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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

The relation between GABA levels in the SMA region and bimanual coordination

Annelore Struyven

Fraukje Voets

Scriptie ingediend tot het behalen van de graad van master in de revalidatiewetenschappen en de kinesitherapie, afstudeerrichting revalidatiewetenschappen en kinesitherapie bij neurologische aandoeningen

PROMOTOR :

Prof. dr. Raf MEESEN

COPROMOTOR :

dr. Stefanie VERSTRAELEN

BEGELEIDER :

Mevrouw Joana FRIESKE

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Universiteit Hasselt

Campus Hasselt:

Martelarenlaan 42 | 3500 Hasselt

Campus Diepenbeek:

Agoralaan Gebouw D | 3590 Diepenbeek

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Acknowledgements

This experimental study is situated within the domain of neurological science, specifically focusing on motor control, cognition, and the brain. Previous research has explored the role of GABA neurotransmitters in motor control, particularly in the context of aging, but primarily in different brain regions than our focus. Due to the lack of evidence on GABA levels in the supplementary motor area (SMA) among younger and older adults, this study aims to address this gap by investigating the influence of GABA levels on bimanual coordination in the SMA of young, healthy adults. The research question was developed in collaboration with our supervisor.

This master's thesis is part of the larger research project for Frieske Joana's PhD which focuses on the understanding of healthy aging. The thesis was supervised by Prof. Dr. Meesen Raf, Dr. Verstraelen Stefanie and Frieske Joana. Data collection took place at Gasthuisberg Hospital in Leuven from late 2023 to early 2024. This thesis was completed collaboratively with other PhD students and first-year master students. We did not contribute to the research design and methods, as participant recruitment and measurements were overseen by PhD students and first-year master students. We observed one measurement session to understand the procedure better. Data analysis and writing were conducted independently with guidance and feedback from Frieske Joana and Verstraelen Stefanie and some final feedback from Meesen Raf.

Abstract

Bimanual coordination is a concept that cannot be ignored in everyday life e.g. playing the piano, cooking, driving a car. These skills require the ability to synchronize and control movements involving both hands simultaneously, which is a fundamental aspect of human motor function. Findings suggest that this function is regulated by a brain chemical neurotransmitter called gamma-aminobutyric acid (GABA) which helps regulate the activity of our brain cells in specific parts of the brain. This study focuses on the supplementary motor area (SMA), which is involved in planning and executing bimanual movements.

This study explored how the concentrations of GABA+ levels in the SMA relates to our ability to coordinate movements using the bimanual tracking task (BTT). The amount of GABA+ levels was captured by Edited Magnetic Resonance Spectroscopy (MRS).

Levels of GABA+ in the SMA of the brain were examined with MRS in 12 healthy young participants (20-40 years). While the participants were lying in the scanner for approximately 1 hour different scans were made. During the last 16 minutes of the session, the patient would perform the BTT. The data being analyzed is from the MRS scan at resting state and the performance of the BTT task.

The hypothesis of this study proposed that people with higher concentrations of GABA+ levels in the SMA would demonstrate better performance on the BTT. However, the findings indicate no significant correlation between GABA+ levels and BTT scores, suggesting no relationship between GABA+ concentrations in the SMA and participant's performance on the BTT. Which means that GABA+ concentrations can not be used as a predictor of the BTT score.

Keywords: gamma-aminobutyric acid (GABA), supplementary motor area (SMA), bimanual coordination, Bimanual Tracking Task (BTT), Magnetic Resonance Spectroscopy (MRS)

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1. Introduction

Consider a scenario where a person is preparing a salad, with the salad and tomatoes already placed in the bowl, leaving only the cucumber to be sliced. As the person proceeds to cut the cucumber, it becomes essential for them to intermittently pause and push the cucumber forward to prevent accidentally cutting their fingers. This action represents a bimanual task wherein the initiation and cessation of cutting are influenced in part by the neurotransmitter Gamma-aminobutyric acid (GABA) (Maes et al., 2021).
GABA is a neurotransmitter in the central nervous system of the human body. It acts as an inhibitory neurotransmitter to temper neuronal activity in the brain. It does this by binding to specific receptors on the surface of neurons, leading to a reduction in neural excitation. This inhibitory function of GABA is essential for maintaining balance and preventing excessive excitability in the nervous system (Petroff, 2002).

