Neuroscience

# Reevaluating the Neural Noise Hypothesis in Dyslexia: Insights from EEG and 7T MRS Biomarkers

Reviewed Preprint
v1 • September 5, 2024
Not revised

**Agnieszka Glica, Katarzyna Wasilewska, Julia Jurkowska, Jarosław Żygierewicz, Bartosz Kossowski, Katarzyna Jednoróg**

Laboratory of Language Neurobiology, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Pasteur 3 Street, 02-093 Warsaw, Poland • Faculty of Physics, University of Warsaw, Pasteur 5 Street, 02-093 Warsaw, Poland • Laboratory of Brain Imaging, Nencki Institute of Experimental Biology, Polish Academy of Sciences, Pasteur 3 Street, 02-093 Warsaw, Poland



## Abstract

The neural noise hypothesis of dyslexia posits an imbalance between excitatory and inhibitory (E/I) brain activity as an underlying mechanism of reading difficulties. This study provides the first direct test of this hypothesis using both indirect EEG power spectrum measures in 120 Polish adolescents and young adults (60 with dyslexia, 60 controls) and direct glutamate (Glu) and gamma-aminobutyric acid (GABA) concentrations from magnetic resonance spectroscopy (MRS) at 7T MRI scanner in half of the sample. Our results, supported by Bayesian statistics, show no evidence of E/I balance differences between groups, challenging the hypothesis that cortical hyperexcitability underlies dyslexia. These findings suggest alternative mechanisms must be explored and highlight the need for further research into the E/I balance and its role in neurodevelopmental disorders.

### eLife assessment

The authors combined neurophysiological (electroencephalography [EEG]) and neurochemical (magnetic resonance spectroscopy [MRS]) measures to empirically evaluate the neural noise hypothesis of developmental dyslexia. Their results are **solid**, supported by consistent findings from the two complementary methodologies and Bayesian statistics. Additional analyses, particularly on the neurochemical measures, are necessary to further substantiate the results. This study is **useful** for understanding the neural mechanisms of dyslexia and neural development in general.

https://doi.org/10.7554/eLife.99920.1.sa3

## Introduction

According to the neural noise hypothesis of dyslexia, reading difficulties stem from an imbalance between excitatory and inhibitory (E/I) neural activity (Hancock et al., 2017). The hypothesis predicts increased cortical excitation leading to more variable and less synchronous neural firing. This instability supposedly results in disrupted sensory representations and impedes phonological awareness and multisensory integration skills, crucial for learning to read (Hancock et al., 2017). Yet, studies testing this hypothesis are lacking.

The non-invasive measurement of the E/I balance can be derived through assessment of glutamate (Glu) and gamma-aminobutyric acid (GABA) neurotransmitters concentration via magnetic resonance spectroscopy (MRS) (Finkelman et al., 2022) or through global, indirect estimations from the electroencephalography (EEG) signal (Ahmad et al., 2022).

Direct measurements of Glu and GABA yielded conflicting findings. Higher Glu concentrations in the midline occipital cortex correlated with poorer reading performance in children (Del Tufo et al., 2018; Pugh et al., 2014), while elevated Glu levels in the anterior cingulate cortex (ACC) corresponded to greater phonological skills (Lebel et al., 2016). Elevated GABA in the left inferior frontal gyrus was linked to reduced verbal fluency in adults (Nakai and Okanoya, 2016), and increased GABA in the midline occipital cortex in children was associated with slower reaction times in a linguistic task (Del Tufo et al., 2018). However, notable null findings exist regarding dyslexia status and Glu levels in the ACC among children (Horowitz-Kraus et al., 2018) as well as Glu and GABA levels in the visual and temporo-parietal cortices in both children and adults (Kossowski et al., 2019).

Both beta (~13-28 Hz) and gamma (> 30 Hz) oscillations may serve as E/I balance indicators (Ahmad et al., 2022), as greater GABA-ergic activity has been associated with greater beta power (Jensen et al., 2005; Porjesz et al., 2002) and gamma power or peak frequency (Brunel and Wang, 2003; Chen et al., 2017). Resting-state analyses often reported nonsignificant beta power associations with dyslexia (Babiloni et al., 2012; Fraga González et al., 2018; Xue et al., 2020), however, one study indicated lower beta power in dyslexic compared to control boys (Fein et al., 1986). Mixed results were also observed during tasks. One study found decreased beta power in the dyslexic group (Spironelli et al., 2008), while the other increased beta power relative to the control group (Rippon and Brunswick, 2000). Insignificant relationship between resting gamma power and dyslexia was reported (Babiloni et al., 2012; Lasnick et al., 2023). When analyzing auditory steady-state responses, the dyslexic group had a lower gamma peak frequency, while no significant differences in gamma power were observed (Rufener and Zaehle, 2021). Essentially, the majority of studies in dyslexia examining gamma frequencies evaluated cortical entrainment to auditory stimuli (Lehongre et al., 2011; Marchesotti et al., 2020; Van Hirtum et al., 2019). Therefore, the results from these tasks do not provide direct evidence of differences in either gamma power or peak frequency between the dyslexic and control groups.

The EEG signal comprises both oscillatory, periodic activity, and aperiodic activity, characterized by a gradual decrease in power as frequencies rise (1/f signal) (Donoghue et al., 2020). Recently recognized as a biomarker of E/I balance, a lower exponent of signal decay (flatter slope) indicates a greater dominance of excitation over inhibition in the brain, as shown by the simulation models of local field potentials, ratio of AMPA/$GABA_a$ synapses in the rat hippocampus (Gao et al., 2017) and recordings under propofol or ketamine in macaques and humans (Gao et al., 2017; Waschke et al., 2021). However, there are also pharmacological studies providing mixed results (Colombo et al., 2019; Salvatore et al., 2024). Nonetheless, the 1/f signal has shown associations with various conditions putatively characterized by changes in E/I balance, such as early development in infancy (Schaworonkow and Voytek, 2021), healthy aging (Voytek et al., 2015) and

neurodevelopmental disorders like ADHD (Ostlund et al., 2021), autism spectrum disorder (Manyukhina et al., 2022) or schizophrenia (Molina et al., 2020). Despite its potential relevance, the evaluation of the 1/f signal in dyslexia remains limited to one study, revealing flatter slopes among dyslexic compared to control participants at rest (Turri et al., 2023), thereby lending support to the notion of neural noise in dyslexia.

Here, we examined both indirect (1/f signal, beta, and gamma oscillations during both rest and a spoken language task) and direct (Glu and GABA) biomarkers of E/I balance in participants with dyslexia and age-matched controls. The neural noise hypothesis predicts flatter slopes of 1/f signal, decreased beta and gamma power, and higher Glu concentrations in the dyslexic group. Furthermore, we tested the relationships between different E/I measures. Flatter slopes of 1/f signal should be related to higher Glu level, while enhanced beta and gamma power to increased GABA level.

# Results

## No evidence for group differences in the EEG E/I biomarkers

We recruited 120 Polish adolescents and young adults – 60 with dyslexia diagnosis and 60 controls matched in sex, age, and family socio-economic status. The dyslexic group scored lower in all reading and reading-related tasks and higher in the Polish version of the Adult Reading History Questionnaire (ARHQ-PL) (Bogdanowicz et al., 2015),where a higher score indicates a higher risk of dyslexia (see Table S1 in the Supplementary Material). Although all participants were within the intellectual norm, the dyslexic group scored lower on the IQ scale (including nonverbal subscale only) than the control group. However, the Bayesian statistics did not provide evidence for the difference between groups in the nonverbal IQ.

We analyzed the aperiodic (exponent and offset) components of the EEG signal at rest and during a spoken language task, where participants listened to a sentence and had to indicate its veracity. Due to a technical error, the signal from one person (a female from the dyslexic group) was not recorded during most of the language task and was excluded from the analyses. Hence, the results are provided for 119 participants – 59 in the dyslexic and 60 in the control group.

First, aperiodic parameter values were averaged across all electrodes and compared between groups (dyslexic, control) and conditions (resting state, language task) using a 2×2 repeated measures ANOVA. Age negatively correlated both with the exponent ($r$ = -.27, $p$ = .003, $BF_{10}$ = 7.96) and offset ($r$ = -.40, $p$ < .001, $BF_{10}$ = 3174.29) in line with previous investigations (Cellier et al., 2021; McSweeney et al., 2021; Schaworonkow and Voytek, 2021; Voytek et al., 2015), therefore we included age as a covariate. Post-hoc tests are reported with Bonferroni corrected $p$-values.

For the mean exponent, we found a significant effect of age ($F$(1,116) = 8.90, $p$ = .003, $\eta^2_p$ = .071, $BF_{incl}$ = 10.47), while the effects of condition ($F$(1,116) = 2.32, $p$ = .131, $\eta^2_p$ = .020, $BF_{incl}$ = 0.39) and group ($F$(1,116) = 0.08, $p$ = .779, $\eta^2_p$ = .001, $BF_{incl}$ = 0.40) were not significant and Bayes Factor did not provide evidence for either inclusion or exclusion. Interaction between group and condition ($F$(1,116) = 0.16, $p$ = .689, $\eta^2_p$ = .001, $BF_{incl}$ = 0.21) was not significant and Bayes Factor indicated against including it in the model.

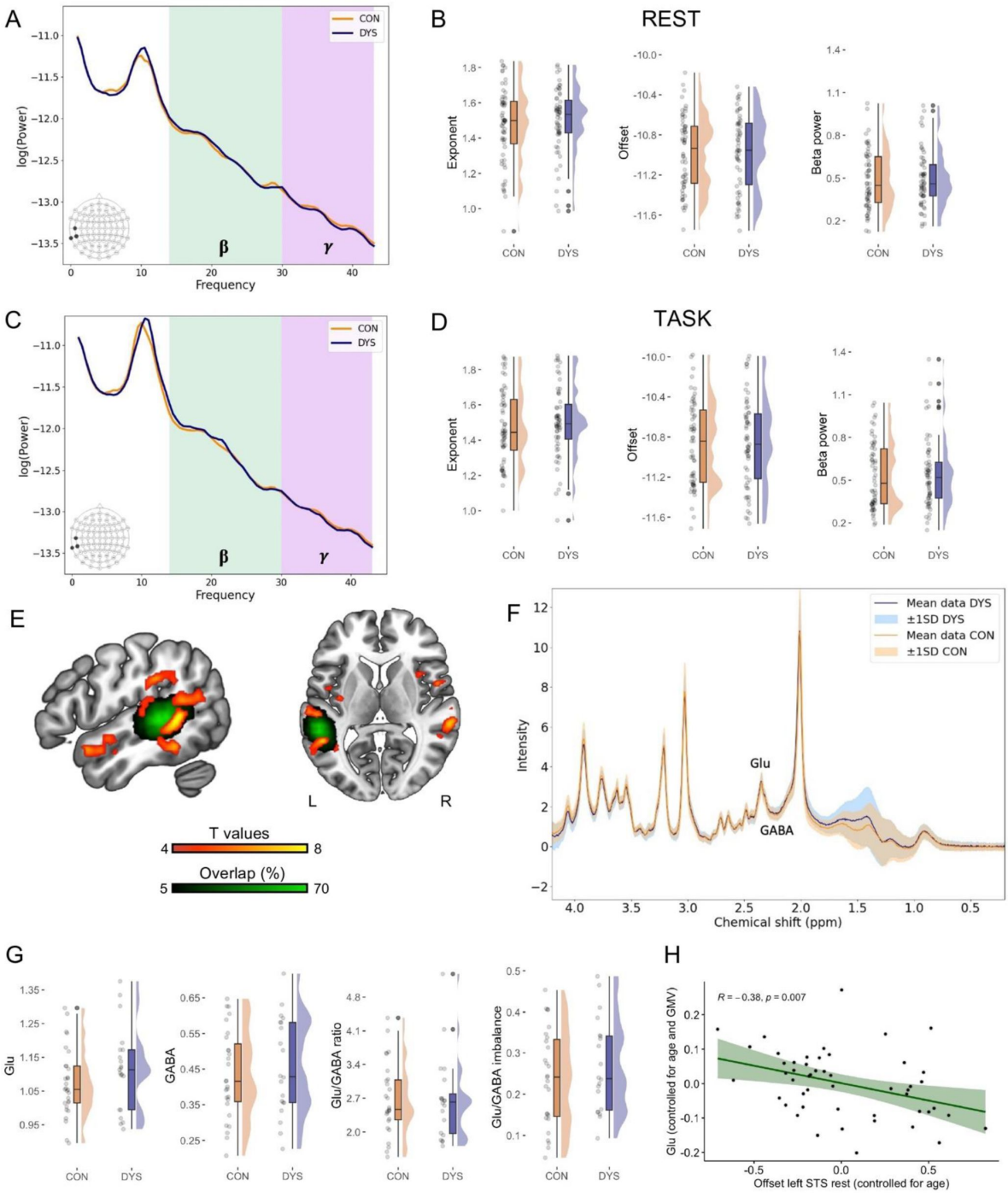
For the mean offset, we found significant effects of age ($F$(1,116) = 22.57, $p$ < .001, $\eta^2_p$ = .163, $BF_{incl}$ = 1762.19) and condition ($F$(1,116) = 23.04, $p$ < .001, $\eta^2_p$ = .166, $BF_{incl}$ > 10000) with post-hoc comparison indicating that the offset was lower in the resting state condition ($M$ = -10.80, $SD$ = 0.21) than in the language task ($M$ = -10.67, $SD$ = 0.26, $p_{corr}$ < .001). The effect of group ($F$(1,116) = 0.00, $p$ = .964, $\eta^2_p$ = .000, $BF_{incl}$ = 0.54) was not significant while Bayes Factor did not provide

evidence for either inclusion or exclusion. Interaction between group and condition was not significant ($F(1,116) = 0.07$, $p = .795$, $\eta^2_p = .001$, $BF_{incl} = 0.22$) and Bayes Factor indicated against including it in the model.

