sauvé et al., 2019). Other studies have identified age-related alterations in the distribution of EEG amplitudes elicited during rhythm perception and production (Sauvé et al., 2022), potentially reflecting altered GABA-dependent gating of irrelevant auditory information. In this context, increased timing variability in older age may reflect failed gating of noise in oscillatory patterns (Schirmer et al., 2020).

Recent advances in proton magnetic resonance spectroscopy (MRS) acquisition and analytic techniques permit accurate quantification of GABA in vivo (Puts and Edden, 2012). Proton MRS studies have shown that GABA is associated with age-related changes in sensory perception, including general hearing loss (Gao et al., 2015), decreased speech-in-noise perception (Dobri and Ross, 2021; Harris et al., 2022), and dedifferentiation of neural response to auditory stimuli (Lalwani et al., 2019); however, to our knowledge, only one previous study has examined associations between cerebral metabolite levels and rhythm production (Honda et al., 2023). If GABA levels and rhythm performance are tightly linked, it may have implications both for the use of rhythm assessments in neuropsychological evaluation and for the development of musical activities as potential tools to improve brain aging. Honda et al (Honda et al., 2023) recently examined region-specific associations between right caudate glutamate-glutamine (Glx) levels and musical rhythm processing and production; right caudate Glx was negatively correlated with performance on a production measure of sensorimotor sensitivity to amplitude change, whereas Glx in the dACC was uncorrelated with performance. Note that the MRS sequence and analytic approach used by Honda et al do not allow for the analysis of GABA. Thus, while this study indicates that cerebral metabolite levels are implicated in rhythm production, the specific role of GABAergic inhibition remains unknown, as does the extent to which changes in GABA underlie age-related changes in rhythm production.

The present study builds on this literature by investigating associations between dorsomedial frontal GABA+/H2O and musical rhythm production in healthy younger and older adults (age ranges 18–35 and 55–79); the dorsomedial frontal cortex was chosen due to known age-cognition associations (Porges et al., 2017). We hypothesized that older adults would show lower GABA+/H2O, as well as greater absolute timing error and greater exercise-to-exercise variability (mean successive squared difference) on a novel rhythm production task than younger adults. Additionally, we hypothesized that lower dorsomedial frontal GABA+/H2O concentrations would be associated with greater timing error, with a stronger effect for more-challenging exercises (i.e.,

GABA+/H2O-difficulty interaction). Because prior studies have identified GABA-sensorimotor associations specific to older adults (Maes et al., 2022), we stratified our model of GABA+/H2O-difficulty interaction by age. Finally, we examined the independent and interactive contributions of GABA+/H2O and age group to exercise-to-exercise variability.

2. Methods

2.1. Ethics statement

The Internal Review Board of the University of Florida approved the study protocol and written informed consent form before data collection began (IRB202100384). All participants signed consent forms prior to participation.

2.2. Recruitment

Participants were recruited for a parent study measuring effects of age on neuroimaging and behavioral metrics of rhythm perception and production. Participants were recruited from undergraduate courses, retirement communities, community events, and study flyers posted around the Gainesville, Florida community. Sixty participants were recruited for the full parent study; due to cost, a subset of 30 participants (50 %) were selected for MRS imaging. Participants were selected for imaging based on scanner availability.

2.3. Protocol

Participants attended two contact periods: 1) a telephone screening interview to determine eligibility using the telephone version of the Mini-Mental State Examination (Newkirk et al., 2004); and 2) consent, health eligibility screening, assessment of cognitive function, self-report surveys, MRI scan, and assessment of rhythm learning and performance.