Edited Magnetic Resonance Spectroscopy (MRS) can be used to capture GABA levels in the brain. This non-invasive analytical technique is used in medical imaging and research to examine the chemical composition of tissues or substances (Li et al., 2022). It provides information about the concentration and distribution of various metabolites. It is used to enhance the detection of neurotransmitters at low concentrations, like GABA, that may not be distinguishable in a standard MR spectrum (Saleh et al., 2016).

GABA can be found, among other brain regions, in the supplementary motor area (SMA). The SMA lies in the medial surface of the cortex, from the frontal agranular cortex rostral to the primary motor cortex (M1) (Tanji, 1994). The SMA is interconnected with various brain regions, including the MI, prefrontal cortex (PFC), and other areas involved in sensory processing, for example, the posterior parietal cortex (PPC) (Whitlock, 2017). This network allows for the integration of sensory information with motor planning and execution.
The SMA was found to activate during distal as well as proximal limb movement (Tanji, 1994).
According to Knierem (2020), M1 is responsible for coordinating movement on the contralateral side of the body and requires a minimal amount of stimulation to elicit movements. On the other hand, the SMA is more engaged in coordinating and planning

movements that engage both sides of the body. It is responsible for sequential or consecutive movements, whether they are simple or complex. To execute these movements the SMA needs a higher amount of stimulation and a more complex form of motor planning. It uses higher cognitive functions than the M1 to plan and perform these movements (Knierem, 2020).

A more complex task in which the SMA seems to be involved is the bimanual tracking task (BTT) (Van Ruitenbeek et al., 2022). Bimanual tracking task (BTT) involves the simultaneous and coordinated use of both hands to control the position or movement of a target or object. The BTT requires a combination of visual tracking skills and bimanual motor coordination, demanding participants to translate visual information into coordinated hand movements. This is where GABA plays a crucial role. It must ensure that a finger ceases a particular movement at a specific speed, allowing for a transition to another speed or a change in the finger's direction (Boisgontier et al., 2018).

Several studies have identified the role of GABA neurotransmitters and motor control in the context of aging. In these studies, the region of interest (ROI) has mostly been focused on the M1 or the sensorimotor cortex (SM1). In Maes et al. (2021) they found that elevated GABA levels correlated with enhanced manual dexterity among older adults, whereas increased GABA levels were indicative of poorer performance on bimanual coordination tasks in young adults. More research is still needed on this topic to fully understand the neurochemical mechanisms underlying bimanual coordination.
Up until now, very little is known about the specific role of GABA in the SMA in relation to motor control. In a study conducted by Draper et al. (2014), they found that the concentrations of GABA in the SMA in persons with Tourette syndrome show a negative correlation with performance on tasks assessing the nonconscious control of motor outputs, for example, the STOP task, in which participants had to respond to arrow stimuli by pressing a button corresponding to the arrow's direction. During the test, if an auditory signal (a beep) occurs, they must withhold their response. In prior research in a healthy population, exemplified by the study conducted by Boy et al. (2010), it was found that elevated GABA levels in the SMA were linked to decreased responsiveness of subconscious motor mechanisms, such as reflexes, in young adults. However, while these studies appear to

endorse the notion that elevated GABA levels are associated with worse performance, other research suggests that higher GABA levels are connected to enhanced fine-tuning of neural activity, consequently promoting better performance. More precisely, heightened thalamic GABA/water levels were indicative of improved response selection, as reported by Dharmadhikari et al. (2015).
Overall there is a lack of evidence about the GABA levels in SMA in younger and older adults and this study tries to fill the gap in the evidence about younger adults.

In the current study, we aim to investigate the influence of GABA levels on bimanual coordination in the SMA. We examine bimanual coordination performance using the BTT in young healthy adults. We hypothesize that higher GABA levels will be associated with better performance of the BTT due to its inhibitory characteristics and lower GABA levels will be associated with poorer performance. Hence, we expect a positive correlation between GABA levels and BTT performance.