Next, we restricted analyses to language regions and averaged exponent and offset values from the frontal electrodes corresponding to the left (F7, FT7, FC5) and right inferior frontal gyrus (F8, FT8, FC6), as well as temporal electrodes, corresponding to the left (T7, TP7, TP9) and right superior temporal sulcus, STS (T8, TP8, TP10)(Giacometti et al., 2014)(Scrivener and Reader, 2022). A 2×2×2×2 (group, condition, hemisphere, region) repeated measures ANOVA with age as a covariate was applied. Power spectra from the left STS at rest and during the language task are presented in **Figure 1A** and **C**, while the results for the exponent, offset, and beta power are presented in **Figure 1B** and **D**.

For the exponent, there were significant effects of age ($F(1,116) = 14.00$, $p < .001$, $\eta^2_p = .108$, $BF_{incl} = 11.46$) and condition $F(1,116) = 4.06$, $p = .046$, $\eta^2_p = .034$, $BF_{incl} = 1.88$), however, Bayesian statistics did not provide evidence for either including or excluding the condition factor. Furthermore, post-hoc comparisons did not reveal significant differences between the exponent at rest ($M = 1.51$, $SD = 0.17$) and during the language task ($M = 1.51$, $SD = 0.18$, $p_{corr} = .546$). There was also a significant interaction between region and group, although Bayes Factor indicated against including it in the model ($F(1,116) = 4.44$, $p = .037$, $\eta^2_p = .037$, $BF_{incl} = 0.25$). Post-hoc comparisons indicated that the exponent was higher in the frontal than in the temporal region both in the dyslexic ($M_{frontal} = 1.54$, $SD_{frontal} = 0.15$, $M_{temporal} = 1.49$, $SD_{temporal} = 0.18$, $p_{corr} < .001$) and in the control group ($M_{frontal} = 1.54$, $SD_{frontal} = 0.17$, $M_{temporal} = 1.46$, $SD_{temporal} = 0.20$, $p_{corr} < .001$). The difference between groups was not significant either in the frontal ($p_{corr} = .858$) or temporal region ($p_{corr} = .441$). The effects of region ($F(1,116) = 1.17$, $p = .282$, $\eta^2_p = .010$, $BF_{incl} > 10000$) and hemisphere ($F(1,116) = 1.17$, $p = .282$, $\eta^2_p = .010$, $BF_{incl} = 12.48$) were not significant, although Bayesian statistics indicated in favor of including them in the model. Furthermore, the interactions between condition and group ($F(1,116) = 0.18$, $p = .673$, $\eta^2_p = .002$, $BF_{incl} = 3.70$), and between region, hemisphere, and condition ($F(1,116) = 0.11$, $p = .747$, $\eta^2_p = .001$, $BF_{incl} = 7.83$) were not significant, however Bayesian statistics indicated in favor of including these interactions in the model. The effect of group ($F(1,116) = 0.12$, $p = .733$, $\eta^2_p = .001$, $BF_{incl} = 1.19$) was not significant, while Bayesian statistics did not provide evidence for either inclusion or exclusion. Any other interactions were not significant and Bayes Factor indicated against including them in the model.

In the case of offset, there were significant effects of condition ($F(1,116) = 20.88$, $p < .001$, $\eta^2_p = .153$, $BF_{incl} > 10000$) and region ($F(1,116) = 6.18$, $p = .014$, $\eta^2_p = .051$, $BF_{incl} > 10000$). For the main effect of condition, post-hoc comparison indicated that the offset was lower in the resting state condition ($M = -10.88$, $SD = 0.33$) than in the language task ($M = -10.76$, $SD = 0.38$, $p_{corr} < .001$), while for the main effect of region, post-hoc comparison indicated that the offset was lower in the temporal ($M = -10.94$, $SD = 0.37$) as compared to the frontal region ($M = -10.69$, $SD = 0.34$, $p_{corr} < .001$). There was also a significant effect of age ($F(1,116) = 20.84$, $p < .001$, $\eta^2_p = .152$, $BF_{incl} = 0.23$) and interaction between condition and hemisphere, ($F(1,116) = 4.35$, $p = .039$, $\eta^2_p = .036$, $BF_{incl} = 0.21$), although Bayes Factor indicated against including these factors in the model. Post-hoc comparisons for the condition*hemisphere interaction indicated that the offset was lower in the resting state condition than in the language task both in the left ($M_{rest} = -10.85$, $SD_{rest} = 0.34$, $M_{task} = -10.73$, $SD_{task} = 0.40$, $p_{corr} < .001$) and in the right hemisphere ($M_{rest} = -10.91$, $SD_{rest} = 0.31$, $M_{task} = -10.79$, $SD_{task} = 0.37$, $p_{corr} < .001$) and that the offset was lower in the right as compared to the left hemisphere both at rest ($p_{corr} < .001$) and during the language task ($p_{corr} < .001$). The interactions between region and condition ($F(1,116) = 1.76$, $p = .187$, $\eta^2_p = .015$, $BF_{incl} > 10000$), hemisphere and group ($F(1,116) = 1.58$, $p = .211$, $\eta^2_p = .013$, $BF_{incl} = 1595.18$), region and group ($F(1,116) = 0.27$, $p = .605$, $\eta^2_p = .002$, $BF_{incl} = 9.32$), as well as between region, condition, and group ($F(1,116) = 0.21$, $p = .651$, $\eta^2_p = .002$, $BF_{incl} = 2867.18$) were not significant, although Bayesian statistics indicated in favor of including them in the model. The effect of group ($F(1,116) = 0.18$, $p = .673$, $\eta^2_p = .002$, $BF_{incl} < 0.00001$) was not




## Figure 1.

Overview of the main results obtained in the study. **(A)** Power spectral densities averaged across 3 electrodes (T7, TP7, TP9) corresponding to the left superior temporal sulcus (STS) separately for dyslexic (DYS) and control (CON) groups at rest and **(C)** during the language task. **(B)** Plots illustrating results for the exponent, offset, and the beta power from the left STS electrodes at rest and **(D)** during the language task. **(E)** Group results (CON > DYS) from the fMRI localizer task for words compared to the control stimuli ($p < .05$ FWE cluster threshold) and overlap of the MRS voxel placement across participants. **(F)** MRS spectra separately for DYS and CON groups. **(G)** Plots illustrating results for the Glu, GABA, Glu/GABA ratio and the Glu/GABA imbalance. **(H)** Semi-partial correlation between offset at rest (left STS electrodes) and Glu controlling for age and gray matter volume (GMV).

significant and Bayesian statistics indicated against including it in the model. Any other interactions were not significant and Bayesian statistics indicated against including them in the model or did not provide evidence for either inclusion or exclusion.

Then, we analyzed the aperiodic-adjusted brain oscillations. Since the algorithm did not find the gamma peak (30-43 Hz) above the aperiodic component in the majority of participants, we report the results only for the beta (14-30 Hz) power. We performed a similar regional analysis as for the exponent and offset with a 2×2×2×2 (group, condition, hemisphere, region) repeated measures ANOVA. However, we did not include age as a covariate, as it did not correlate with any of the periodic measures. The sample size was 117 (DYS $n$ = 57, CON $n$ = 60) since in 2 participants the algorithm did not find the beta peak above the aperiodic component in the left frontal electrodes during the task.

The analysis revealed a significant effect of condition ($F(1,115) = 8.58$, $p = .004$, $\eta^2_p = .069$, $BF_{incl} = 5.82$) with post-hoc comparison indicating that the beta power was greater during the language task ($M = 0.53$, $SD = 0.22$) than at rest ($M = 0.50$, $SD = 0.19$, $p_{corr} = .004$). There were also significant effects of region ($F(1,115) = 10.98$, $p = .001$, $\eta^2_p = .087$, $BF_{incl} = 23.71$), and hemisphere ($F(1,115) = 12.08$, $p < .001$, $\eta^2_p = .095$, $BF_{incl} = 23.91$). For the main effect of region, post-hoc comparisons indicated that the beta power was greater in the temporal ($M = 0.52$, $SD = 0.21$) as compared to the frontal region ($M = 0.50$, $SD = 0.19$, $p_{corr} = .001$), while for the main effect of hemisphere, post-hoc comparisons indicated that the beta power was greater in the right ($M = 0.52$, $SD = 0.20$) than in the left hemisphere ($M = 0.51$, $SD = 0.20$, $p_{corr} < .001$). There was a significant interaction between condition and region ($F(1,115) = 12.68$, $p < .001$, $\eta^2_p = .099$, $BF_{incl} = 55.26$) with greater beta power during the language task as compared to rest significant in the temporal ($M_{rest} = 0.50$, $SD_{rest} = 0.20$, $M_{task} = 0.55$, $SD_{task} = 0.24$, $p_{corr} < .001$), while not in the frontal region ($M_{rest} = 0.49$, $SD_{rest} = 0.18$, $M_{task} = 0.51$, $SD_{task} = 0.22$, $p_{corr} = .077$). Also, greater beta power in the temporal as compared to the frontal region was significant during the language task ($p_{corr} < .001$), while not at rest ($p_{corr} = .283$). The effect of group ($F(1,115) = 0.05$, $p = .817$, $\eta^2_p = .000$, $BF_{incl} < 0.00001$) was not significant and Bayes Factor indicated against including it in the model. Any other interactions were not significant and Bayesian statistics indicated against including them in the model or did not provide evidence for either inclusion or exclusion.

Additionally, building upon previous findings which demonstrated differences in dyslexia in aperiodic and periodic components within the parieto-occipital region (Turri et al., 2023), we have included analyses for the same cluster of electrodes in the Supplementary Material. However, in this region, we also did not find evidence for group differences either in the exponent, offset or beta power.

## No evidence for group differences in Glu and GABA concentrations in the left STS

In total, 59 out of 120 participants underwent MRS session at 7T MRI scanner - 29 from the dyslexic group (13 females, 16 males) and 30 from the control group (14 females, 16 males). The MRS voxel was placed in the left STS, in a region showing highest activation for both visual and auditory words (compared to control stimuli) localized individually in each participant, based on an fMRI task (see **Figure 1E** for overlap of the MRS voxel placement across participants and **Figure 1F** for MRS spectra). We decided to analyze the neurometabolites' levels derived from the left STS, as this region is consistently related to functional and structural differences in dyslexia across languages (Yan et al., 2021).