2.4. Inclusion/exclusion criteria

Individuals with any of the following were ineligible to participate in this study: unstable or uncontrolled serious medical conditions (e.g., unstable cancer or poorly-controlled diabetes); physical impairment precluding motor response or lying still for 1 h; inability to walk two blocks without stopping; hearing or vision deficits precluding participation in study procedures, including inability to complete telephone cognitive screening, inability to hear through headphones, or inability to hear clapping during the rhythm task; preexisting dementia or mild cognitive impairment (MCI); neuropsychiatric illness (e.g., schizophrenia or uncontrolled Major Depressive Disorder); other significant neurological disorder (e.g., history of stroke); or currently practicing music more than 30 min weekly. All participants scored 25 or higher on the telephone version of the Mini-Mental State Examination, consistent with grossly intact cognitive performance, and were aged between 18–35 or 55–79. Participants self-categorized as beginner musicians (no prior instrument, vocal, or music composition training) or amateur musicians (no more than 30 min of music practice/week). Full-scale IQ (FSIQ) was estimated with the Test of Premorbid Function (Wechsler, 2011).

2.5. Imaging data acquisition and processing

All participants were imaged on a Siemens Prisma 3 T 64-channel scanner (Siemens Corp., Erfurt, Germany). First, T1-weighted MPRAGE structural images were acquired (sagittal FOV = 256 mm, 256x256 matrix, slice thickness = 1.00 mm, TR/TE = 1230 ms/2.26 ms) for voxel localization and tissue segmentation. MRS HERMES-edited data were subsequently acquired using the following parameters. Acquisitions were edited for GABA and GSH, applying GABA editing pulses at 1.9 ppm and GSH editing pulses at 4.56 ppm per the standard

HERMES editing scheme (Saleh et al., 2016). 320 averages were acquired (80 per subspectrum, interleaved). 4096 data points were collected. Spectral width was 4000 Hz. Scan duration was 10:56. A 30 x 30 x 30 mm^3 frontal voxel was located on the midline, superior to the genu of the corpus callosum. Non-water-suppressed reference data were acquired after HERMES data collection using the same parameters except for number of averages (8). Total scan time was approximately one hour.

Data were analyzed per standard procedure in Osprey 2.5.0 (Oeltzschner et al., 2020), implemented in MATLAB2022a. Data in vendor native format were receiver-coil combined using water reference data. Individual transients were aligned within subspectra using probabilistic spectral registration, averaged, and eddy-current corrected (Klose, 1990); subspectra were then aligned by L2 norm optimization, and GABA- and GSH-edited difference spectra were generated. Difference spectra were fitted using the default vendor-specific HERMES GABA/GSH basis set included in Osprey. Macromolecule and lipid basis functions were modeled using the 3to2MM approach, which has been shown to yield good reproducibility for GABA-edited HERMES data (Hupfeld et al., 2023). Because the detected GABA signal at 3.02 ppm contains co-edited contributions from macromolecules (Edden et al., 2012), it will be referred to henceforth as GABA+ .

As part of the Osprey workflow, the MRS voxel was coregistered to T1-weighted structural images in native space, structural images were segmented, and gray matter/white matter/CSF fractions within the voxel were estimated using SPM12 functions (Penny et al., 2007). Water-referenced and tissue-corrected metabolite concentrations were calculated using the Gasparovic correction to account for disparities in water visibility and relaxation times across tissue types (Gasparovic et al., 2006); because GABA is more highly-concentrated in white matter and tissue correction approach may impact interpretation of age effects (Porges et al., 2017), GABA+/H2O was also quantified using the α-correction and no tissue correction (Harris et al., 2015). Full details on the analytic approach are reported in Supplementary Table S1, which lists consensus-recommended parameters for MRS reporting (Lin et al., 2021).