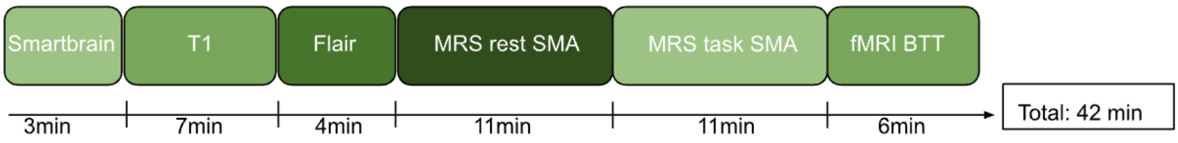
2. Methode

2.1. Experimental design and procedure

Figure 1 shows the timeline of the MRI-session, where we will focus on the MRS scan of the SMA in resting state. The participant would lay in the MRI-scanner for approximately 1 hour while undergoing different scans. During the first 25 minutes of the session, the patient has to lay still while the MRI performed anatomical scans: a smartbrain scan (3 minutes), a T1 scan (7 minutes), a FLAIR scan (4 minutes) followed by a MRS scan of the SMA at resting state (11 minutes). During the last 16 minutes of the session, the participant would perform the BTT while the MRI acquired a MRS scan of the SMA during task state (11 minutes) and a fMRI (6 minutes). During the third and fourth sessions, participants will undergo Transcranial Magnetic Stimulation (TMS) procedures lasting up to 1.5 hours. These sessions will involve determining the Resting Motor Threshold (rMT), performing the Bimanual Tracking Task (BTT) and Corticospinal Excitability (CSE) assessments, and receiving either real or sham Continuous Theta Burst Stimulation (cTBS).
The data being analyzed is from the MRS scan at resting state and the performance of the BTT task.

Figure 1

MRI Timeline



Note. Bimanual Tracking Task (BTT), Functional Magnetic Resonance Imaging (fMRI), Magnetic Resonance Spectroscopy (MRS), Supplementary Motor Area (SMA)

2.2. Participants

In this study 12 young adults (7 female/5 male, aged 21 – 39 years, mean ± SD = 24,58 ± 5,47) participated. All participants were healthy, right handed (Oldfield, 1971) adults between the age of 20 and 40 with corrected-to-normal vision showing no contra-indications for MRI were indicated.

Participants were excluded if they were regular smokers, had a history of major neurological diseases (including prior brain trauma) or known structural abnormalities in the brain, had a history of diseases that could interfere with the examination (especially those related to the liver, kidneys, upper limbs, diabetes, or cancer), had a mental disorder (such as depression, bipolar disorder, schizophrenia, or psychosis), showed significant abnormalities on the MRI scan of the brain (including structural damages indicating injury, as well as lesions, inflammation, swelling, and bleeding), experienced claustrophobia, were pregnant or breastfeeding at the time of the study , used illicit drugs or had a history of drug or alcohol abuse, chronically used medication, especially sedatives or sleep medication (although contraceptives were allowed), had difficulty performing the motor exercises of the study, had a history of regular high bimanual coordinative demands within the past 5 years, or had previously participated in a motor control study using the same task. Additionally, participants with contra-indications for undergoing an MR examination, such as the presence of magnetizable material in the body, were excluded. The researcher conducted a standard MRI screening to assess eligibility. Participants who did not understand the study procedures or did not agree with the study program were also excluded. Furthermore, there were restrictions on the amount of caffeine (<4 units/day) and alcohol (<2 units/day) participants could consume on both the day before and the day of the MR examination and TMS measurements.

All participants provided informed consent before the experiment. The study protocol adhered to the Declaration of Helsinki (1964) and received approval from the Ethics Committee Research of UZ/KU Leuven (study number S66028).
The participants were recruited through posters in hospitals, university campuses or through social media posts.

