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Faculteit Revalidatiewetenschappen

master in de revalidatiewetenschappen en de kinesitherapie

Masterthesis

Age-Related Changes in SMA GABA Levels and Their Impact on Bimanual Coordination

Wietse Vandebril
Nina Verheyden

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

PROMOTOR :
Prof. dr. Raf MEESEN

BEGELEIDER :
Mevrouw Joana FRIESKE

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Acknowledgements

This experimental study is situated within the field of neuroscience, with particular attention to motor control, cognitive processes and brain function. Previous research on bimanual coordination has focused primarily on the role of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) in various brain regions, with limited attention to the Supplementary Motor Area (SMA). Since little is known about the contribution of GABA levels in the SMA to bimanual coordination, this study aims to fill a gap in the existing literature. The research question was formulated in consultation with our supervisor, Frieske Joana.

This master's thesis is part of Frieske Joana's broader PhD research, focusing on bimanual performance in the context of healthy aging. Supervision was provided by Prof. Dr. Raf Meesen and Frieske Joana. Data collection took place at UZ Leuven, Campus Gasthuisberg, between late 2023 and mid-2024, in collaboration with other PhD students and first-year master's students. We actively participated in collecting the data with them. The data analysis and writing of this master's thesis were then done independently, with substantive support and interim feedback from Frieske Joana, and final editing by Prof. Dr. Meesen.

Abstract

Background Bimanual coordination is essential for many daily actions, but tends to deteriorate with age. Neurochemical processes may contribute to this, particularly the inhibitory neurotransmitter GABA in the Supplementary Motor Area (SMA). However, it is unclear how GABA levels in the SMA change with age and how these changes are related to motor performance.

Objectives This study investigated (1) whether resting GABA levels in the SMA differ between younger and older adults, and (2) whether task-related GABA modulation is related to performance on the Bimanual Tracking Task (BTT), a validated measure of bimanual coordination.

Methods Fifty-two right-handed, healthy participants (27 younger and 25 older adults) performed the BTT in an MRI scanner. GABA concentrations in the SMA were measured via Magnetic Resonance Spectroscopy (MRS) both at rest and during the task. An independent t-test was used to compare GABA resting levels between young and older adults. Linear models were used to analyze the relationship between GABA modulation and BTT performance.

Results No significant difference was found in resting GABA levels between younger and older adults ($p = 0.0813$). GABA modulation did not significantly predict BTT performance ($p = 0.9767$), and there was no interaction with age group. However, older adults did perform significantly worse than younger ones ($p < 0.0001$).

Conclusion Although age affects bimanual coordination, differences in resting GABA or task-related GABA modulation in the SMA do not appear to explain this decline. Further research is needed into other brain regions and multimodal explanatory models.

Keywords: Bimanual Coordination; Gamma-Aminobutyric Acid (GABA); Supplementary Motor Area (SMA); Bimanual Tracking Task (BTT); Magnetic Resonance Spectroscopy (MRS); aging.

1. Introduction

Bimanual coordination, the simultaneous use of both hands, is an essential part of activities of daily living, such as cooking or dressing. A decline in bimanual coordination performance can limit functional independence in older adults. Moreover, tasks that require both hands are almost twice as frequent in daily life compared to unimanual tasks (Goble et al., 2010; Krehbiel et al., 2017).

Multiple studies have shown that bimanual coordination deteriorates with age. Movements are performed more slowly, less accurately, and with more variability (Maes et al., 2017; Krehbiel et al., 2017). The study of Maes in 2021 confirmed these observations, where the performance on bimanual coordination tasks between young and older adults was compared. They found that older adults performed less accurately on the Purdue Pegboard test, the finger-tapping tasks (simultaneously and alternating), and the Bimanual Tracking Task (BTT) than younger adults. Another finding of this study is that older adults perform less accurately with increasing task complexity. (Maes et al., 2017, 2021). The Bimanual Tracking Task (BTT) is a visual-motor coordination task designed to measure the cooperation between both hands. Participants use two rotary knobs to control a cursor over a computer screen with both hands simultaneously. The task allows evaluation of bimanual coordination under different frequency ratios and movement directions, providing insight into underlying motor control mechanisms. (Sisti et al., 2011).