Quality control was performed by visual inspection of all MR spectra by a trained observer blind to participant group; fit quality (mean relative amplitude residual) and Cr signalnoise ratio (SNR) and linewidth (FWHM) are reported by age group in Supplementary Table S1. Individual GABA + difference spectra for all included participants (N = 26; 14 younger adults) are plotted in Fig. 1. Voxel masks were transformed to MNI152 space and mask overlap calculated among included participants using SPM12 functions; the resulting heatmap was superimposed over a template brain to visualize voxel placement (Fig. 2).
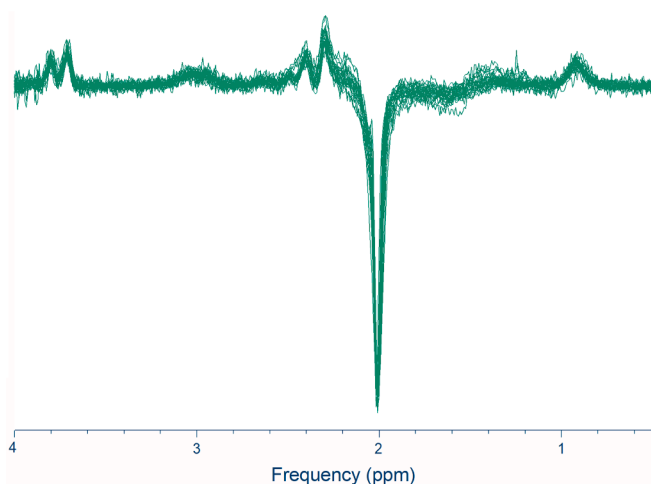

Fig. 1. GABA + difference spectra for all included participants (N = 26).

2.6. Rhythmic musical activity (RMA) task

The Rhythmic Musical Activity task required participants to learn and repeat 30 previously-published rhythm exercises (Starer, 1985). Exercises were selected based upon their relative inclusion of syncopation, i.e., frequency of beats falling on the weak rather than strong metric locations of a written musical time signature. See Figure S1 in supplemental material for a visual depiction of the progressive syncopation of the rhythms.

Each RMA session required participants to learn thirty exercises by mimicking claps demonstrated by a professional musician (AC). The instructor demonstrated each exercise, then asked participants to clap the rhythm they had just heard. A Soundbrenner metronome (Soundbrenner, Berlin, Germany) set to 100 bpm and either a 2/4 or 4/4 time signature established the tempo and meter across all exercises. The metronome was active during demonstrations, practice trials, and performance trials, and was restarted after each trial. All participants completed three learning trials and a performance trial for each exercise. Learning and performance trials were recorded using a Zoom H4 digital audio recorder. These recordings were analyzed for variance from the reference rhythm for timing error using a quantitative assessment described in detail below.

2.7. RMA scoring procedures

The RMA was scored using a novel MATLAB-based tool called RATAT (Rhythm And Timing Assessment Tool), which was developed for the current project by co-author, XV. All audio recordings were uploaded to RATAT, which enabled consistently applied analyses on participant performance trials. Four trained raters scrubbed the audio recording, isolating each performance trial. Given an initial sampling rate of 44,100 Hz, each performance trial was downsampled to achieve a 1 ms period and then digitally bandpass filtered (n = 500) with a passband of 700 to 1,000 Hz, 100 Hz transition bands, and an 80 dB stopband attenuation on either side of the passband. This filter dampened low-frequency noise, talking, and metronome ticks, leaving all claps as the only identifiable spikes. Using scaled median thresholding for spike detection, performance trials were converted into binary vectors, where the first samples above the threshold, signifying claps, were represented with a '1', and all other samples were represented with '0'. RATAT compared these vectors to the expected rhythm through a series of automated algorithms. Filtering and rating were automatically performed by RATAT; the median thresholding multiplier (250–300 times the median) and performance trial isolation were performed manually. The primary outcome measures used in this analysis exercise-by-exercise absolute timing error (absolute difference between recorded responses and ideal responses in ms; further details are provided in supplementary material) and within-person mean square successive difference, a measure of variability between successive exercises (Von Neumann et al., 1941). MSSD was selected as an outcome variable to capture exercise-to-exercise variability associated with exercise-to-exercise nonlinear increase in task difficulty.

2.8. Statistical approach

Participants were excluded from the present analyses if their MR data failed visual inspection due to substantial lipid contamination (N = 1), if their RMA data were lost due to failure of the audio recorder (N = 2), or if they were unwilling to perform the rhythm task (N = 1). After exclusion, 26 of the 30 participants who underwent MRS imaging were retained in final analyses.