2.3. Data collection

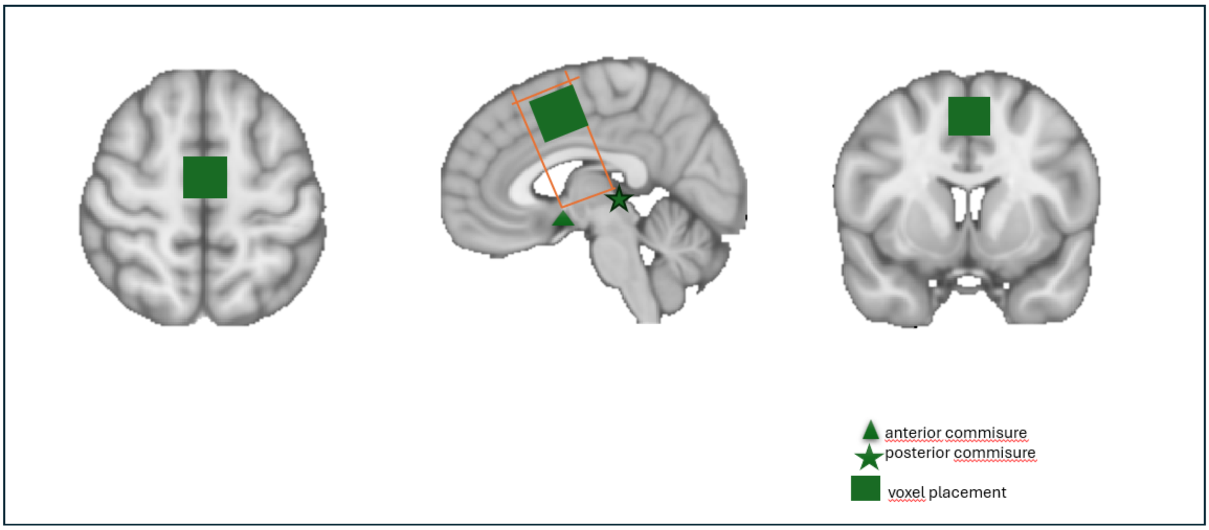
2.3.1. Magnetic resonance spectroscopy

The scanning was completed by Hadamard Encoding and Reconstruction of MEGA-Edited Spectroscopy, from now on referred to as HERMES. HERMES serves as an advanced and powerful tool within MRS for enhancing the identification and resolution of various metabolites in a single experimental setup.
MR spectra were acquired using HERMES editing with 20ms editing pulses applied at 1.9ppm and 4.56ppm with TR/TE = 2000/80ms.

MRS measurements were performed at specific spatial locations, often referred to as voxels. A voxel (volume element) is a three-dimensional unit representing a small portion of the overall image or sample. In this study, a voxel with a dimension of 30x30x30 millimeters is used. Figure 2 shows the voxel placement on SMA in a single subject. First, the voxel has to be oriented completely neutral in all three planes. Next, there a horizontal line was drawn between the anterior commisure (AC) and the posterior commisure in the sagittal plane. Further, two perpendicular lines to the previous (AC-PC) line mark the borders in which the center of the SMA voxel is located. The two perpendicular lines are one from the AC towards the top of the brain and another one from the PC towards the top of the brain. Lastly, it is necessary to make sure that the voxel does not touch the skull or ventricles because it could influence the measurement of GABA levels.

Figure 2

Voxel Placement



Note. An example of how a voxel is placed on the SMA. The green box shows the voxel on the SMA. The orange box represents the horizontal line drawn between the anterior commisure and the posterior commisure and the two perpendicular lines. One line from the AC towards the top of the brain and another one from the PC towards the top of the brain.

2.3.2. MRS-analysis

To perform the analysis of the MRS data program called Osprey is used. Osprey is a comprehensive software package that integrates every stage from preprocessing to linear-combination modeling to quantification and visualization of MRS data. This program can be downloaded in matlab which makes it easier to perform the analysis. The program consists of 7 steps, also referred to as modules. First, all the data and images as well as the parameters for data processing and linear combination modeling, are specified. Second, the raw spectroscopic data and extracts of all necessary information for the subsequent modules were imported. Thirdly all essential procedures are executed to convert the raw, unaligned, unaveraged data into spectra that are prepared for modeling. Next, a linear combination of basis functions was applied to model the processed spectra. The following modules guaranteed the accuracy of the voxel placement and overlayed the voxel mask with the probability maps of the grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Subsequently, the fractional tissue volumes for GM, WM, and CSF are calculated using an implemented formula. In the final step diverse quantitative results are computed, contingent on the modeling parameters established during the first module.