To better understand the decline in bimanual coordination, it is essential to look at the role of neurophysiological processes, such as the action of Gamma-aminobutyric acid (GABA). GABA is the most important inhibitory neurotransmitter in the brain. It reduces the excitability of nearby neurons by hyperpolarizing membrane potentials, thus reducing the likelihood of firing. This is necessary for regulating neural activity and thus refining motor performance during bimanual tasks (Li et al., 2024). Research by Maes et al. (2021) shows that high levels of GABA are found in the Supplementary Motor Area (SMA) compared to other brain regions, indicating that this area could play a vital role during bimanual tasks. Higher GABA levels in the brain in young adults were associated with reduced performance during the BTT. At the same time, no significant relationship was observed in older adults (Maes et al., 2021). In particular, the SMA plays an essential role in internally controlling movements and coordinating cooperation between the two hemispheres of the brain (Sadato et al., 1997; Swinnen & Wenderoth, 2004 in Maes et al., 2021). The study by Goble et al. (2010) found

increased activation of the Supplementary Motor Area (SMA) in older adults while performing bimanual coordination tasks using functional MRI. These findings suggested a compensatory mechanism to correct the reduction in bimanual coordination (Goble et al., 2010).

Chalavi et al. (2018) found that lower resting GABA levels in primary sensorimotor cortex (SM1) were associated with higher accuracy in bimanual coordination during initial performance of the BTT. Nevertheless, this relationship disappeared as task performance progressed. (Chalavi et al., 2018). Maes et al. (2022) found that GABA levels in the SM1 decline during bimanual coordination tasks in younger and older adults. Notably, the deterioration was larger in older adults. Another finding of this study was that a greater decline in GABA levels in older adults is associated with better task performance, while in younger adults, this was associated with lower performance. (Maes et al., 2022). However, GABA levels in rest and task-related GABA levels reflect different features of GABA tone (Maes et al., 2022). Functional MRS (fMRS) is a technique that uses MRS to measure changes in metabolite concentrations (for example GABA) in response to external stimuli by collecting data at different time points associated with stimulus presentation. (Pasanta et al., 2023). This will benefit the understanding of the functional role of neurotransmitters like GABA.

Because of the lack of studies available that look into the age-related changes of GABA levels, specifically in the SMA during bimanual coordination, this study further investigates this relationship with the following two-part research question: How do GABA levels in the Supplementary Motor Area (SMA) change with aging, and how are changes in GABA levels related to motor performance in bimanual tasks? Because of GABA's function in regulating neural activity and refining motor performance and previous evidence, this study hypothesizes that GABA rest levels will be lower in the SMA in older adults compared to younger adults and that greater GABA modulation in the SMA are associated with a better score on the BTT test in older adults.

2. Methods

2.1. Participants

Twenty-seven younger (15 females, aged between 20-39, mean ± SD 25.3 ± 4.8) and twenty-five older adults (15 females, aged between 61-79, mean ± SD 68.4 ± 4.8) participated in this study. All participants were right-handed, verified using the Edinburgh Handedness Inventory (≥ 50). Participants had no contraindications to the MRI, had good physical fitness (measured by the International Physical Activity Questionnaire), and good mental health (measured by the Beck Depression Inventory-II, score ≤ 13). The Montreal Cognitive Assessment (MOCA) was administered to assess participants' cognition. Participants with a score lower than 25 were excluded from the study. Participants read and signed the informed consent form, and the ethics committee from UZ Leuven approved the study on 24th January 2022 (S66028).

2.2. Experimental design

Participants were screened in building De Nayer, KU Leuven Sportcampus Arenberg, during the first session. Various questionnaires and bimanual coordination tests (see 2.3) were completed. During this first session, participants lay down in the mock scanner to experience the environment of an MRI scan. The MRI, MRS, and fMRI measurements were performed in the second session.