Due to insufficient magnetic homogeneity or interruption of the study by the participants, 5 participants from the dyslexic group had to be excluded. We excluded further 4 participants due to poor quality of the obtained spectra thus the results for Glu are reported for 50 participants - 21 in the dyslexic (12 females, 9 males) and 29 in the control group (13 females, 16 males). In the case of

GABA, we additionally excluded 3 participants based on the Cramér-Rao Lower Bounds (CRLB) > 20%. Therefore, the results for GABA, Glu/GABA ratio and Glu/GABA imbalance are reported for 47 participants - 20 in the dyslexic (12 females, 8 males) and 27 in the control group (11 females, 16 males). Demographic and behavioral characteristics for the subsample of 47 participants are provided in the Table S2.

For each metabolite, we performed a separate univariate ANCOVA with the effect of group being tested and voxel's gray matter volume (GMV) as a covariate (see **Figure 1G**). For the Glu analysis, we also included age as a covariate, due to negative correlation between variables ($r$ = -.35, $p$ = .014, $BF_{10}$ = 3.41). The analysis revealed significant effect of GMV ($F$(1,46) = 8.18, $p$ = .006, $\eta^2_p$ = .151, $BF_{incl}$ = 12.54), while the effects of age ($F$(1,46) = 3.01, $p$ = .090, $\eta^2_p$ = .061, $BF_{incl}$ = 1.15) and group ($F$(1,46) = 1.94, $p$ = .170, 1 = .040, $BF_{incl}$ = 0.63) were not significant and Bayes Factor did not provide evidence for either inclusion or exclusion.

Conversely, GABA did not correlate with age ($r$ = -.11, $p$ = .481, $BF_{10}$ = 0.23), thus age was not included as a covariate. The analysis revealed a significant effect of GMV ($F$(1,44) = 4.39, $p$ = .042, $\eta^2_p$ = .091, $BF_{incl}$ = 1.64), however Bayes Factor did not provide evidence for either inclusion or exclusion. The effect of group was not significant ($F$(1,44) = 0.49, $p$ = .490, $\eta^2_p$ = .011, $BF_{incl}$ = 0.35) although Bayesian statistics did not provide evidence for either inclusion or exclusion.

Also, Glu/GABA ratio did not correlate with age ($r$ = -.05, $p$ = .744, $BF_{10}$ = 0.19), therefore age was not included as a covariate. The results indicated that the effect of GMV was not significant ($F$(1,44) = 0.95, $p$ = .335, $\eta^2_p$ = .021, $BF_{incl}$ = 0.43) while Bayes Factor did not provide evidence for either inclusion or exclusion. The effect of group was not significant ($F$(1,44) = 0.01, $p$ = .933, $\eta^2_p$ = .000, $BF_{incl}$ = 0.29) and Bayes Factor indicated against including it in the model.

Following a recent study examining developmental changes in both EEG and MRS E/I biomarkers (McKeon et al., 2024), we calculated an additional measure of Glu/GABA imbalance, computed as the absolute residual value from the linear regression of Glu predicted by GABA with greater values indicating greater Glu/GABA imbalance. Alike the previous work (McKeon et al., 2024), we took the square root of this value to ensure a normal distribution of the data. This measure did not correlate with age ($r$ = -.05, $p$ = .719, $BF_{10}$ = 0.19); thus, age was not included as a covariate. The results indicated that the effect of GMV was not significant ($F$(1,44) = 0.63, $p$ = .430, $\eta^2_p$ = .014, $BF_{incl}$ = 0.37) while Bayes Factor did not provide evidence for either inclusion or exclusion. The effect of group was not significant ($F$(1,44) = 0.74, $p$ = .396, $\eta^2_p$ = .016, $BF_{incl}$ = 0.39) although Bayesian statistics did not provide evidence for either inclusion or exclusion.

## Correspondence between Glu and GABA concentrations and EEG E/I biomarkers is limited

Next, we investigated correlations between Glu and GABA concentrations in the left STS and EEG markers of E/I balance. Semi-partial correlations were performed (**Table 1**) to control for confounding variables - for Glu the effects of age and GMV were regressed, for GABA, Glu/GABA ratio and Glu/GABA imbalance the effect of GMV was regressed, while for exponents and offsets the effect of age was regressed. For zero-order correlations between variables see Table S3.

Glu negatively correlated with offset in the left STS both at rest ($r$ = -.38, $p$ = .007, $BF_{10}$ = 6.28; **Figure 1H**) and during the language task ($r$ = -.37, $p$ = .009, $BF_{10}$ = 5.05), while any other correlations between Glu and EEG markers were not significant and Bayesian statistics indicated in favor of null hypothesis or provided absence of evidence for either hypothesis. Furthermore, Glu/GABA imbalance positively correlated with exponent at rest both averaged across all electrodes ($r$ = .29, $p$ = .048, $BF_{10}$ = 1.21), as well as in the left STS electrodes ($r$ = .35, $p$ = .017, $BF_{10}$ = 2.87) although Bayes Factor provided absence of evidence for either alternative or null hypothesis.

| Variable | 1. *r* ($BF_{10}$) | 2. | 3. | 4. | 5. | 6. | 7. | 8. |
|---|---|---|---|---|---|---|---|---|
| *EEG resting state* | | | | | | | | |
| 1. Glu | – | | | | | | | |
| 2. GABA | .32*$_a$ (1.82) | – | | | | | | |
| 3. Glu/GABA ratio | -.08$_a$ (0.21) | -.91***$_a$ (>10000) | – | | | | | |
| 4. Glu/GABA imbalance | .12$_a$ (0.25) | .31*$_a$ (1.63) | -.18$_a$ (0.37) | – | | | | |
| 5. Exponent mean (rest) | -.03 $_b$ (0.18) | .04$_a$ (0.19) | -.11$_a$ (0.23) | .29*$_a$ (1.21) | – | | | |
| 6. Offset mean (rest) | -.21$_b$ (0.49) | .08$_a$ (0.21) | -.17$_a$ (0.35) | .25$_a$ (0.69) | .68***$_c$ (>10000) | – | | |
| 7. Exponent left STS (rest) | -.16$_b$ (0.32) | .01$_a$ (0.18) | -.07$_a$ (0.20) | .35*$_a$ (2.87) | .68***$_c$ (>10000) | .45***$_c$ (>10000) | – | |
| 8. Offset left STS (rest) | -.38**$_b$ (6.28) | -.10$_a$ (0.23) | .02$_a$ (0.18) | .18$_a$ (0.38) | .18*$_c$ (0.80) | .47***$_c$ (>10000) | .66***$_c$ (>10000) | – |
| 9. Beta power left STS (rest) | -.12$_b$ (0.25) | .17$_a$ (0.33) | -.25$_a$ (0.74) | .01$_a$ (0.18) | .18*$_c$ (0.80) | .21*$_c$ (1.40) | .51***$_c$ (>10000) | .59***$_c$ (>10000) |
| *EEG language task* | | | | | | | | |
| 5. Exponent mean (task) | -.10$_b$ (0.22) | .06$_a$ (0.20) | -.15$_a$ (0.29) | .21$_a$ (0.49) | – | | | |
| 6. Offset mean (task) | -.26$_b$ (0.92) | .09$_a$ (0.22) | -.20$_a$ (0.43) | .22$_a$ (0.53) | .72***$_c$ (>10000) | – | | |

**Table 1.**

**Semi-partial Correlations Between Direct and Indirect Markers of Excitatory-Inhibitory Balance. For Glu the Effects of Age and Gray Matter Volume (GMV) Were Regressed, for GABA, Glu/GABA Ratio and Glu/GABA Imbalance the Effect of GMV was Regressed, While for Exponents and Offsets the Effect of Age was Regressed**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 7. Exponent left STS (task) | -.20$_b$ (0.44) | .01$_a$ (0.18) | -.09$_a$ (0.22) | .22$_a$ (0.51) | .65***$_c$ (>10000) | .51***$_c$ (>10000) | – | |
| 8. Offset left STS (task) | -.37**$_b$ (5.05) | -.08$_a$ (0.21) | .00$_a$ (0.18) | .15$_a$ (0.30) | .29**$_c$ (18.31) | .55***$_c$ (>10000) | .77***$_c$ (>10000) | – |
| 9. Beta power left STS (task) | -.19$_b$ (0.42) | .16$_a$ (0.32) | -.22$_a$ (0.55) | -.03$_a$ (0.19) | .05$_c$ (0.13) | .13$_c$ (0.31) | .47***$_c$ (>10000) | .60***$_c$ (>10000) |

*Note.* $r$ – Pearson's correlation coefficient; $BF_{10}$ – Bayes Factor indicating ratio of the likelihood of an alternative hypothesis (H1) to a null hypothesis (H0); mean - values averaged across all electrodes; left STS - values averaged across 3 electrodes corresponding to the left superior temporal sulcus (T7, TP7, TP9).
***$p < .001$ (uncorrected); **$p < .01$ (uncorrected); *$p < .05$ (uncorrected)
[a]$n = 47$; [b]$n = 50$; [c]$n = 119$

**Table 1.** (continued)

Conversely, GABA and Glu/GABA ratio were not significantly correlated with any of the EEG markers and Bayesian statistics indicated in favor of null hypothesis or provided absence of evidence for either hypothesis.

## Testing the paths from neural noise to reading

The neural noise hypothesis of dyslexia predicts impact of the neural noise on reading through the impairment of 1) phonological awareness, 2) lexical access and generalization and 3) multisensory integration (Hancock et al., 2017). Therefore, we analyzed correlations between these variables, reading skills and direct and indirect markers of E/I balance. For the composite score of phonological awareness, we averaged z-scores from phoneme deletion, phoneme and syllable spoonerisms tasks. For the composite score of lexical access and generalization we averaged z-scores from objects, colors, letters and digits subtests from rapid automatized naming (RAN) task, while for the composite score of reading we averaged z-scores from words and pseudowords read per minute, and text reading time in reading comprehension task. The outcomes from the RAN and reading comprehension task have been transformed from raw time scores to items/time scores in order to provide the same direction of relationships for all z-scored measures, with greater values indicating better skills. For the multisensory integration score we used results from the redundant target effect task reported in our previous work (Glica et al., 2024), with greater values indicating a greater magnitude of multisensory integration.

Age positively correlated with multisensory integration ($r$ = .38, $p$ < .001, $BF_{10}$ = 87.98), composite scores of reading ($r$ = .22, $p$ = .014, $BF_{10}$ = 2.24) and phonological awareness ($r$ = .21, $p$ = .021, $BF_{10}$ = 1.59), while not with the composite score of RAN ($r$ = .13, $p$ = .151, $BF_{10}$ = 0.32). Hence, we regressed the effect of age from multisensory integration, reading and phonological awareness scores and performed semi-partial correlations (**Table 2**, for zero-order correlations see Table S4).

Phonological awareness positively correlated with offset in the left STS at rest ($r$ = .18, $p$ = .049, $BF_{10}$ = 0.77) and with beta power in the left STS both at rest ($r$ = .23, $p$ = .011, $BF_{10}$ = 2.73; **Figure 2A**) and during the language task ($r$ = .23, $p$ = .011, $BF_{10}$ = 2.84; **Figure 2B**), although Bayes Factor provided absence of evidence for either alternative or null hypothesis. Furthermore, multisensory integration positively correlated with GABA concentration ($r$ = .31, $p$ = .034, $BF_{10}$ = 1.62) and negatively with Glu/GABA ratio ($r$ = -.32, $p$ = .029, $BF_{10}$ = 1.84), although Bayes Factor provided absence of evidence for either alternative or null hypothesis. Any other correlations between reading skills and E/I balance markers were not significant and Bayesian statistics indicated in favor of null hypothesis or provided absence of evidence for either hypothesis.

Given that beta power correlated with phonological awareness, and considering the prediction that neural noise impedes reading by affecting phonological awareness — we examined this relationship through a mediation model. Since phonological awareness correlated with beta power in the left STS both at rest and during language task, the outcomes from these two conditions were averaged prior to the mediation analysis. Macro PROCESS v4.2 (Hayes, 2017) on IBM SPSS Statistics v29 with model 4 (simple mediation) with 5000 Bootstrap samples to assess the significance of indirect effect was employed. Since age correlated both with phonological awareness and reading, we also included age as a covariate.