Osprey stores all quantitative results for the entire job in comma-separated value tables (CSV). This format allows easy access and integration with external software tools like JMP or SPSS for subsequent statistical analysis and visualization (Oeltzschner et al., 2020). Only the alpha corrected GABA+ levels will be used in the statistical analysis from the quantitative results.

2.4. Bimanual Tracking Task

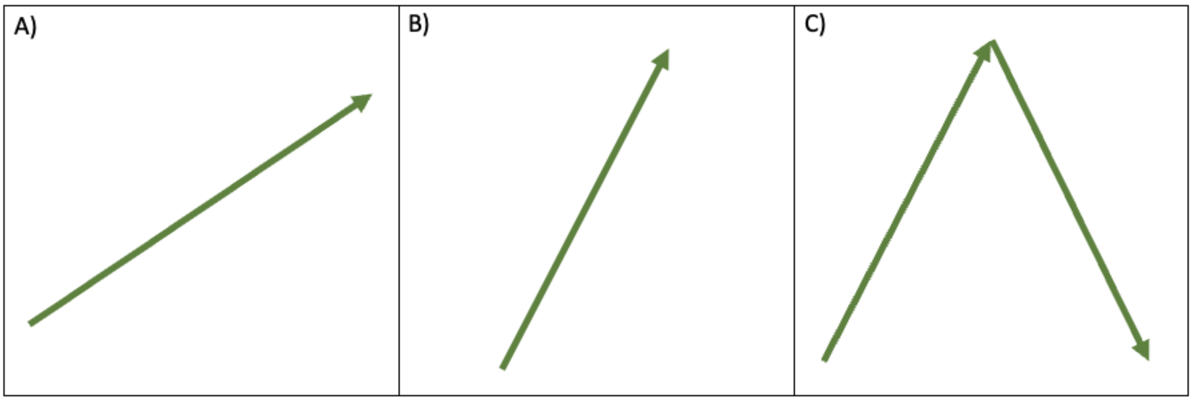
The BTT is a bimanual visuomotor tracking task performed with two fingers moving discs connected to a computer display. By moving the two discs, a cursor will move up and down with one disc and left and right with the other disc. The goal is to follow a line with the cursor by moving the two discs simultaneously. The two hands have to work together and constantly adapt to each other (Boisgontier et al., 2018).

Figure 3 shows the three different conditions the participants had to perform. The first one, called Line11, had a frequency ratio of 1:1 for both hands. The second one, Line31, had a frequency ratio of 3:1, which means that the left finger had to turn three times faster than the right finger. For these two conditions, both fingers had to turn to the left as in clockwise movements. The third one, Angle31, also had a frequency ratio of 3:1 but when the participant reached the top of the angle, they had to switch the direction of the right finger to anti-clockwise.

The conditions are divided into six possible block designs. The block designs were randomized across the participants to avoid an order effect, which means that the order of the presentation of each condition changed depending on which version of the block design the participant got. How well these conditions were performed, were expressed as percentages.

Figure 3

Conditions BTT



Note. This visual represents A) Line 11, B) Line 31 and B) Angle 31. The point of the arrow indicates which path the cursor needs to follow.

2.5. Statistical analysis

The statistical analysis was performed with JMP, a statistical software package utilized for data visualization, exploratory data analysis, and statistical modeling. Correlation analyses were performed to look into the relationship between GABA+ levels at rest within the SMA and the performance of the BTT. The Pearson correlation analysis was performed using a Fit Y by X model where BTT score was placed as the dependent variable and GABA+ levels as the independent variable. The conditions for this analysis included ensuring normality of both variables, independence of data and linearity. These were performed using a distribution analysis and the graph created through Fit Y by X. The Spearman correlation analysis was performed using the multivariate model. With the Spearman correlation analysis being a non-parametric test, there were no assumptions that needed to be ensured.