2.3. Bimanual Tracking Task (BTT)

The Bimanual Tracking Task (BTT) was used to assess bimanual coordination. The task consisted of a planning phase and an execution phase, in which the line was visualized first (planning phase). A signal indicated the start of the execution phase. The dials' direction and frequency determined how the cursor was moved. The participant followed the lines as accurately as possible by turning both knobs bimanually, with a red line appearing as visual feedback. This allowed for different combinations (Figure 1). The frequencies are the difference between the rotation speed between the left and right hand (left:right). Frequency 1:1 indicates turning both knobs simultaneously at the same rate. Frequency 3:1 means turning the knob three times faster with the left hand than with the right hand. One angle was used with a frequency of 3:1, in which the turning of the left knob changes from clockwise to counterclockwise. The BTT was assessed based on tracking error (Figure 2). Scores were

calculated offline by comparing the participant's actual movement trajectory (red line) with the target pattern (blue line). For each point in the trajectory, the closest point on the target pattern was identified. It was marked as "covered" (green points) if such a point was reached. The final score was expressed as the percentage of covered points relative to the total number of target points. (Zivari Adab et al., 2020). An accurate, smooth, consistent movement closely following the target pattern results in a high score. Deviations, as well as moving too fast or too slow, reduce the score. A disadvantage of this scoring method is that if the participant's actual movement trajectory is parallel to the target pattern, this would also give a high score. For this reason, Hehl et al. (2025) modified the scoring so that this parallel line cannot receive a perfect score.

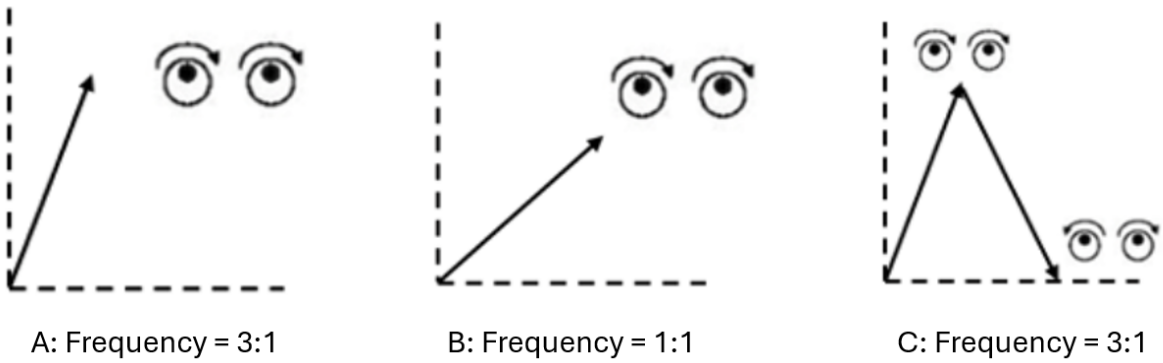


Figure 1: Frequencies of the BTT task.