The results indicated that both effects of beta power in the left STS ($b$ = .96, $t$(116) = 2.71, $p$ = .008, $BF_{incl}$ = 7.53) and age ($b$ = .06, $t$(116) = 2.55, $p$ = .012, $BF_{incl}$ = 5.98) on phonological awareness were significant. The effect of phonological awareness on reading was also significant ($b$ = .69, $t$(115) = 8.16, $p$ < .001, $BF_{incl}$ > 10000), while the effects of beta power ($b$ = -.42, $t$(115) = -1.25, $p$ = .213, $BF_{incl}$ = 0.52) and age ($b$ = .03, $t$(115) = 1.18, $p$ = .241, $BF_{incl}$ = 0.49) on reading were not significant when controlling for phonological awareness. Finally, the indirect effect of beta power on reading through phonological awareness was significant ($b$ = .66, SE = .24, 95% CI = [.24, 1.18]), while the total effect of beta power was not significant ($b$ = .24, $t$(116) = 0.61, $p$ = .546, $BF_{incl}$ = 0.41). The results from the mediation analysis are presented in **Figure 2D**.

| Variable | 1.<br>*r*<br>($BF_{10}$) | 2. | 3. | 4. |
|---|---|---|---|---|
| *EEG resting state* | | | | |
| 1. Reading | – | | | |
| 2.Phonological awareness | .60***$_c$<br>(>10000) | – | | |
| 3. RAN | .71***$_c$<br>(>10000) | .48***$_c$<br>(>10000) | – | |
| 4.Multisensory integration | .16$_d$<br>(0.41) | .25*$_d$<br>(2.09) | .02$_d$<br>(0.14) | – |

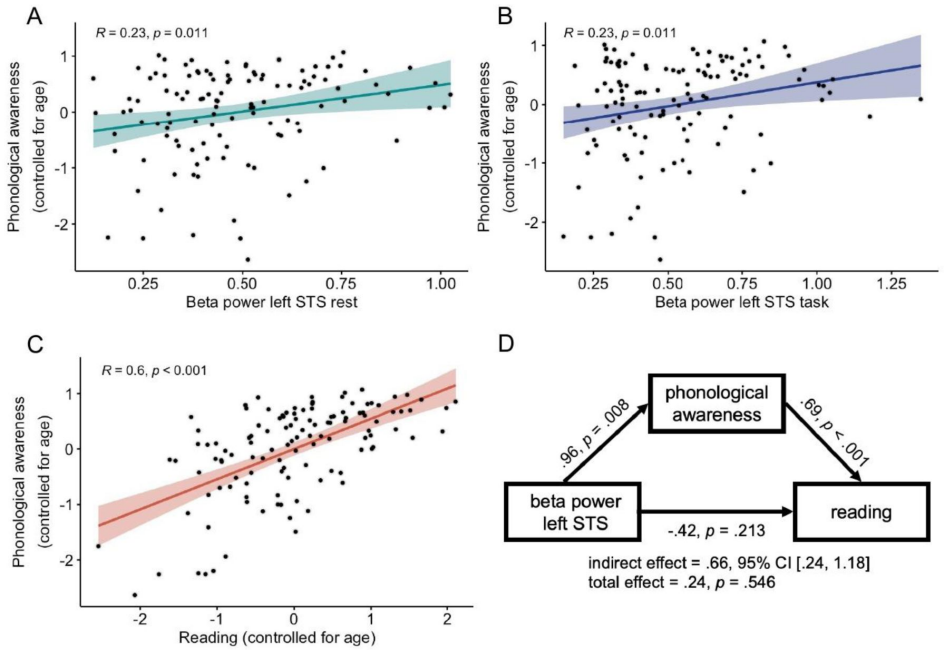
**Table 2.**

**Semi-partial Correlations Between Reading, Phonological Awareness, Rapid Automatized Naming, Multisensory Integration and Markers of Excitatory-Inhibitory Balance. For Reading, Phonological Awareness and Multisensory Integration the Effect of Age was Regressed, for Glu the Effects of Age and Gray Matter Volume (GMV) Were Regressed, for GABA, Glu/GABA Ratio and Glu/GABA Imbalance the Effect of GMV was Regressed, While for Exponents and Offsets the Effect of Age was Regressed**

| | | | | |
|---|---|---|---|---|
| 5. Glu | -.03$_b$ (0.18) | -.12$_b$ (0.25) | -.05$_b$ (0.19) | .03$_b$ (0.18) |
| 6. GABA | -.18$_a$ (0.36) | -.06$_a$ (0.20) | -.23$_a$ (0.56) | .31*$_a$ (1.62) |
| 7. Glu/GABA ratio | .07$_a$ (0.20) | .04$_a$ (0.19) | .09$_a$ (0.22) | -.32*$_a$ (1.84) |
| 8. Glu/GABA imbalance | -.21$_a$ (0.47) | -.08$_a$ (0.21) | -.20$_a$ (0.44) | .17$_a$ (0.33) |
| 9. Exponent mean (rest) | -.08$_c$ (0.17) | .10$_c$ (0.20) | -.06$_c$ (0.14) | .02$_d$ (0.14) |
| 10. Offset mean (rest) | .06$_c$ (0.14) | .14$_c$ (0.35) | .03$_c$ (0.12) | .16$_d$ (0.38) |
| 11. Exponent left STS (rest) | -.08$_c$ (0.16) | .06$_c$ (0.14) | -.04$_c$ (0.12) | -.04$_d$ (0.14) |
| 12. Offset left STS (rest) | .12$_c$ (0.25) | .18*$_c$ (0.77) | .08$_c$ (0.17) | .08$_d$ (0.18) |
| 13. Beta power left STS (rest) | .04$_c$ (0.13) | .23*$_c$ (2.73) | -.04$_c$ (0.12) | .05$_d$ (0.15) |
| *EEG language task* | | | | |
| 9. Exponent mean (task) | -.07$_c$ (0.16) | .13$_c$ (0.30) | -.10$_c$ (0.21) | .01$_d$ (0.14) |
| 10. Offset mean (task) | .05$_c$ (0.13) | .14$_c$ (0.34) | .01$_c$ (0.12) | .18$_d$ (0.50) |
| 11. Exponent left STS (task) | -.03$_c$ (0.12) | .09$_c$ (0.18) | -.07$_c$ (0.15) | -.04$_d$ (0.14) |
| 12. Offset left STS (task) | .13$_c$ (0.28) | .18$_c$ (0.71) | .07$_c$ (0.15) | .09$_d$ (0.19) |
| 13. Beta power left STS (task) | .07$_c$ (0.15) | .23*$_c$ (2.84) | .02$_c$ (0.12) | .15$_d$ (0.33) |

*Note.* $r$ – Pearson's correlation coefficient; $BF_{10}$ – Bayes Factor indicating ratio of the likelihood of an alternative hypothesis (H1) to a null hypothesis (H0); mean - values averaged across all electrodes; left STS - values averaged across 3 electrodes corresponding to the left superior temporal sulcus (T7, TP7, TP9).
***$p < .001$ (uncorrected); **$p < .01$ (uncorrected); *$p < .05$ (uncorrected)
[a]$n = 47$; [b]$n = 50$; [c]$n = 119$; [d]$n = 87$

**Table 2.** (continued)




## Figure 2.

Associations between beta power, phonological awareness and reading. **(A)** Semi-partial correlation between phonological awareness controlling for age and beta power (in the left STS electrodes) at rest and **(B)** during the language task. **(C)** Partial correlation between phonological awareness and reading controlling for age. **(D)** Mediation analysis results. Unstandardized b regression coefficients are presented. Age was included in the analysis as a covariate. 95% CI - 95% confidence intervals. left STS - values averaged across 3 electrodes corresponding to the left superior temporal sulcus (T7, TP7, TP9).

Although similar mediation analysis could have been conducted for the Glu/GABA ratio, multisensory integration, and reading based on the correlations between these variables, we did not test this model due to the small sample size (47 participants), which resulted in insufficient statistical power.

## Discussion

The current study aimed to validate the neural noise hypothesis of dyslexia (Hancock et al., 2017) utilizing E/I balance biomarkers from EEG power spectra and ultra-high-field MRS. Contrary to its predictions, we did not observe differences either in 1/f slope, beta power, or Glu and GABA concentrations in participants with dyslexia. Relations between E/I balance biomarkers were limited to significant correlations between Glu and the offset when controlling for age, and between Glu/GABA imbalance and the exponent.

In terms of indirect markers, our study found no evidence of group differences in the aperiodic components of the EEG signal. In most of the models, we did not find evidence for either including or excluding the effect of the group when Bayesian statistics were evaluated. The only exception was the regional analysis for the offset, where results indicated against including the group factor in the model. These findings diverge from previous research on an Italian cohort, which reported decreased exponent and offset in the dyslexic group at rest, specifically within the parieto-occipital region, but not the frontal region (Turri et al., 2023). Despite our study involving twice the number of participants and utilizing a longer acquisition time, we observed no group differences, even in the same cluster of electrodes (refer to Supplementary Material). The participants in both studies were of similar ages. The only methodological difference – EEG acquisition with eyes open in our study versus both eyes-open and eyes-closed in the work by Turri and colleagues (2023) – cannot fully account for the overall lack of group differences observed. The diverging study outcomes highlight the importance of considering potential inflation of effect sizes in studies with smaller samples.

Although a lower exponent of the EEG power spectrum has been associated with other neurodevelopmental disorders, such as ADHD (Ostlund et al., 2021) or ASD (but only in children with IQ below average) (Manyukhina et al., 2022), our study suggests that this is not the case for dyslexia. Considering the frequent comorbidity of dyslexia and ADHD (Germanò et al., 2010; Langer et al., 2019), increased neural noise could serve as a common underlying mechanism for both disorders. However, our specific exclusion of participants with a comorbid ADHD diagnosis indicates that the EEG spectral exponent cannot serve as a neurobiological marker for dyslexia in isolation. No information regarding such exclusion criteria was provided in the study by Turri et al. (2023); thus, potential comorbidity with ADHD may explain the positive findings related to dyslexia reported therein.

Regarding the aperiodic-adjusted oscillatory EEG activity, Bayesian statistics for beta power, indicated in favor of excluding the group factor from the model. Non-significant group differences in beta power at rest have been previously reported in studies that did not account for aperiodic components (Babiloni et al., 2012; Fraga González et al., 2018; Xue et al., 2020). This again contrasts with the study by Turri et al. (2023), which observed lower aperiodic-adjusted beta power (at 15-25 Hz) in the dyslexic group. Concerning beta power during task, our results also contrast with previous studies which showed either reduced (Spironelli et al., 2008) or increased (Rippon and Brunswick, 2000) beta activity in participants with dyslexia. Nevertheless, since both of these studies employed phonological tasks and involved children's samples, their relevance to our work is limited.

In terms of direct neurometabolite concentrations derived from the MRS, we found no evidence for group differences in either Glu, GABA or Glu/GABA imbalance in the language-sensitive left STS. Conversely, the Bayes Factor suggested against including the group factor in the model for the Glu/GABA ratio. While no previous study has localized the MRS voxel based on the individual activation levels, nonsignificant group differences in Glu and GABA concentrations within the temporo-parietal and visual cortices have been reported in both children and adults (Kossowski et al., 2019), as well as in the ACC in children (Horowitz-Kraus et al., 2018). Although our MRS sample size was half that of the EEG sample, previous research reporting group differences in Glu concentrations involved an even smaller dyslexic cohort (10 participants with dyslexia and 45 typical readers in Pugh et al., 2014). Consistent with earlier studies that identified group differences in Glu and GABA concentrations (Del Tufo et al., 2018; Pugh et al., 2014) we reported neurometabolite levels relative to total creatine (tCr), indicating that the absence of corresponding results cannot be ascribed to reference differences. Notably, our analysis of the fMRI localizer task revealed greater activation in the control group as compared to the dyslexic group within the left STS for words than control stimuli (see **Figure 1E** and the Supplementary Material) in line with previous observations (Blau et al., 2009; Dębska et al., 2021; Yan et al., 2021).