To further look at the complexity within the three conditions of the BTT and GABA+ levels, a multivariate model was used. The conditions of this analysis were the same as in the previous correlation analyses. The multivariate model was performed where the BTT score for each line individually was the dependent variable and GABA+ levels was the independent variable.

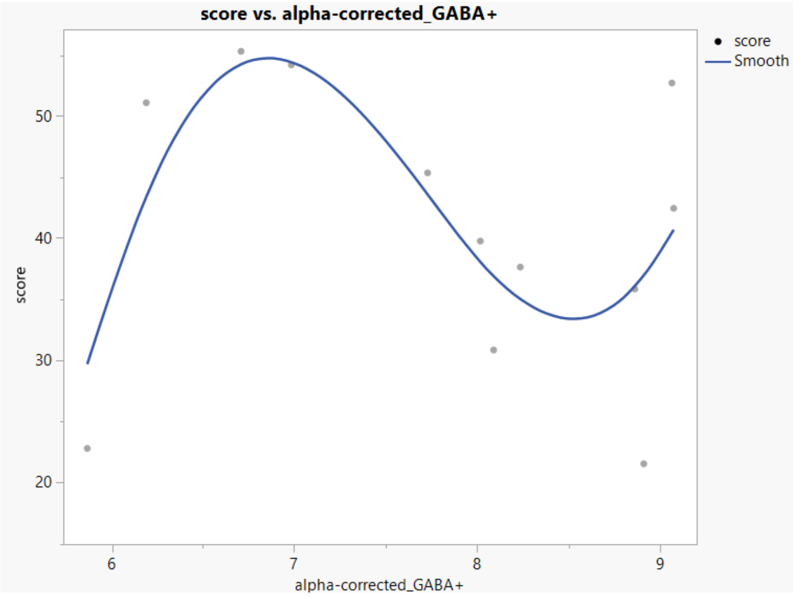
A linear regression analysis was conducted to investigate the relationship between variables GABA+ levels and BTT score. The conditions of this analysis were normality of the residuals, independence of data, linearity and homoscedasticity. These were performed using a FIT Y BY X model using the function linear fit and plot of residuals. The regression analysis was performed using a FIT Y BY X model using the fit line. The dependent variable represents BTT score, while the independent variable represents GABA+ levels. The regression equation was modeled as: $Y = \beta_0 + \beta_1 * X + \varepsilon$, where Y refers to the BTT score, β_0 is the intercept, β_1 refers to the GABA+ levels and is the slope of the regression line , and ε is the error term.

3. Results

In the output, the Pearson correlation for continuous variables was examined. This output should be interpreted with caution because no linearity could be seen in the visual output of the data, which could partially explain the not significant correlation. The P-value of 0,6247 ($p < 0,05$) indicated that there was no significant correlation between GABA+ levels and the BTT score. The correlation coefficient had a value of -0,15761 which is close to zero which indicated a very weak and negative correlation (Faizi & Alvi, 2023). In addition to the Pearson correlation, the non-parametric variant, the Spearman correlation, was also performed to make sure the conclusion was valid. The P-value of 0,5128 ($p < 0,05$) indicated that there was no significant correlation between GABA + levels and the BTT score and confirmed the conclusion. The correlation coefficient had a value of -0,2098 which is close to zero and indicates a very weak and negative correlation (Faizi & Alvi, 2023). Figure 4 shows a visualization of the correlation.

Figure 4

Correlation between GABA+ levels and BTT score



Note. In the graph the gray dots represent the overall score of each participant on the BTT. The blue line shows the relation between the GABA+ levels and the overall score of the BTT. The gray dots exhibit a high degree of spreading, while the blue line crosses among them, thereby visually indicating the absence of correlation.