All analyses were conducted in R 4.2.2 (R Core Team, 2022), using the R packages rstatix for bivariate analyses (Kassambara, 2023), gtsummary for table generation (Sjoberg et al., 2021), lmerTest for mixed effects modeling (Kuznetsova et al., 2017), robustbase for linear regressions robust to outlier outcome values (Maechler et al., 2022), and
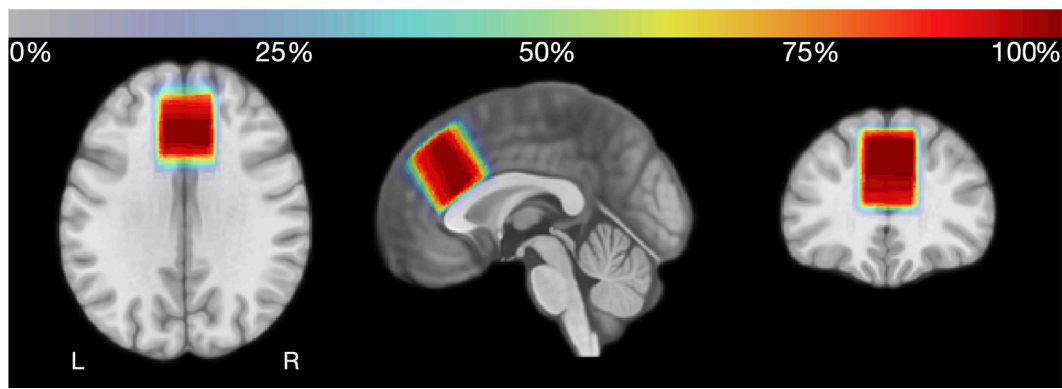
Fig. 2. Voxel location over the dorsomedial frontal region, superior to the genu of the corpus callosum (center of mass MNI 2, 30, 32). Heatmap color represents percent overlap between participants (N = 26).

parameters for coefficient standardization (Lüdecke et al., 2020).

Association between age group (younger/older) and demographic variables (sex, race/ethnicity, musical experience, estimated FSIQ, and years of education) was assessed with independent-samples t-tests for continuous variables and Fisher's exact test for categorical variables.

Association between age group (younger/older) and GABA+/H2O was assessed with an independent-samples *t*-test. To assess association between GABA+/H2O and performance on an exercise-by-exercise basis, a linear mixed effects model was fit to predict absolute timing error. Fixed effects of age group, exercise number (1–30), GABA+/H2O, and exercise number-by-GABA+/H2O interaction were modeled. Random effects terms were modeled for individual participant intercepts; random slopes for exercise were dropped due to low variance explained. The model is reported in full in Equation A1. Pseudo-standardized parameters are reported using Satterthwaite's method for CI estimation. To assess age group differences in exercise-by-GABA+/H2O interaction, follow-up mixed effects models were performed stratified by age group, with exercise number, GABA+/H2O, and exercise number-by-GABA+/H2O interaction as fixed terms and individual participant intercepts as random effects terms. To assess the robustness of findings to GABA+/H2O tissue correction approach, models were repeated using α-corrected GABA+/H2O.

To assess the impact of age and GABA+/H2O on intra-individual variability (IIV), robust linear regressions were fit to predict MSSD from GABA+/H2O and age group. Robust Wald tests were used to assess improvements in model fit with inclusion of an age-GABA+/H2O interaction term. Supplementary robust linear regressions were fit using α-corrected GABA+/H2O, again to assess the robustness of findings to varying tissue correction approaches.

3. Results

3.1. Participants

After exclusion, 26 participants were retained in final analyses. Participant demographic characteristics are reported by group in Table 1. Age groups did not differ on sex (p = 0.65), race (p = 0.69), estimated FSIQ (t(18.6) = -1.23, p = 0.24, d = -0.49), or musical experience (p > 0.9); older adults reported higher mean educational attainment (t(23.5) = 1.89, p = 0.071, d = 0.74).