Irrespective of dyslexia status, we found negative correlations between age and exponent and offset, consistent with previous research (Cellier et al., 2021; McSweeney et al., 2021; Schaworonkow and Voytek, 2021; Voytek et al., 2015) and providing further evidence for maturational changes in the aperiodic components (indicative of increased E/I ratio). At the same time, in line with previous MRS works (Kossowski et al., 2019; Marsman et al., 2013), we observed a negative correlation between age and Glu concentrations. This suggests a contrasting pattern to EEG results, indicating a decrease in neuronal excitation with age. We also found a condition-dependent change in offset, with a lower offset observed at rest than during the language task. The offset value represents the uniform shift in power across frequencies (Donoghue et al., 2020), with a higher offset linked to increased neuronal spiking rates (Manning et al., 2009). Change in offset between conditions is consistent with observed increased alpha and beta power during the task, indicating elevated activity in both broadband (offset) and narrowband (alpha and beta oscillations) frequency ranges during the language task.

In regard to relationships between EEG and MRS E/I balance biomarkers, we observed a negative correlation between the offset in the left STS (both at rest and during the task) and Glu levels, after controlling for age and GMV. This correlation was not observed in zero-order correlations (see Supplementary Material). Contrary to our predictions, informed by previous studies linking the exponent to E/I ratio (Colombo et al., 2019; Gao et al., 2017; Waschke et al., 2021), we found the correlation with Glu levels to involve the offset rather than the exponent. This outcome was unexpected, as none of the referenced studies reported results for the offset. However, given the strong correlation between the exponent and offset observed in our study ($r$ = .68, $p$ < .001, $BF_{10}$ > 10000 and $r$ = .72, $p$ < .001, $BF_{10}$ > 10000 at rest and during the task respectively) it is conceivable that similar association might be identified for the offset if it were analyzed.

Nevertheless, previous studies examining relationships between EEG and MRS E/I balance biomarkers (McKeon et al., 2024; van Bueren et al., 2023) did not identify a similar negative association between Glu and the offset. Instead, one study noted a positive correlation between the Glu/GABA ratio and the exponent (van Bueren et al., 2023), which was significant in the intraparietal sulcus but not in the middle frontal gyrus. This finding presents counterintuitive evidence, suggesting that an increased E/I balance, as indicated by MRS, is associated with a higher aperiodic exponent, considered indicative of decreased E/I balance. In line with this pattern, another study discovered a positive relationship between the exponent and Glu levels in the dorsolateral prefrontal cortex (McKeon et al., 2024). Furthermore, they observed a positive correlation between the exponent and the Glu/GABA imbalance measure, calculated as the absolute residual value of a linear relationship between Glu and GABA (McKeon et al., 2024), a

finding replicated in the current work. This implies that a higher spectral exponent might not be directly linked to MRS-derived Glu or GABA levels, but rather to a greater disproportion (in either direction) between these neurotransmitters. These findings, alongside the contrasting relationships between EEG and MRS biomarkers and age, suggest that these methods may reflect distinct biological mechanisms of E/I balance.

Evidence regarding associations between neurotransmitters levels and oscillatory activity also remains mixed. One study found a positive correlation between gamma peak frequency and GABA concentration in the visual cortex (Muthukumaraswamy et al., 2009), a finding later challenged by a study with a larger sample (Cousijn et al., 2014). Similarly, a different study noted a positive correlation between GABA in the left STS and gamma power (Balz et al., 2016), another study, found non-significant relation between these measures (Wyss et al., 2017). Moreover, in a simultaneous EEG and MRS study, an event-related increase in Glu following visual stimulation was found to correlate with greater gamma power (Lally et al., 2014). We could not investigate such associations, as the algorithm failed to identify a gamma peak above the aperiodic component for the majority of participants. Also, contrary to previous findings showing associations between GABA in the motor and sensorimotor cortices and beta power (Cheng et al., 2017; Gaetz et al., 2011) or beta peak frequency (Baumgarten et al., 2016), we observed no correlation between Glu or GABA levels and beta power. However, these studies placed MRS voxels in motor regions which are typically linked to movement-related beta activity (Baker et al., 1999; Rubino et al., 2006; Sanes and Donoghue, 1993) and did not adjust beta power for aperiodic components, making direct comparisons with our findings limited.

Finally, we examined pathways posited by the neural noise hypothesis of dyslexia, through which increased neural noise may impact reading: phonological awareness, lexical access and generalization, and multisensory integration (Hancock et al., 2017). Phonological awareness was positively correlated with the offset in the left STS at rest, and with beta power in the left STS, both at rest and during the task. Additionally, multisensory integration showed correlations with GABA and the Glu/GABA ratio. Since the Bayes Factor did not provide conclusive evidence supporting either the alternative or null hypothesis, these associations appear rather weak. Nonetheless, given the hypothesis's prediction of a causal link between these variables, we further examined a mediation model involving beta power, phonological awareness, and reading skills. The results suggested a positive indirect effect of beta power on reading via phonological awareness, whereas both the direct (controlling for phonological awareness and age) and total effects (without controlling for phonological awareness) were not significant. This finding is noteworthy, considering that participants with dyslexia exhibited reduced phonological awareness and reading skills, despite no observed differences in beta power. Given the cross-sectional nature of our study, further longitudinal research is necessary to confirm the causal relation among these variables. The effects of GABA and the Glu/GABA ratio on reading, mediated by multisensory integration, warrant further investigation. Additionally, considering our finding that only males with dyslexia showed deficits in multisensory integration (Glica et al., 2024), sex should be considered as a potential moderating factor in future analyses. We did not test this model here due to the smaller sample size for GABA measurements.

Our findings suggest that the neural noise hypothesis, as proposed by Hancock and colleagues (2017), does not fully explain the reading difficulties observed in dyslexia. Despite the innovative use of both EEG and MRS biomarkers to assess excitatory-inhibitory (E/I) balance, neither method provided evidence supporting an E/I imbalance in dyslexic individuals. Importantly, our study focused on adolescents and young adults, and the EEG recordings were conducted during rest and a spoken language task. These factors may limit the generalizability of our results. Future research should include younger populations and incorporate a broader array of tasks, such as reading and phonological processing, to provide a more comprehensive evaluation of the E/I balance hypothesis. Additionally, our findings are consistent with another study by Tan et al. (2022), which found no evidence for increased variability ('noise') in

behavioral and fMRI response patterns in dyslexia. Together, these results highlight the need to explore alternative neural mechanisms underlying dyslexia and suggest that cortical hyperexcitability may not be the primary cause of reading difficulties.

In conclusion, while our study challenges the neural noise hypothesis as a sole explanatory framework for dyslexia, it also underscores the complexity of the disorder and the necessity for multifaceted research approaches. By refining our understanding of the neural underpinnings of dyslexia, we can better inform future studies and develop more effective interventions for those affected by this condition.

# Materials and methods

## Participants

A total of 120 Polish participants aged between 15.09 and 24.95 years ($M$ = 19.47, $SD$ = 3.06) took part in the study. This included 60 individuals with a clinical diagnosis of dyslexia performed by the psychological and pedagogical counseling centers (28 females and 32 males) and 60 control participants without a history of reading difficulties (28 females and 32 males). All participants were right-handed, born at term, without any reported neurological/psychiatric diagnosis and treatment (including ADHD), without hearing impairment, with normal or corrected-to-normal vision, and IQ higher than 80 as assessed by the Polish version of the Abbreviated Battery of the Stanford-Binet Intelligence Scale-Fifth Edition (SB5) (Roid et al., 2017).

The study was approved by the institutional review board at the University of Warsaw, Poland (reference number 2N/02/2021). All participants (or their parents in the case of underaged participants) provided written informed consent and received monetary remuneration for taking part in the study.

## Reading and Reading-Related Tasks

Participants' reading skills were assessed by multiple paper-pencil tasks described in detail in our previous work (Glica et al., 2024). Briefly, we evaluated words and pseudowords read in one minute (Szczerbiński and Pelc-Pękała, 2013), rapid automatized naming (Fecenec et al., 2013), and reading comprehension speed. We also assessed phonological awareness by a phoneme deletion task (Szczerbiński and Pelc-Pękała, 2013) and spoonerisms tasks (Bogdanowicz et al., 2016), as well as orthographic awareness (Awramiuk and Krasowicz-Kupis, 2013). Furthermore, we evaluated non-verbal perception speed (Ciechanowicz and Stańczak, 2006) and short-term and working memory by forward and backward conditions from the Digit Span subtest from the WAIS-R (Wechsler, 1981). We also assessed participants' multisensory audiovisual integration by a redundant target effect task, which results have been reported in our previous work (Glica et al., 2024).

## Electroencephalography Acquisition and Procedure

EEG was recorded from 62 scalp and 2 ear electrodes using the Brain Products system (actiCHamp Plus, Brain Products GmbH, Gilching, Germany). Data were recorded in BrainVision Recorder Software (Vers. 1.22.0002, Brain Products GmbH, Gilching, Germany) with a 500 Hz sampling rate. Electrodes were positioned in line with the extended 10-20 system. Electrode Cz served as an online reference, while the Fpz as a ground electrode. All electrodes' impedances were kept below 10 kΩ. Participants sat in a chair with their heads on a chin-rest in a dark, sound-attenuated, and electrically shielded room while the EEG was recorded during both a 5-minute eyes-open resting state and the spoken language comprehension task. The paradigm was prepared in the Presentation software (Version 20.1, Neurobehavioral Systems, Inc., Berkeley, CA, *www.neurobs.com*).

During rest, participants were instructed to relax and fixate their eyes on a white cross presented centrally on a black background. After 5 minutes, the spoken language comprehension task automatically started. The task consisted of 3 to 5 word-long sentences recorded in a speech synthesizer which were presented binaurally through sound-isolating earphones. After hearing a sentence, participants were asked to indicate whether the sentence was true or false by pressing a corresponding button. In total, there were 256 sentences – 128 true (e.g., “Plants need water”) and 128 false (e.g., “Dogs can fly”).

Sentences were presented in a random order in two blocks of 128 trials. At the beginning of each trial, a white fixation cross was presented centrally on a black background for 500 ms, then a blank screen appeared for either 500, 600, 700, or 800 ms (durations set randomly and equiprobably) followed by an auditory sentence presentation. The length of sentences ranged between 1.17 and 2.78 seconds and was balanced between true ($M$ = 1.82 seconds, $SD$ = 0.29) and false sentences ($M$ = 1.82 seconds, $SD$ = 0.32; $t(254)$ = -0.21, $p$ = .835; $BF_{10}$ = 0.14). After a sentence presentation, a blank screen was displayed for 1000 ms before starting the next trial. To reduce participants’ fatigue, a 1-minute break between two blocks of trials was introduced, and it took approximately 15 minutes to complete the task.

## fMRI Acquisition and Procedure

MRI data were acquired using Siemens 3T Trio system with a 32-channel head coil. Structural data were acquired using whole brain 3D T1-weighted image (MP_RAGE, TI = 1100 ms, GRAPPA parallel imaging with acceleration factor PE = 2, voxel resolution = $1mm^3$, dimensions = 256×256×176). Functional data were acquired using whole-brain echo planar imaging sequence (TE = 30ms, TR = 1410 ms, flip angle FA = 90°, FOV = 212 mm, matrix size = 92×92, 60 axial slices 2.3mm thick, 2.3×2.3 mm in-plane resolution, multiband acceleration factor = 3). Due to a technical issue, data from two participants were acquired with a 12-channel coil (see Supplementary Material).

The fMRI task served as a localizer for later MRS voxel placement in language-sensitive left STS. The task was prepared using Presentation software (Version 20.1, Neurobehavioral Systems, Inc., Berkeley, CA, *www.neurobs.com*) and consisted of three runs, each lasting 5 minutes and 9 seconds. Two runs involved the presentation of visual stimuli, while the third run of auditory stimuli. In each run, stimuli were presented in 12 blocks, with 14 stimuli per block. In visual runs, there were four blocks from each category: 1) 3 to 4 letters-long words, 2) the same words presented as a false font string (BACS font) (Vidal et al., 2017), and 3) strings of 3 to 4-long consonants. Similarly, in the auditory run, there were four blocks from each category: 1) words recorded in a speech synthesizer, 2) the same words presented backward, and 3) consonant strings recorded in a speech synthesizer. Stimuli within each block were presented for 800 ms with a 400 ms break in between. The duration of each block was 16.8 seconds. Between blocks, a fixation cross was displayed for 8 seconds. Participants performed a 1-back task to maintain focus. The blocks were presented in a pseudorandom order and each block included 2 to 3 repeated stimuli.