The multivariate output shows a non-significant effect of the GABA+ levels on the BTT score of Line11 with a P-value of 0,7671 ($p < 0,05$). Also, Line31 with a P-value of 0,5163 ($p < 0,05$), as well as Angle31 with a P-value of 0,6782 ($p < 0,05$), resulted in a non-significant effect. The correlation coefficient for Line11 had a value of -0,0958, for Line31 a value of -0,2081 and for Angle31 a value of -0,1339 which are all close to zero indicating a very weak and negative correlation (Faizi & Alvi, 2023). This output should be interpreted with caution because no linearity could be seen in the visual output of the data, which could partially explain the not significant correlation.

The results of the regression analysis indicated that GABA+ levels had not a significant effect on the BTT (F_{11}= 0,2551, $p = 0,6244$), indicating that changes in GABA+ levels don't have a predictive value for the BTT score. The $\beta 1$ estimate value of the GABA+ levels is -1,6215 and the P-value of the model is 0,6244 ($p < 0,05$) which is not significant.

4. Discussion

The current study aimed to investigate the influence of GABA levels on bimanual coordination in the SMA among young healthy adults. By examining bimanual coordination performance using the BTT while lying in a MRI scanner where a MRS scan was performed, the study tried to understand the predictive role of GABA, an inhibitory neurotransmitter, in motor control tasks.

The findings of this study provide valuable insights into the relationship between GABA levels and bimanual coordination. Unlike the initial hypothesis, the results of the correlation analyses did not show a significant correlation between GABA levels in the SMA and performance on the BTT. This suggests that variations in GABA levels may not directly predict or influence bimanual coordination abilities in the SMA in young healthy adults. The results of the regression analyses suggest that there is no relationship between GABA+ levels and how well the participant performed on the BTT. These results don't support the hypothesis that GABA+ levels are a significant predictor of BTT scores.

Previous studies have predominantly focused on regions such as the primary motor cortex (M1) (Loomes et al., 2023) or the sensorimotor cortex (SM1) (Hu et al., 2022) when investigating the relationship between GABA levels and motor function. However, the current study expands this focus to include the SMA, a region known for its involvement in motor planning and coordination of movements involving both sides of the body.

The existing literature about GABA+ levels and bimanual coordination has been inconsistent. There were a number of studies e.g. Draper et al. (2014) and Boy et al. that found the same negative correlation but there were other studies e.g. Dharmadhikari et al. (2015) and Li et al. (2022) that found a positive correlation. In summary, research findings regarding the relationship between GABA levels and motor performance are complex and sometimes contradictory. Draper et al. (2014) observed a negative correlation between GABA concentrations in the SMA and motor performance in individuals with Tourette syndrome, suggesting that higher GABA levels may impair nonconscious control of motor outputs. Similarly, Boy et al. (2010) found that elevated GABA levels in the SMA were associated with decreased cortical responsiveness in healthy young adults, implying a potential negative impact on motor function. However, contrasting these findings, other studies, such as that by Dharmadhikari et al. (2015), have suggested that higher GABA levels, particularly in the thalamus, may actually enhance response selection and improve performance. Li et al.

(2022) suggested that higher levels of GABA+ assist in improving performance by enhancing the way neural information is represented during task execution and by better managing distractions and suppressing unwanted responses.

The lack of a significant correlation between GABA levels and bimanual coordination performance in the SMA suggests that other factors or neural mechanisms may play a more substantial role in mediating bimanual motor tasks. It is possible that additional neurotransmitters, neural networks, or cognitive processes contribute to the coordination of movements between the hands. For instance, as GABA functions as an inhibitory neurotransmitter, its counterpart, glutamate, acts as an excitatory neurotransmitter. Alterations in glutamate and GABA metabolism may significantly influence the regulation of cortical excitability (Petroff, 2002). It may be worth considering to focus on the excitatory component of bimanual coordination rather than the inhibitory component. However, in addition to GABA and glutamate, various other neurotransmitters may also play a role.
Or following Swinnen and Gooijers (2015), who suggest that due to the complexity of these bimanual movements, various motor brain regions need an effective coordination to perform motor actions. Furthermore, the study of Gerloff and Andres (2002) suggests that a broad cortical network is involved in bimanual motor activities. Maes et al. (2021) proposed that the following four regions were the most important for bimanual coordination. Firstly, the SM1 which is the main output of motor control (Sadato et al., 1997). Secondly, the SMA which is involved in coordinating and planning more complex bimanual movements (Knierem, 2020). Thirdly, the dorsal premotor cortex (PMd) which is more responsible for the cognitive side of performing bimanual tasks such as motor learning (Abe & Hanakawa, 2009). Lastly, the dorsolateral prefrontal cortex (DLPFC) which is involved in the motor control of bimanual coordination with a strong correlation to spatiotemporal complexity (Debaere et al., 2004). Further research should look into the coordination between these regions needed to perform bimanual movements.