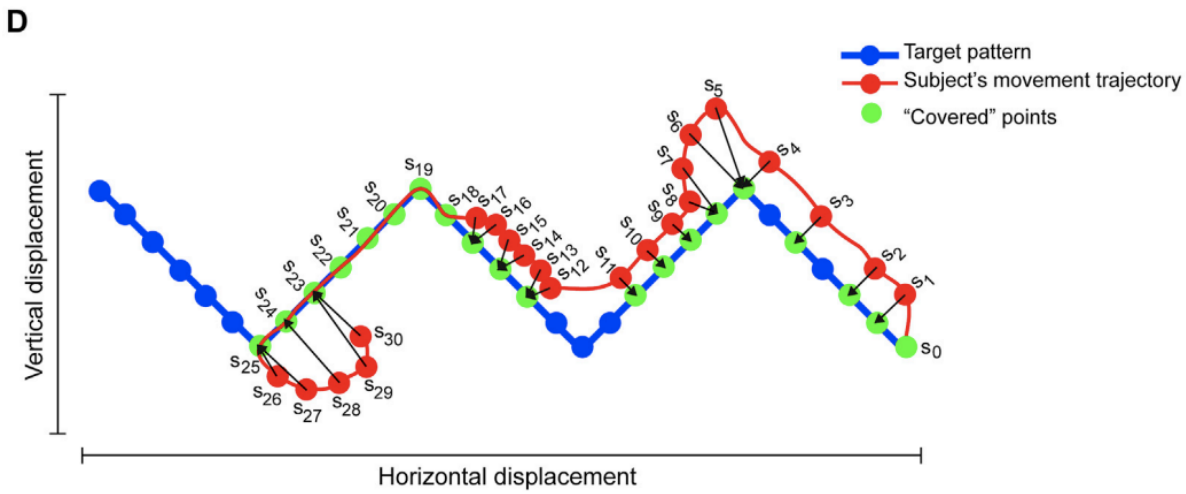


Figure 2: Assessment of the BTT-task, figure adapted from Zivari Adab et al., 2020.

2.4. Procedure

The participants arrived at UZ Leuven Campus Gasthuisberg, where they were registered before the MRI session. MRI safety questionnaires were reviewed again during this session, and all metal and magnetic objects were removed. The participant received earplugs and headphones for noise protection and was placed inside the MRI scanner (Philips Achieva dStream 3 Tesla scanner with a 32-channel head coil). To ensure minimal movement during the scan, the head is stabilized. The BTT task equipment is positioned atop the participant and adjusted accordingly. An emergency button was provided to the participant for use in an emergency. A laser was aligned at the center of the participant's head, and the mirror was adjusted to allow them to see a screen. The participant was then gently moved into the MRI scanner. Communication remained open throughout the procedure via a microphone.

The session began with a T1-weighted structural scan, followed by a FLAIR scan. Here, brain abnormalities are checked. For the MRS sequence, a 3 × 3 × 3 cm^3 voxel was placed on the SMA, just above the pons, in the sagittal plane. This was done by drawing two vertical lines through the anterior and posterior commissure. The top of the voxel ran parallel to the skull, as shown in Figure 3.

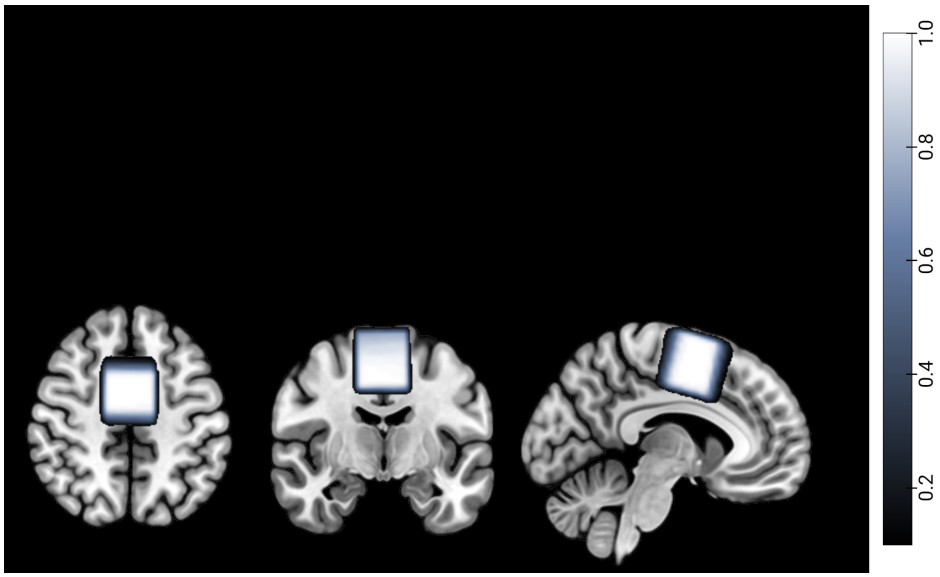


Figure 3: Placement of the voxel on the SMA.