3.2. Main outcome

There was no bivariate association between GABA+/H2O and age group (t(22.3) = 0.82, p = 0.42, d = -0.33).

Full results of the linear mixed effects model are reported in Table 2. We observed a significant interaction between exercise number and GABA+/H2O (β = -0.59, 95 % CI = −1.01 − −0.17, p = 0.006), such that

Table 1
Participant demographics.

Characteristic	Older Adult, N = 12[1]	Younger Adult, N = 14[1]	p-value[2]
Sex			0.65
Female	10 (83 %)	10 (71 %)	
Male	2 (17 %)	4 (29 %)	
Age	67.75 (5.40)	21.50 (4.38)	< 0.001
Years of Education	16.17 (2.89)	14.00 (2.94)	0.071
Estimated FSIQ[3]	109.17 (12.31)	114.29 (8.17)	0.24
Race/Ethnicity			0.69
Asian	1 (8.3 %)	3 (21 %)	
Latine	1 (8.3 %)	2 (14 %)	
White	10 (83 %)	9 (64 %)	
Musical Experience			> 0.9
Amateur	4 (33 %)	4 (29 %)	
Beginner	8 (67 %)	10 (71 %)	

[1] n (%); Mean (SD).
[2] Independent-samples *t*-test; Fisher's exact test.
[3] Test of Premorbid Function

Table 2
Results of linear mixed models pooled across age groups (N = 26). Outcome variable was absolute timing error (s) for a given exercise.

Characteristic	β	95 % CI[1]	p-value
Exercise	0.91	0.51, 1.32	< 0.001
GABA+/H2O	−0.06	−0.51, 0.30	0.8
Age Group			
Younger Adult	—	—	
Older Adult	0.66	0.37, 0.96	< 0.001
Exercise x GABA+/H2O	−0.59	−1.01, −0.17	0.006

No. Obs. = 778; Sigma = 894; Log-likelihood = -6,391; AIC = 12,796; BIC = 12,828; REMLcrit = 12,782; Residual df = 771.
[1] CI = Confidence Interval.

participants with lower GABA+/H2O performed worse on later exercises (Fig. 3). Additionally, we observed a significant main effect of age group, such that older adults performed worse overall (β = 0.66, 95 % CI = 0.37 − 0.96, p < 0.001), and of exercise number, such that performance was overall worse on later exercises (β = 0.91, 95 % CI = 0.51, 1.32, p < 0.001). The main effect of GABA+/H2O was not significant (β = -0.06, 95 % CI = −0.51, 0.30, p = 0.8). Supplementary models using α-corrected GABA+/H2O and tissue-uncorrected GABA+/H2O are reported in Supplementary Table S2; results were similar to findings from the main model.

When results were stratified by age group, both older (β = -0.62, 95 % CI = −1.22 − −0.003, p = 0.041) and younger (β = -0.60, 95 % CI = −1.17 − −0.02, p = 0.043) participants showed similar exercise number-
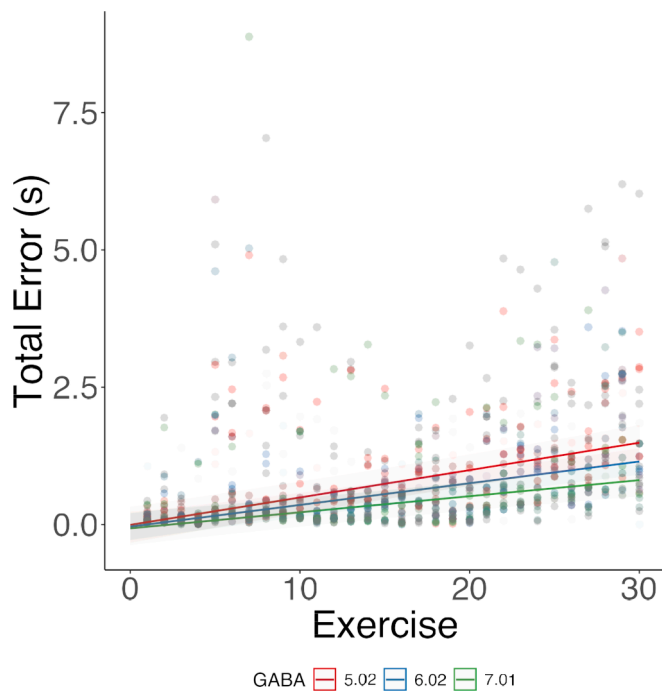
Fig. 3. Association between exercise number and absolute timing error differs by GABA+/H2O concentration (N = 26). On average, later exercises were more difficult to perform; consequently, the interaction suggests that performance decrement with increasing difficulty is GABA-dependent. For ease of visualization, slopes are plotted at mean GABA+/H2O ± 1 SD.