## MRS Acquisition and Procedure

The GE 7T system with a 32-channel coil was utilized. Structural data were acquired using whole brain 3D T1-weighted image (3D-SPGR BRAVO, TI = 450ms, TE = 2.6ms, TR = 6.6ms, flip angle = 12 deg, bandwidth = ±32.5kHz, ARC acceleration factor PE = 2, voxel resolution = 1mm, dimensions = 256 x 256 x 180). MRS spectra with 320 averages were acquired from the left STS using single-voxel spectroscopy semiLaser sequence (Deelchand et al., 2021) (voxel size = 15 x 15 x 15 mm, TE = 28ms, TR = 4000ms, 4096 data points, water suppressed using VAPOR). Eight averages with unsuppressed water as a reference were collected.

To localize left STS, T1-weighted images from fMRI and MRS sessions were coregistered and fMRI peak coordinates were used as a center of voxel volume for MRS. Voxels were then adjusted to include only the brain tissue. During the acquisition, participants took part in a simple

orthographic task.

## Statistical Analyses

## EEG data

The continuous EEG signal was preprocessed in the EEGLAB (Delorme and Makeig, 2004). The data were filtered between 0.5 and 45 Hz (Butterworth filter, 4th order) and re-referenced to the average of both ear electrodes. The data recorded during the break between blocks, as well as bad channels, were manually rejected. The number of rejected channels ranged between 0 and 4 (*M* = 0.19, *SD* = 0.63). Next, independent component analysis (ICA) was applied. Components were automatically labeled by ICLabel (Pion-Tonachini et al., 2019), and those classified with 50-100% source probability as eye blinks, muscle activity, heart activity, channel noise, and line noise, or with 0-50% source probability as brain activity, were excluded. Components labeled as "other" were visually inspected, and those identified as eye blinks and muscle activity were also rejected. The number of rejected components ranged between 11 and 46 (*M* = 28.43, *SD* = 7.26). Previously rejected bad channels were interpolated using the nearest neighbor spline (Perrin et al., 1989, 1987).

The preprocessed data were divided into a 5-minute resting-state signal and a signal recorded during a spoken language comprehension task using MNE (Gramfort, 2013) and custom Python scripts. The signal from the task was cut up based on the event markers indicating the beginning and end of a sentence. Only trials with correct responses given between 0 and 1000 ms after the end of a sentence were included. The signals recorded during every trial were further multiplied by the Tukey window with α = 0.01 in order to normalize signal amplitudes at the beginning and end of every trial. This allowed a smooth concatenation of signals recorded during task trials, resulting in a continuous signal derived only when participants were listening to the sentences.

The continuous signal from the resting state and the language task was epoched into 2-second-long segments. An automatic rejection criterion of +/-200 μV was applied to exclude epochs with excessive amplitudes. The number of epochs retained in the analysis ranged between 140–150 (*M* = 149.66, *SD* = 1.20) in the resting state condition and between 102–226 (*M* = 178.24, *SD* = 28.94) in the spoken language comprehension task.

Power spectral density (PSD) for 0.5-45 Hz in 0.5 Hz increments was calculated for every artifact-free epoch using Welch's method for 2-second-long data segments windowed with a Hamming window with no overlap. The estimated PSDs were averaged for each participant and each channel separately for the resting state condition and the language task. Aperiodic and periodic (oscillatory) components were parameterized using the FOOOF method (Donoghue et al., 2020). For each PSD, we extracted parameters for the 1-43 Hz frequency range using the following settings: *peak_width_limits* = [1, 12], *max_n_peaks* = infinite, *peak_threshold* = 2.0, *mean_peak_height* = 0.0, *aperiodic_mode* = 'fixed'. Apart from broad-band aperiodic parameters (exponent and offset), we also extracted power, bandwidth, and the center frequency parameters for the theta (4-7 Hz), alpha (7-14 Hz), beta (14-30 Hz) and gamma (30-43 Hz) bands. Since in the majority of participants, the algorithm did not find the peak above the aperiodic component in theta and gamma bands, we calculated the results only for the alpha and beta bands. The results for other periodic parameters than the beta power are reported in Supplementary Material.

Apart from the frequentist statistics, we also performed Bayesian statistics using JASP (JASP Team, 2023). For Bayesian repeated measures ANOVA, we reported the Bayes Factor for the inclusion of a given effect ($BF_{incl}$) with the 'across matched model' option, as suggested by Keysers and colleagues (2020), calculated as a likelihood ratio of models with a presence of a specific factor to equivalent models differing only in the absence of the specific factor. For Bayesian *t*-tests and

correlations, we reported the $BF_{10}$ value, indicating the ratio of the likelihood of an alternative hypothesis to a null hypothesis. We considered $BF_{incl/10} > 3$ and $BF_{incl/10} < 1/3$ as evidence for alternative and null hypotheses respectively, while $1/3 < BF_{incl/10} < 3$ as the absence of evidence (Keysers et al., 2020).

## fMRI data

### MRS voxel localization in the native space

The data were analyzed using Statistical Parametric Mapping (SPM12, Wellcome Trust Centre for Neuroimaging, London, UK) run on MATLAB R2020b (The MathWorks Inc., Natick, MA, USA). First, all functional images were realigned to the participant's mean. Then, T1-weighted images were coregistered to functional images for each subject. Finally, fMRI data were smoothed with a 6mm isotropic Gaussian kernel.

In each subject, the left STS was localized in the native space as a cluster in the middle and posterior left superior temporal sulcus, exhibiting higher activation for visual words versus false font strings and auditory words versus backward words (logical AND conjunction) at $p < .01$ uncorrected. For 6 participants, the threshold was lowered to $p < .05$ uncorrected, while for another 6 participants, the contrast from the auditory run was changed to auditory words versus fixation cross due to a lack of activation for other contrasts.

In the Supplementary Material, we also performed the group-level analysis of the fMRI data (Tables S5-S7 and Figure S1).

## MRS data

MRS data were analyzed using fsl-mrs version 2.0.7 (Clarke et al., 2021). Data stored in pfile format were converted into NIfTI-MRS using spec2nii tool. We then used the *fsl_mrs_preproc* function to automatically perform coil combination, frequency and phase alignment, bad average removal, combination of spectra, eddy current correction, shifting frequency to reference peak and phase correction.

To obtain information about the percentage of WM, GM and CSF in the voxel we used the *svs_segmentation* with results of *fsl_anat* as an input. Voxel segmentation was performed on structural images from a 3T scanner, coregistered to 7T structural images in SPM12. Next, quantitative fitting was performed using *fsl_mrs* function. As a basis set, we utilized a collection of 27 metabolite spectra simulated using FID-A (Simpson et al., 2017) and a script tailored for our experiment. We supplemented this with synthetic macromolecule spectra provided by *fsl_mrs*. Signals acquired with unsuppressed water served as water reference.

Spectra underwent quantitative assessment and visual inspection and those with linewidth higher than 20Hz, %CRLB higher than 20%, and poor fit to the model were excluded from the analysis (see Table S8 in the Supplementary Material for a detailed checklist). Glu and GABA concentrations were expressed as a ratio to total-creatine (tCr; Creatine + Phosphocreatine).

# Data Availability Statement

Behavioral data, raw and preprocessed EEG data, 2$^{nd}$ level fMRI data, preprocessed MRS data and Python script for the analysis of preprocessed EEG data can be found at OSF: *https://osf.io/4e7ps/*

## Acknowledgements

This study was supported by the National Science Centre grant (2019/35/B/HS6/01763) awarded to Katarzyna Jednoróg.

We gratefully acknowledge valuable discussions with Ralph Noeske from GE Healthcare for his support in setting up the protocol for an ultra-high field MR spectroscopy and sharing the set-up for basis set simulation in FID-A.

# References


Ahmad J *et al.* (2022) **From mechanisms to markers: Novel noninvasive EEG proxy markers of the neural excitation and inhibition system in humans** *Transl Psychiatry* **12** https://doi.org/10.1038/s41398-022-02218-z

Awramiuk E, Krasowicz-Kupis G (2014) **Reading and spelling acquisition in Polish: Educational and linguistic determinants** *L1-Educ Stud Lang Lit* **14**:1–24 https://doi.org/10.17239/L1ESLL-2014.01.13

Babiloni C *et al.* (2012) **Cortical sources of resting state EEG rhythms are abnormal in dyslexic children** *Clin Neurophysiol* **123**:2384–2391 https://doi.org/10.1016/j.clinph.2012.05.002

Baker SN, Kilner JM, Pinches EM, Lemon RN (1999) **The role of synchrony and oscillations in the motor output** *Exp Brain Res* **128**:109–117 https://doi.org/10.1007/s002210050825

Balz J, Keil J, Roa Romero Y, Mekle R, Schubert F, Aydin S, Ittermann B, Gallinat J, Senkowski D (2016) **GABA concentration in superior temporal sulcus predicts gamma power and perception in the sound-induced flash illusion** *Neuroimage* **125**:724–730 https://doi.org/10.1016/j.neuroimage.2015.10.087

Baumgarten TJ, Oeltzschner G, Hoogenboom N, Wittsack H-J, Schnitzler A, Lange J (2016) **Beta peak frequencies at rest correlate with endogenous GABA+/Cr concentrations in sensorimotor cortex areas** *PLoS One* **11** https://doi.org/10.1371/journal.pone.0156829

Blau V, van Atteveldt N, Ekkebus M, Goebel R, Blomert L. (2009) **Reduced neural integration of letters and speech sounds links phonological and reading deficits in adult dyslexia** *Curr Biol* **19**:503–508 https://doi.org/10.1016/j.cub.2009.01.065

Bogdanowicz KM, Wiejak K, Krasowicz-Kupis G, Gawron N. (2015) **Ocena przydatności kwestionariusza Adult Reading History Questionnaire do diagnozy rodzinnego ryzyka dysleksji w Polsce. [Evaluation of the usefulness of The Adult Reading History Questionnaire for identification of familial risk of dyslexia in Poland]** *Edukacja* **1**:117–138

Bogdanowicz M, Sajewicz-Radtke U, Radtke BM, Kalka D, Karpińska E, Bogdanowicz KM, Łockiewicz M (2016) **Bateria metod diagnozy przyczyn niepowodzeń szkolnych u uczniów powyżej 16. roku życia. BATERIA-16 plus [B-16]** *[A battery of methods for diagnosing the causes of school failure in students over 16 years of age. BATTERY-16 plus [B-16]]*

Brunel N, Wang X-J (2003) **What determines the frequency of fast network oscillations with irregular neural discharges? I. Synaptic dynamics and excitation-inhibition balance** *J Neurophysiol* **90**:415–430 https://doi.org/10.1152/jn.01095.2002

Cellier D, Riddle J, Petersen I, Hwang K (2021) **The development of theta and alpha neural oscillations from ages 3 to 24 years** *Dev Cogn Neurosci* **50** https://doi.org/10.1016/j.dcn.2021.100969

Chen G, Zhang Y, Li X, Zhao X, Ye Q, Lin Y, Tao HW, Rasch MJ, Zhang X (2017) **Distinct inhibitory circuits orchestrate cortical beta and gamma band oscillations** *Neuron* **96**:1403–1418 https://doi.org/10.1016/j.neuron.2017.11.033

Cheng C-H, Tsai S-Y, Liu C-Y, Niddam DM (2017) **Automatic inhibitory function in the human somatosensory and motor cortices: An MEG-MRS study** *Sci Rep* **7** https://doi.org/10.1038/s41598-017-04564-1

Ciechanowicz A, Stańczak J (2006) **Testy Uwagi i Spostrzegawczości: TUS: podręcznik** *[Attention and Perceptiveness Tests: TUS: handbook]*

Clarke WT, Stagg CJ, Jbabdi S (2021) **FSL-MRS: An end-to-end spectroscopy analysis package** *Magn Reson Med* **85**:2950–2964 https://doi.org/10.1002/mrm.28630

Colombo MA *et al.* (2019) **The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine** *Neuroimage* **189**:631–644 https://doi.org/10.1016/j.neuroimage.2019.01.024