Considering these factors, new hypotheses could be developed for future research to explore these aspects more thoroughly, aiming to provide a comprehensive understanding of bimanual coordination mechanisms.

5. Limitations

This study does have a few limitations. First of all, the sample size of only 12 people is very small. A small sample size can introduce bias because the results may not be representative of the broader population. This may have contributed to the absence of a certain correlation between GABA+ levels and BTT, but this is an assumption. It also reduced the strength and the generalizability of the findings. Another limitation of the sample size is that there were more women than men included. Including a larger and more diverse sample could provide a more comprehensive understanding of the relationship between GABA levels and bimanual coordination. A third limitation is that placing the voxel on the scans is done manually. This may have resulted in the voxels not being uniformly aligned due to human errors. Because humans were doing this task, there's a chance they made mistakes. As a result, the voxels might not all be lined up perfectly across the scans. This inconsistency could affect the accuracy and reliability of the results. Toward the future in longitudinal studies, using automatic voxel positioning looks promising because it can make results more reliable. The results demonstrate in Bishop et al. (2021) that automated voxel placement reduces variability and increases reproducibility. The findings in Deelchand et al. (2022) showed that the automated method saved time and made it easier to get good spectroscopic data. This simple-to-use approach could make collecting MRS data in hospitals much smoother.

Some additional limitations were matters that were taken into account less or not at all, but which could have an influence such as hormonal imbalances, dietary fluctuations, the amount of sleep, stress. Hormonal imbalances, which may play a role in influencing GABA+ levels. Specifically, changes in the levels of estradiol, progesterone, and the progesterone metabolite allopregnanolone can have significant effects on the functioning of the GABA system in the brain (Gilfarb & Leuner, 2022). Results indicate that the high-fat diet leads to a decrease in GABA levels in both the prefrontal cortex (PFC) compared to a standard diet (Reichelt & Rank, 2017). Park et al. (2020) mentioned that a shorter duration of sleep correlated with reduced GABA levels in the anterior cingulate cortex (ACC) and the motor prefrontal cortex (PFC). The PFC plays a role in executing high level cognitive functions which can have an influence on the planning and coordination of the SMA.

6. Conclusion

Contrary to our initial hypothesis that posited a positive relationship where higher GABA levels would correlate with better BTT performance, due to GABA's inhibitory characteristics, our findings revealed no significant correlation between GABA+ levels and BTT scores.
The absence of a discernible relationship between GABA concentrations in the SMA and bimanual coordination performance contradicts some existing literature, which has linked higher GABA levels with better performance. But there is also some evidence that has linked higher GABA levels with worse performance.
This discrepancy highlights the complexity of GABA's role in motor control, particularly within the SMA, underscoring the need for further studies to unravel the mechanisms of bimanual motor tasks.
Furthermore, while prior research has often focused on motor areas like the primary motor cortex (M1) and the sensorimotor cortex (SM1), our study extends this scope to the supplementary motor area (SMA), suggesting that factors beyond GABA+ levels may be crucial in modulating bimanual coordination. These findings prompt a broader investigation into additional neurotransmitters, neural circuits and other cognitive processes that could play significant roles in coordinating bimanual activity.
Given the limited sample size and other methodological constraints, future research should aim for a bigger and more diverse sample size, more attention to sleep quantity, hormonal imbalances and dietary fluctuations and maybe find a standardized method to place the voxel.
In conclusion, while our study did not find a direct link between GABA levels in the SMA and bimanual task performance, it opens the door to new hypotheses and research options, potentially leading to a more comprehensive understanding of motor control dynamics.

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