by-GABA+/H2O interaction effects on absolute error. The main effect of exercise was again significant for both groups, such that timing error was greater on later exercises (ps < 0.01); the main effect of GABA+/H2O was not significant for either group (ps > 0.05; Table 3). Again, findings were similar in supplementary models using α-corrected GABA+/H2O and tissue-uncorrected GABA+/H2O (Supplementary Table S3).

Robust linear regression revealed that older adults showed greater MSSD overall (β = 0.86, 95 % CI = 0.21 – 1.50, p = 0.012; Fig. 4). A trend-level inverse association was apparent between GABA+/H2O and MSSD (β = -0.25, 95 % CI = −0.55 – 0.04, p = 0.089), such that higher GABA+/H2O was associated with lower exercise-to-exercise intra-individual variability (i.e., more-consistent performance). Inclusion of age-by-GABA+/H2O interaction term did not improve model fit (W(1) = 0.47, p = 0.49).

4. Discussion

We tested associations between dorsomedial frontal GABA+/H2O levels and rhythm production in older and younger adults. GABA+/H2O concentrations did not differ by age group, and older age was associated

Table 3
Linear mixed effects models of absolute timing error (s) stratified by age group.

Characteristic	Older Adult (N = 12)			Younger Adult (N = 14)		
	β	95 % CI[1]	p-value	β	95 % CI[1]	p-value
Exercise	0.87	0.29, 1.44	0.003	1.06	0.50, 1.62	< 0.001
GABA+/H2O	−0.07	−0.82, 0.68	0.9	−0.07	−0.93, 0.78	0.9
Exercise x GABA+/H2O	−0.62	−1.22, −0.03	0.041	−0.60	−1.17, −0.02	0.043

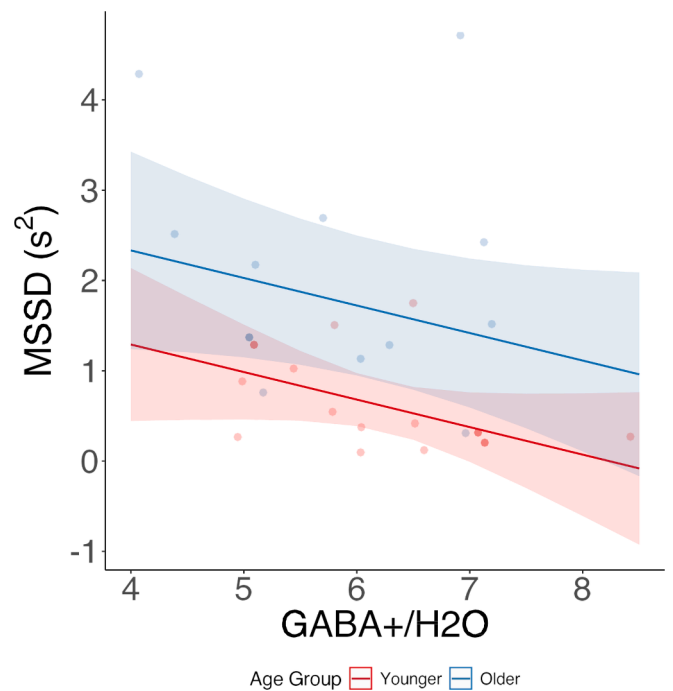[1] CI = Confidence Interval.