Cousijn H, Haegens S, Wallis G, Near J, Stokes MG, Harrison PJ, Nobre AC (2014) **Resting GABA and glutamate concentrations do not predict visual gamma frequency or amplitude** *Proc Natl Acad Sci* **111**:9301–9306 https://doi.org/10.1073/pnas.1321072111

Dębska A, Banfi C, Chyl K, Dzięgiel-Fivet G, Kacprzak A, Łuniewska M, Plewko J, Grabowska A, Landerl K, Jednoróg K (2021) **Neural patterns of word processing differ in children with dyslexia and isolated spelling deficit** *Brain Struct Funct* **226**:1467–1478 https://doi.org/10.1007/s00429-021-02255-2

Deelchand DK *et al.* (2021) **Across-vendor standardization of semi-LASER for single-voxel MRS at 3T** *NMR Biomed* **34** https://doi.org/10.1002/nbm.4218

Del Tufo SN, Frost SJ, Hoeft F, Cutting LE, Molfese PJ, Mason GF, Rothman DL, Fulbright RK, Pugh KR (2018) **Neurochemistry predicts convergence of written and spoken language: A proton magnetic resonance spectroscopy study of cross-modal language integration** *Front Psychol* **9** https://doi.org/10.3389/fpsyg.2018.01507

Delorme A, Makeig S (2004) **EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis** *J Neurosci Methods* **134**:9–21 https://doi.org/10.1016/j.jneumeth.2003.10.009

Donoghue T *et al.* (2020) **Parameterizing neural power spectra into periodic and aperiodic components** *Nat Neurosci* **23**:1655–1665 https://doi.org/10.1038/s41593-020-00744-x

Fecenec D, Jaworowska A, Matczak A, Stańczak J, Zalewska E (2013) **Test szybkiego nazywania (TSN)** *[Rapid Automatized Naming Task]*

Fein G, Galin D, Yingling CD, Johnstone J, Davenport L, Herron J (1986) **EEG spectra in dyslexic and control boys during resting conditions** *Electroencephalogr Clin Neurophysiol* **63**:87–97 https://doi.org/10.1016/0013-4694(86)90001-5

Finkelman T, Furman-Haran E, Paz R, Tal A (2022) **Quantifying the excitatory-inhibitory balance: A comparison of SemiLASER and MEGA-SemiLASER for simultaneously measuring GABA and glutamate at 7T** *Neuroimage* **247** https://doi.org/10.1016/j.neuroimage.2021.118810

Fraga González G, Smit DJA, van der Molen MJW, Tijms J, Stam CJ, de Geus EJC, van der Molen MW. (2018) **EEG resting state functional connectivity in adult dyslexics using phase lag index and graph analysis** *Front Hum Neurosci* **12** https://doi.org/10.3389/fnhum.2018.00341

Gaetz W, Edgar JC, Wang DJ, Roberts TPL (2011) **Relating MEG measured motor cortical oscillations to resting γ-Aminobutyric acid (GABA) concentration** *Neuroimage* **55**:616–621 https://doi.org/10.1016/j.neuroimage.2010.12.077

Gao R, Peterson EJ, Voytek B (2017) **Inferring synaptic excitation/inhibition balance from field potentials** *Neuroimage* **158**:70–78 https://doi.org/10.1016/j.neuroimage.2017.06.078

Germanò E, Gagliano A, Curatolo P (2010) **Comorbidity of ADHD and Dyslexia** *Dev Neuropsychol* **35**:475–493 https://doi.org/10.1080/87565641.2010.494748

Giacometti P, Perdue KL, Diamond SG (2014) **Algorithm to find high density EEG scalp coordinates and analysis of their correspondence to structural and functional regions of the brain** *J Neurosci Methods* **229**:84–96 https://doi.org/10.1016/j.jneumeth.2014.04.020

Glica A, Wasilewska K, Kossowski B, Żygierewicz J, Jednoróg K (2024) **Sex differences in low-level multisensory integration in developmental dyslexia** *J Neurosci* **44** https://doi.org/10.1523/JNEUROSCI.0944-23.2023

Gramfort A (2013) **MEG and EEG data analysis with MNE-Python** *Front Neurosci* **7**:267–267 https://doi.org/10.3389/fnins.2013.00267

Hancock R, Pugh KR, Hoeft F (2017) **Neural noise hypothesis of developmental dyslexia** *Trends Cogn Sci* **21**:434–448 https://doi.org/10.1016/j.tics.2017.03.008

Hayes AF (2017) **Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach**

Horowitz-Kraus T, Brunst KJ, Cecil KM (2018) **Children with dyslexia and typical readers: Sex-based choline differences revealed using proton magnetic resonance spectroscopy acquired within anterior cingulate cortex** *Front Hum Neurosci* **12** https://doi.org/10.3389/fnhum.2018.00466

JASP Team (2023) **JASP Team. (2023) JASP Version 0.18.1**

Jensen O, Goel P, Kopell N, Pohja M, Hari R, Ermentrout B (2005) **On the human sensorimotor-cortex beta rhythm: Sources and modeling** *Neuroimage* **26**:347–355 https://doi.org/10.1016/j.neuroimage.2005.02.008

Keysers C, Gazzola V, Wagenmakers E-J (2020) **Using Bayes factor hypothesis testing in neuroscience to establish evidence of absence** *Nat Neurosci* **23**:788–799 https://doi.org/10.1038/s41593-020-0660-4

Kossowski B, Chyl K, Kacprzak A, Bogorodzki P, Jednoróg K (2019) **Dyslexia and age related effects in the neurometabolites concentration in the visual and temporo-parietal cortex** *Sci Rep* **9** https://doi.org/10.1038/s41598-019-41473-x

Lally N, Mullins PG, Roberts M V., Price D, Gruber T, Haenschel C (2014) **Glutamatergic correlates of gamma-band oscillatory activity during cognition: A concurrent ER-MRS and EEG study** *Neuroimage* **85**:823–833 https://doi.org/10.1016/j.neuroimage.2013.07.049

Langer N, Benjamin C, Becker BLC, Gaab N (2019) **Comorbidity of reading disabilities and ADHD: Structural and functional brain characteristics** *Hum Brain Mapp* **40**:2677–2698 https://doi.org/10.1002/hbm.24552

Lasnick OHM, Hancock R, Hoeft F (2023) **Left-dominance for resting-state temporal low-gamma power in children with impaired word-decoding and without comorbid ADHD** *PLoS One* **18** https://doi.org/10.1371/journal.pone.0292330

Lebel C, MacMaster FP, Dewey D (2016) **Brain metabolite levels and language abilities in preschool children** *Brain Behav* **6** https://doi.org/10.1002/brb3.547

Lehongre K, Ramus F, Villiermet N, Schwartz D, Giraud A-L (2011) **Altered low-gamma sampling in auditory cortex accounts for the three main facets of dyslexia** *Neuron* **72**:1080–1090 https://doi.org/10.1016/j.neuron.2011.11.002

Manning JR, Jacobs J, Fried I, Kahana MJ (2009) **Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans** *J Neurosci* **29**:13613–13620 https://doi.org/10.1523/JNEUROSCI.2041-09.2009

Manyukhina VO, Prokofyev AO, Galuta IA, Goiaeva DE, Obukhova TS, Schneiderman JF, Altukhov DI, Stroganova TA, Orekhova E V (2022) **Globally elevated excitation– inhibition ratio in children with autism spectrum disorder and below-average intelligence** *Mol Autism* **13** https://doi.org/10.1186/s13229-022-00498-2

Marchesotti S, Nicolle J, Merlet I, Arnal LH, Donoghue JP, Giraud A-L (2020) **Selective enhancement of low-gamma activity by tACS improves phonemic processing and reading accuracy in dyslexia** *PLoS Biol* **18** https://doi.org/10.1371/journal.pbio.3000833

Marsman A, Mandl RCW, van den Heuvel MP, Boer VO, Wijnen JP, Klomp DWJ, Luijten PR, Hilleke E. HP (2013) **Glutamate changes in healthy young adulthood** *Eur Neuropsychopharmacol* **23**:1484–1490 https://doi.org/10.1016/j.euroneuro.2012.11.003

McKeon SD, Perica MI, Parr AC, Calabro FJ, Foran W, Hetherington H, Moon C-H, Luna B (2024) **Aperiodic EEG and 7T MRSI evidence for maturation of E/I balance supporting the development of working memory through adolescence** *Dev Cogn Neurosci* **66** https://doi.org/10.1016/j.dcn.2024.101373

McSweeney M, Morales S, Valadez EA, Buzzell GA, Fox NA (2021) **Longitudinal age- and sex-related change in background aperiodic activity during early adolescence** *Dev Cogn Neurosci* **52** https://doi.org/10.1016/j.dcn.2021.101035

Molina JL, Voytek B, Thomas ML, Joshi YB, Bhakta SG, Talledo JA, Swerdlow NR, Light GA (2020) **Memantine effects on electroencephalographic measures of putative excitatory/inhibitory balance in schizophrenia** *Biol Psychiatry Cogn Neurosci Neuroimaging* **5**:562–568 https://doi.org/10.1016/j.bpsc.2020.02.004

Muthukumaraswamy SD, Edden RAE, Jones DK, Swettenham JB, Singh KD (2009) **Resting GABA concentration predicts peak gamma frequency and fMRI amplitude in response to visual stimulation in humans** *Proc Natl Acad Sci* **106**:8356–8361 https://doi.org/10.1073/pnas.0900728106

Nakai T, Okanoya K (2016) **Individual variability in verbal fluency correlates with γ-aminobutyric acid concentration in the left inferior frontal gyrus** *Neuroreport* **27**:987–991 https://doi.org/10.1097/WNR.0000000000000645

Ostlund BD, Alperin BR, Drew T, Karalunas SL (2021) **Behavioral and cognitive correlates of the aperiodic (1/f-like) exponent of the EEG power spectrum in adolescents with and without ADHD** *Dev Cogn Neurosci* **48** https://doi.org/10.1016/j.dcn.2021.100931

Perrin F, Pernier J, Bertnard O, Giard MH, Echallier JF (1987) **Mapping of scalp potentials by surface spline interpolation** *Electroencephalogr Clin Neurophysiol* **66**:75–81 https://doi.org/10.1016/0013-4694(87)90141-6

Perrin F, Pernier J, Bertrand O, Echallier JF (1989) **Spherical splines for scalp potential and current density mapping** *Electroencephalogr Clin Neurophysiol* **72**:184–187 https://doi.org/10.1016/0013-4694(89)90180-6

Pion-Tonachini L, Kreutz-Delgado K, Makeig S. (2019) **ICLabel: An automated electroencephalographic independent component classifier, dataset, and website** *Neuroimage* **198**:181–197 https://doi.org/10.1016/j.neuroimage.2019.05.026

Porjesz B *et al.* (2002) **Linkage disequilibrium between the beta frequency of the human EEG and a GABAA receptor gene locus** *Proc Natl Acad Sci* **99**:3729–3733 https://doi.org/10.1073/pnas.052716399

Pugh KR *et al.* (2014) **Glutamate and choline levels predict individual differences in reading ability in emergent readers** *J Neurosci* **34**:4082–4089 https://doi.org/10.1523/JNEUROSCI.3907-13.2014

Rippon G, Brunswick N (2000) **Trait and state EEG indices of information processing in developmental dyslexia** *Int J Psychophysiol* **36**:251–265 https://doi.org/10.1016/S0167-8760(00)00075-1

Roid GH, Sajewicz-Radtke U, Radtke BM, Lipowska M (2017) **Skala Inteligencji Stanford-Binet, Edycja Piąta. [Stanford-Binet Intelligence Scales, Fifth Edition]. Gdańsk**

Rubino D, Robbins KA, Hatsopoulos NG (2006) **Propagating waves mediate information transfer in the motor cortex** *Nat Neurosci* **9**:1549–1557 https://doi.org/10.1038/nn1802

Rufener KS, Zaehle T (2021) **Dysfunctional auditory gamma oscillations in developmental dyslexia: A potential target for a tACS-based intervention** *Prog Brain Res* **264**:211–232 https://doi.org/10.1016/bs.pbr.2021.01.016