2.4.1. MRS data acquisition

Spectroscopic data were collected with a Hadamard Encoding and Reconstruction of MEGA-Edited Spectroscopy (HERMES) sequence, using a repetition time (TR) of 2000 ms and an echo time (TE) of 80 ms. Three hundred twenty water-suppressed signal averages and 16 unsuppressed scan averages were recorded, with a spectral width of 3 kHz and 1024 data points.

Spectroscopic data were preprocessed and quantified using Gannet software package version 3.3.2, a specialized tool for the analysis of GABA-edited MRS data. (Edden et al., 2014). To prepare the data for analysis, zero-filling was performed and a 3 Hz exponential line broadening filter was applied. Frequency and phase corrections were subsequently carried out using spectral registration. (Mikkelsen et al., 2018).

A three-Gaussian model with a least-squares fitting was applied to the difference spectra within the 2.79 to 4.10 ppm range to measure the GABA+ (3.0 ppm) and Glx (3.75 ppm) peaks. To obtain metabolite concentrations, the water signal was modeled using a Gaussian-Lorentzian model between 3.8 and 5.6 ppm. Through the use of Statistical Parametric Mapping (SPM), Grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) were segmented from high-resolution T1-weighted images. MRS voxels were subsequently aligned with their respective anatomical images. Tissue correction of metabolite concentrations was performed using group-normalized alpha-correction. (Harris et al., 2015; Porges et al., 2017).

Visual inspection was carried out for all processed data to assess spectral quality and detect potential artifacts. Quantitative data quality assessment of GABA+ and Glx was based on fitting error (>12%), signal-to-noise ratio (SNR) and full-width-half-maximum (FWHM). Data falling more than three standard deviations (SD) from the group mean on either SNR or FWHM were removed from further analysis. One participant exhibited a GABA+ fit error of approximately 19% in the task condition. However, upon inspection of the unaligned spectrum, the fit error, SNR, and FWHM values were within acceptable limits, and both Glx and GABA peaks were clearly visible. Two participants (older adults: n = 2) were excluded due to insufficient data quality in the resting-state condition.

After this, the participant performed the BTT task. During the task, another MRS measurement was administered. Finally, an fMRI was performed while the participant continued the BTT task. All collected data were exported, which included MRS and BTT-outcomes. The participant was carefully removed from the scanner.

Afterward, the participant's fatigue and discomfort were assessed using a VAS scale, and any questions were addressed. The MRI scanner is then cleaned and prepared for subsequent use.

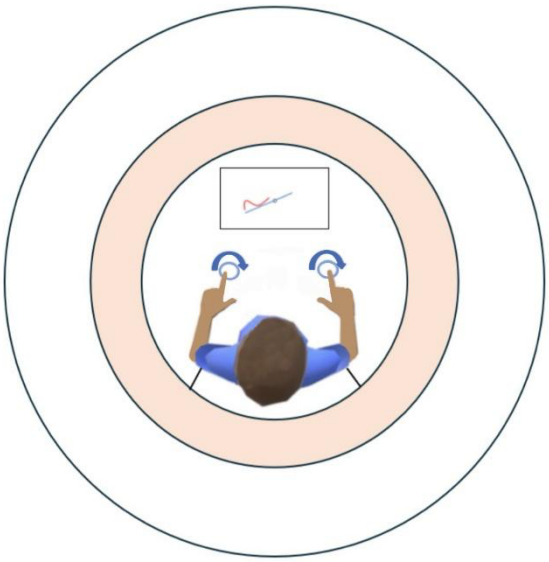


Figure 4: Performance of the BTT in the MRI.

2.5. Statistical analysis

All analyses were performed in JMP, a software tool for visualizing data, performing exploratory analyses, and building statistical models. Because the research question has two parts, the statistical analysis is discussed for each part separately. The data of Older Adults 40 and 44 were excluded from the statistical analysis, because of the absent GABA rest values or missing data points due to poor spectral quality in both cases..