Fig. 4. Older adults showed greater mean successive squared difference (a metric of intra-individual variability) overall. At a trend level, greater GABA+/H2O was associated with reduced intra-individual variability, with no evidence for interaction.

with overall greater absolute timing error on a novel rhythm task. GABA+/H2O moderated the association between exercise number (a proxy for task difficulty) and absolute timing error, such that individuals with lower GABA+/H2O showed increasing performance decrement in response to increasing task demands; this interaction was seen in both older and younger adults. Older age and lower GABA+/H2O were independently associated with higher MSSD, an index of exercise-to-exercise intra-individual variability, but there was no evidence for GABA+/H2O −age interaction. These findings indicate that GABAergic inhibition may play a critical role in complex rhythm production and that this role is similar in older and younger adults.

Participants with lower GABA+/H2O showed less ability to adapt to increasing task difficulty: in later exercises, participants were required to adapt responses to shifting time signatures and to incorporate syncopation into reproduced rhythms. The difficulty of executing a rhythmic pattern is linked to a number of pattern features, including tempo (Repp et al., 2002), interval ratio between beats (e.g., binary vs. ternary subdivisions) (Drake, 1993), and syncopation (Keller and Repp, 2005; Fitch and Rosenfeld, 2007; Vuust and Witek, 2014). Increasingly-complex rhythms or patterns that deviate from the predicted rhythm are typically more difficult to encode, recall, and reproduce (Iannarilli et al., 2013). Consequently, moderation by GABA+/H2O may reflect increasing dependence upon precise timekeeping mechanisms as complexity increases. Because the RMA task was developed from standardized musical training exercises, the increasing task demands likely reflected variations in real-world task demands encountered during music processing or musical training, increasing the ecological validity and applicability of our findings.

The trend toward inverse association between GABA+/H2O and MSSD is consistent with existing models of rhythm entrainment. Intra-individual variability in timing during rhythm performance may reflect neural noise interfering with internal timekeeping mechanisms (MacDonald et al., 2006). Because oscillatory entrainment emerges from interactions between coupled excitatory and inhibitory neuronal sub-populations (Large et al., 2015), as well as shunting inhibition by tonic

GABA current (Koh et al., 2023), entrainment deficits may emerge from failures to inhibit irrelevant or competing neuronal firing, leading to instability in oscillatory activity. Consequently, reduced GABAergic inhibitory activity and subsequent failure to maintain an entrained rhythm may drive irregular deviations from the beat. Furthermore, because MSSD reflects exercise-to-exercise variability, increased MSSD may additionally reflect failure to adapt to sudden increases in task difficulty (i.e., inability to rapidly and precisely encode and reproduce a more-complex rhythmic structure).

Within our sample, dorsomedial frontal GABA+/H2O concentrations did not differ by age group. While age-related changes in GABA concentrations and GABAergic function have been widely reported in animal and human models (Rozycka and Liguz-Lecznar, 2017), some studies have not reported age-related declines (Cuypers et al., 2021); because our older adult participants were relatively young (with a mean age of 68 years) and were screened for grossly intact cognition, our sample may have experienced comparatively little age-related physiological change (Britton et al., 2023). Given reported effect sizes in the literature (Rowland et al., 2016), our selection criteria, and our small sample size, it is therefore unsurprising that we did not detect age group differences.