Salvatore S V., Lambert PM, Benz A, Rensing NR, Wong M, Zorumski CF, Mennerick S (2024) **Periodic and aperiodic changes to cortical EEG in response to pharmacological manipulation** *J Neurophysiol* **131**:529–540 https://doi.org/10.1152/jn.00445.2023

Sanes JN, Donoghue JP (1993) **Oscillations in local field potentials of the primate motor cortex during voluntary movement** *Proc Natl Acad Sci* **90**:4470–4474 https://doi.org/10.1073/pnas.90.10.4470

Schaworonkow N, Voytek B (2021) **Longitudinal changes in aperiodic and periodic activity in electrophysiological recordings in the first seven months of life** *Dev Cogn Neurosci* **47** https://doi.org/10.1016/j.dcn.2020.100895

Scrivener CL, Reader AT. (2022) **Variability of EEG electrode positions and their underlying brain regions: Visualizing gel artifacts from a simultaneous EEG-fMRI** *dataset Brain Behav* **12** https://doi.org/10.1002/brb3.2476

Simpson R, Devenyi GA, Jezzard P, Hennessy TJ, Near J (2017) **Advanced processing and simulation of MRS data using the FID appliance (FID-A) – an open source, MATLAB-based toolkit** *Magn Reson Med* **77**:23–33 https://doi.org/10.1002/mrm.26091

Spironelli C, Penolazzi B, Angrilli A (2008) **Dysfunctional hemispheric asymmetry of theta and beta EEG activity during linguistic tasks in developmental dyslexia** *Biol Psychol* **77**:123–131 https://doi.org/10.1016/j.biopsycho.2007.09.009

Szczerbiński M, Pelc-Pękała O (2013) **Zestaw metod do diagnozy trudności w czytaniu** *[A Set of Tools for Diagnosing Reading Difficulties]*

Tan Y, Chanoine V, Cavalli E, Anton J-L, Ziegler JC (2022) **Is there evidence for a noisy computation deficit in developmental dyslexia?** *Front Hum Neurosci* **16** https://doi.org/10.3389/fnhum.2022.919465

Turri C, Di Dona G, Santoni A, Zamfira DA, Franchin L, Melcher D, Ronconi L. (2023) **Periodic and aperiodic EEG features as potential markers of developmental dyslexia** *Biomedicines* **11** https://doi.org/10.3390/biomedicines11061607

van Bueren NER, van der Ven SHG, Hochman S, Sella F, Cohen Kadosh R. (2023) **Human neuronal excitation/inhibition balance explains and predicts neurostimulation induced learning benefits** *PLoS Biol* **21** https://doi.org/10.1371/journal.pbio.3002193

Van Hirtum T, Ghesquière P, Wouters J. (2019) **Atypical neural processing of rise time by adults with dyslexia** *Cortex* **113**:128–140 https://doi.org/10.1016/j.cortex.2018.12.006

Vidal C, Content A, Chetail F (2017) **BACS: The Brussels Artificial Character Sets for studies in cognitive psychology and neuroscience** *Behav Res Methods* **49**:2093–2112 https://doi.org/10.3758/s13428-016-0844-8

Voytek B, Kramer MA, Case J, Lepage KQ, Tempesta ZR, Knight RT, Gazzaley A (2015) **Age-related changes in 1/f neural electrophysiological noise** *J Neurosci* **35**:13257–13265 https://doi.org/10.1523/JNEUROSCI.2332-14.2015

Waschke L, Donoghue T, Fiedler L, Smith S, Garrett DD, Voytek B, Obleser J (2021) **Modality-specific tracking of attention and sensory statistics in the human electrophysiological spectral exponent** *eLife* **10** https://doi.org/10.7554/eLife.70068

Wechsler D (1981) **Wechsler Adult Intelligence Scale-Revised (WAIS-R)**

Wyss C, Tse DHY, Kometer M, Dammers J, Achermann R, Shah NJ, Kawohl W, Neuner I (2017) **GABA metabolism and its role in gamma-band oscillatory activity during auditory processing: An MRS and EEG study** *Hum Brain Mapp* **38**:3975–3987 https://doi.org/10.1002/hbm.23642

Xue H, Wang Z, Tan Y, Yang H, Fu W, Xue L, Zhao J (2020) **Resting-state EEG reveals global network deficiency in dyslexic children** *Neuropsychologia* **138** https://doi.org/10.1016/j.neuropsychologia.2020.107343

Yan X, Jiang K, Li H, Wang Z, Perkins K, Cao F (2021) **Convergent and divergent brain structural and functional abnormalities associated with developmental dyslexia** *eLife* **10** https://doi.org/10.7554/eLife.69523

## Editors



**Reviewer #1 (Public Review):**

Summary:

"Neural noise", here operationalized as an imbalance between excitatory and inhibitory neural activity, has been posited as a core cause of developmental dyslexia, a prevalent learning disability that impacts reading accuracy and fluency. This study is the first to systematically evaluate the neural noise hypothesis of dyslexia. Neural noise was measured using neurophysiological (electroencephalography [EEG]) and neurochemical (magnetic resonance spectroscopy [MRS]) in adolescents and young adults with and without dyslexia. The authors did not find evidence of elevated neural noise in the dyslexia group from EEG or MRS measures, and Bayes factors generally informed against including the grouping factor in the models. Although the comparisons between groups with and without dyslexia did not support the neural noise hypothesis, a mediation model that quantified phonological processing and reading abilities continuously revealed that EEG beta power in the left superior temporal sulcus was positively associated with reading ability via phonological awareness. This finding lends support for analysis of associations between neural excitatory/inhibitory factors and reading ability along a continuum, rather than as with a case/control approach, and indicates the relevance of phonological awareness as an intermediate trait that may provide a more proximal link between neurobiology and reading ability. Further research is needed across developmental stages and over a broader set of brain regions to more comprehensively assess the neural noise hypothesis of dyslexia, and alternative neurobiological mechanisms of this disorder should be explored.

Strengths:

The inclusion of multiple methods of assessing neural noise (neurophysiological and neurochemical) is a major advantage of this paper. MRS at 7T confers an advantage of more accurately distinguishing and quantifying glutamate, which is a primary target of this study. In addition, the subject-specific functional localization of the MRS acquisition is an innovative approach. MRS acquisition and processing details are noted in the supplementary materials according to the experts' consensus-recommended checklist (https://doi.org/10.1002/nbm.4484). Commenting on the rigor, the EEG methods is beyond my expertise as a reviewer.

Participants recruited for this study included those with a clinical diagnosis of dyslexia, which strengthens confidence in the accuracy of the diagnosis. The assessment of reading and language abilities during the study further confirms the persistently poorer performance of the dyslexia group compared to the control group.

The correlational analysis and mediation analysis provide complementary information to the main case-control analyses, and the examination of associations between EEG and MRS measures of neural noise is novel and interesting.

The authors follow good practice for open science, including data and code sharing. They also apply statistical rigor, using Bayes Factors to support conclusions of null evidence rather than relying only on non-significant findings. In the discussion, they acknowledge the limitations and generalizability of the evidence and provide directions for future research on this topic.

Weaknesses:

Though the methods employed in the paper are generally strong, there are certain aspects that are not clearly described in the Materials & Methods section, such as a description of the statistical analyses used for hypothesis testing.

With regard to metabolite quantification, it is unclear why the authors chose to analyze and report metabolite values in terms of creatine ratios rather than quantification based on a water reference given that the MRS acquisition appears to support using a water reference. GABA is typically quantified using J-editing sequences as lower field strengths (~3T), and there is some evidence that the GABA signal can be reliably measured at 7T without editing, however, the authors should discuss potential limitations, such as reliability of Glu and GABA measurements with short-TE semi-laser at 7T. In addition, MRS measurements of GABA are known to be influenced by macromolecules, and GABA is often denoted as GABA+ to indicate that other compounds contribute to the measured signal, especially at a short TE and in the absence of symmetric spectral editing. A general discussion of the strengths and limitations of unedited Glu and GABA quantification at 7T is warranted given the interest of this work to researchers who may not be experts in MRS.

Further, the single MRS voxel location is a limitation of the study as neurochemistry can vary regionally within individuals, and the putative excitatory/inhibitory imbalance in dyslexia may appear in regions outside the left temporal cortex (e.g., network-wide or in frontal regions involved in top-down executive processes). While the functional localization of the MRS voxel is a novelty and a potential advantage, it is unclear whether voxel placement based on left-lateralized reading-related neural activity may bias the experiment to be more sensitive to small, activity-related fluctuations in neurotransmitters in the CON group vs. the DYS group who may have developed an altered, compensatory reading strategy.

As the authors note in the discussion, sex could serve as a moderator of associations between neural noise and reading abilities and should be considered in future studies.

Appraisal:

The authors present a thorough evaluation of the neural noise hypothesis of developmental dyslexia in a sample of adolescents and young adults using multiple methods of measuring excitatory/inhibitory imbalances as an indicator of neural noise. The authors concluded that there was no support for the neural noise hypothesis of dyslexia in their study based on null significance and Bayes factors. This conclusion is justified, and further research is called for to more broadly evaluate the neural noise hypothesis in developmental dyslexia.

Impact:

This study provides an exemplary foundation for the evaluation of the neural noise hypothesis of dyslexia. Other researchers may adopt the model applied in this paper to examine neural noise in various populations with/without dyslexia, or across a continuum of reading abilities, to more thoroughly examine the evidence (or lack thereof) for this hypothesis. Notably, the lack of evidence here does not rule out the possibility of a role for neural noise in dyslexia, and the authors point out that presentation with co-occurring conditions, such as ADHD, may contribute to neural noise in dyslexia. Dyslexia remains a multi-faceted and heterogenous neurodevelopmental condition, and many genetic, neurobiological, and environmental factors play a role. This study demonstrates one step toward evaluating neurobiological mechanisms that may contribute to reading difficulties.

https://doi.org/10.7554/eLife.99920.1.sa2

**Reviewer #2 (Public Review):**

Summary:

This study utilized two complementary techniques (EEG and 7T MRI/MRS) to directly test a theory of dyslexia: the neural noise hypothesis. The authors report finding no evidence to support an excitatory/inhibitory balance, as quantified by beta in EEG and Glutamate/GABA ratio in MRS. This is important work and speaks to one potential mechanism by which increased neural noise may occur in dyslexia.

Strengths:

This is a well-conceived study with in-depth analyses and publicly available data for independent review. The authors provide transparency with their statistics and display the raw data points along with the averages in figures for review and interpretation. The data suggest that an E/I balance issue may not underlie deficits in dyslexia and is a meaningful and needed test of a possible mechanism for increased neural noise.

Weaknesses:

The researchers did not include a visual print task in the EEG task, which limits analysis of reading-specific regions such as the visual word form area, which is a commonly hypoactivated region in dyslexia. This region is a common one of interest in dyslexia, yet the researchers measured the I/E balance in only one region of interest, specific to the language network. Further, this work does not consider prior studies reporting neural inconsistency; a potential consequence of increased neural noise, which has been reported in several studies and linked with candidate-dyslexia gene variants (e.g., Centanni et al., 2018, 2022; Hornickel & Kraus, 2013; Neef et al., 2017). While E/I imbalance may not be a cause of increased neural noise, other potential mechanisms remain and should be discussed.

https://doi.org/10.7554/eLife.99920.1.sa1

**Reviewer #3 (Public Review):**

Summary:

This study by Glica and colleagues utilized EEG (i.e., Beta power, Gamma power, and aperiodic activity) and 7T MRS (i.e., MRS IE ratio, IE balance) to reevaluate the neural noise hypothesis in Dyslexia. Supported by Bayesian statistics, their results show solid 'no evidence' of EI balance differences between groups, challenging the neural noise hypothesis. The work will be of broad interest to neuroscientists, and educational and clinical psychologists.

Strengths:

Combining EEG and 7T MRS, this study utilized both the indirect (i.e., Beta power, Gamma power, and aperiodic activity) and direct (i.e., MRS IE ratio, IE balance) measures to reevaluate the neural noise hypothesis in Dyslexia.

Weaknesses:

The authors may need to provide more data to assess the quality of the MRS data.

https://doi.org/10.7554/eLife.99920.1.sa0