2.5.1. How do GABA levels in the Supplementary Motor Area (SMA) change with aging?

To address the first part of the research question, the difference between the GABA rest values in younger and older adults was checked. For this the normality of both groups was checked separately using the Shapiro-Wilk test, as both groups contained fewer than 30 individuals. In addition, the Brown-Forsythe test was used to check whether the variances were homogeneous. Since both assumptions were met, the two-sample t-test was performed. (Attachment 1)

2.5.2. How are changes in GABA levels related to motor performance in bimanual tasks?

To address the second part of the research question, a linear model was used to investigate whether GABA modulation could be a predictor of motor performance (using the BTT scores). (Attachment 2). GABA modulation is the difference between GABA levels during the task and at rest. GABA modulation provides a more robust and targeted measure of task-related changes in GABA levels. This involved examining whether there was a different relationship of GABA modulation on motor performance between the two age groups (young and old). The BTT score was used as the dependent variable. GABA modulation, age group and their interaction were included as the independent variables. This allows to look at the direct effect of GABA modulation on BTT score, but also to examine whether this effect differs between age groups. To check model assumptions, the normality of residuals was tested using the Shapiro-Wilk test, and homoscedasticity and linearity were checked via the residual by predicted plot. The model was then simplified by eliminating non-significant interactions and predictors in order to arrive at an optimal explanatory model.

To further investigate whether the direction of GABA modulation affects the BTT score and whether it differs for the two age groups, the continuous variable GABA modulation was converted to a categorical variable GABA change. This contains two levels: decrease (a negative GABA modulation) and increase (a positive GABA modulation). A linear model was then constructed using BTT score as the dependent variable and GABA change, age group and their interaction as the independent variable. To verify model assumptions, the normality of residuals was tested using the Shapiro-Wilk test, and homoscedasticity and linearity were checked via the residual by predicted plot. The model was then simplified by eliminating non-significant interactions and predictors in order to arrive at an optimal explanatory model.

3. Results

3.1. How do GABA levels in the Supplementary Motor Area (SMA) change with aging?

The GABA rest values were normally distributed in both the younger group (Shapiro-Wilk p = 0.8274) and the older group (p = 0.6764). The variances were equal according to the Brown-Forsythe test (p = 0.8588), allowing an independent sample t-test to be performed. The results of the t-test showed that there was no significant difference in GABA rest between younger and older adults (t = 1.78048 (48), p = 0.0813). Thus, on average, resting GABA levels did not differ between the two age groups.

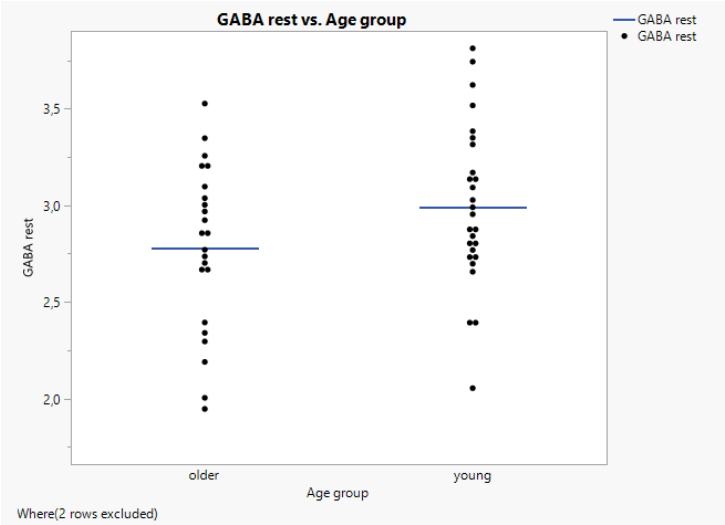


Figure 5: Visualisation of the difference between the GABA rest levels between younger and older adults.