Older adults showed greater absolute timing error and intra-individual variability in timing error even when adjusting for GABA+/H2O; no evidence was seen for effect modification by age. This suggests that the effects of GABA and aging on rhythm production are generally dissociable, at least among cognitively-intact adults. In other words, non-GABAergic aging-related mechanisms may underlie deficits in rhythm production in older adults. General cognitive aging, psychomotor slowing, and structural and functional alterations within the striato-thalamo-cortical circuit have all been linked to age-related changes in timing-related tasks in older adults (Bartholomew et al., 2015; Turgeon et al., 2011; Wild-Wall et al., 2008). Increased intra-individual performance variability in rhythm generation, specifically, is commonly reported in older adults (Schirmer et al., 2020; Gallego Hiroyasu and Yotsumoto, 2021) and has been linked to age-related decline in structural brain integrity (Schirmer et al., 2020). These non-GABAergic mechanisms may potentially explain the age effects observed in our participants.

Participants in the present study had limited or no prior musical training. While it is unclear to what extent interventions can improve neural oscillator entrainment and associated rhythm production abilities, results from observational studies are promising. The neural substrates of rhythm perception and production are believed to be altered by musical training (Grahn and Rowe, 2009). Furthermore, trained musicians show improved oscillatory entrainment to musical rhythms (Doelling and Poeppel, 2015), which may underlie improved rhythm perception and production (Matthews et al., 2016; Slater et al., 2018). Musical training in childhood reduces timing error on tapping tasks (Slater et al., 2013), which may represent refinement of top-down processes regulating induced oscillatory activity (Trainor et al., 2009). However, the plasticity of GABAergic inhibitory activity in response to behavioral intervention remains to be studied. Additionally, it is plausible that pharmacological modulation of GABA would impact rhythm performance by disrupting oscillatory entrainment; this effect remains for further study. If rhythm training can increase brain GABAergic function, it may be a viable intervention to address some aspects of brain aging (Porges et al., 2017); thus our findings may provide a novel explanation for the positive impact of musical practice on cognitive performance in older adults, as well as pointing the way to more targeted interventions.

4.1. Limitations

The present study had several limitations. First, our sample was relatively small; thus we were underpowered to detect small group differences in GABA+/H2O or age differences in the effect of GABA+/ H2O on MMSD. However, interactive effects of GABA+/H2O and exercise number on absolute timing error were similar in magnitude when models were stratified by age group, suggesting that age group differences in this association are unlikely. Second, to limit participant burden and time in scanner, we measured GABA+/H2O only in the dorsomedial frontal region, changes in which have been linked to age-related cognitive decline (Porges et al., 2017); however, rhythm perception and production recruits a network of regions implicated in temporal encoding and prediction, prominently including the thalamus, basal ganglia, cerebellum, and supplementary motor area (Grahn, 2012; Grahn and Brett, 2007). Due to varying task demands across this network, GABA-rhythm associations may vary regionally. Third, increasing exercise difficulty may not fully reflect the changes in task demand associated with individual exercises. Future studies might assess changes in time-defining elements (e.g., beat subdivision and meter) individually to further characterize the impact of inhibitory GABAergic system function on ability to respond dynamically to changing rhythm task demands. Fourth, although all participants had grossly intact hearing, subtle loss of hearing acuity may have impacted performance in older adults. Finally, because easier exercises preceded more-difficult exercises, the effect of exercise number on error may reflect fatigue as well as task difficulty.

In conclusion, frontal GABA+/H2O concentrations moderate the association between exercise difficulty and performance on a novel measure of musical rhythm production. Additionally, frontal GABA+/H2O was associated with increased exercise-to-exercise intra-individual variability, consistent with inhibition failures in neuronal networks driving oscillatory rhythm entrainment. The present study lays the groundwork for further research directly testing the association between GABA levels and neural indices of rhythm production (e.g., selective oscillatory activity at the frequency of the beat).

CRediT authorship contribution statement

Mark K. Britton: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Aaron Colverson:** Writing – original draft, Methodology, Investigation, Conceptualization. **Ronald A. Cohen:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Xavier Velez:** Writing – original draft, Software, Methodology. **Damon G. Lamb:** Writing – review & editing, Supervision, Methodology. **Eric C. Porges:** Writing – review & editing, Supervision, Methodology. **John B. Williamson:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bandc.2024.106230.

Data availability

Data and code are freely available in the associated OSF repository.

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