3.2. How are changes in GABA levels related to motor performance in bimanual tasks?

The residuals of the regression model were normally distributed (Shapiro-Wilk: p = 0.7551). No systematic pattern was found in the residual by predicted plot, indicating a correct linear relationship. The assumption of homoscedasticity was evaluated using a residuals plot. The plot showed no systematic pattern or clear increase in dispersion at higher or lower predicted values, suggesting that the assumption of homoscedasticity was reasonably satisfied. In the complete model, GABA modulation was not a significant predictor of the BTT score (F = 0.0054 (1), p = 0.9419). The interaction with age group was also not significant (F = 0.1863 (1), p = 0.6680), indicating that the effect of GABA modulation on the BTT score did not differ

between younger and older adults. Only age group significantly influenced the BTT score: older adults scored an average of 5.69 points lower than young adults on the BTT task (F = 39.2646 (1), p: <0.0001).

In the simplified model without the interaction between GABA modulation and age group, these results were maintained: GABA modulation did not remain significant (F = 0.0009 (1), p = 0.9767), while age group did remain a significant predictor (F = 40.2680 (1), p = <0.0001). The effect remained strongly significant in the final model with only age group as a predictor (F = 41.36 (1), p < 0.0001).

The mean score per age group was calculated: the older adults scored on average 59.52 on the BTT, while the younger group received an average score of 70.99.

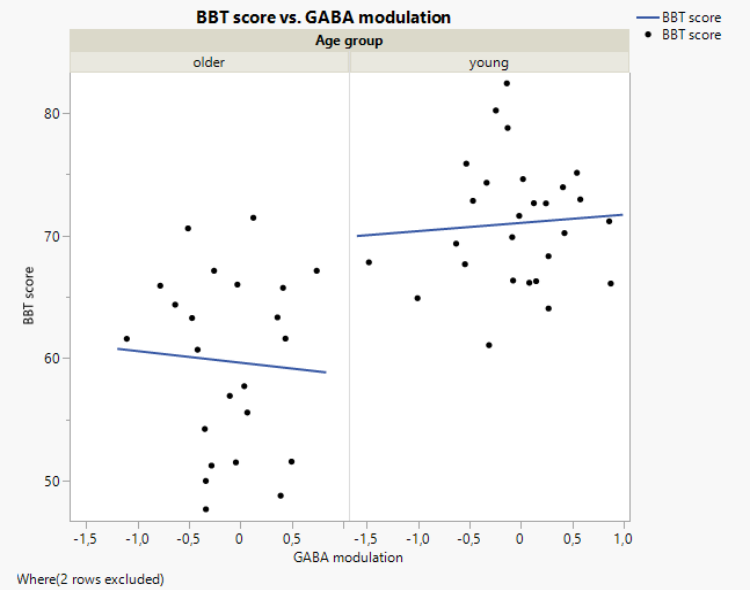


Figure 6: Visualisation of the association between the GABA modulation and the BTT score for younger and older adults.

In the model that examined whether GABA change affects the BTT score and whether it is age-dependent, the residuals were normally distributed (Shapiro-Wilk: p = 0.4120). No systematic pattern was found in the residual by predicted plot, indicating a correct linear relationship. The assumption of homoscedasticity was evaluated using a residuals plot. The plot showed no systematic pattern or clear increase in dispersion at higher or lower predicted values, suggesting that the assumption of homoscedasticity was reasonably satisfied.

The analysis showed no significant main effect of the direction of GABA change on the BTT score (F = 0.0105 (1), p = 0.919). This indicates no significant difference in task performance between participants with a decrease versus an increase in GABA during the task independent of age group.

However, a significant main effect of age group was found here (F = 38.0520 (1), p = < 0.0001), again indicating that younger and older adults differ significantly in their BTT scores independent of the direction of GABA change.

The interaction between GABA change and age group was not significant (F = 0.3983 (1), p = 0.531), suggesting that the effect of GABA change on task performance does not differ between the young and the elderly.

In summary, this model shows that age significantly impacts bimanual performance. At the same time, the direction of GABA modulation does not make a significant contribution, either separately or in interaction with age group.

Table 1

Linear regression model results on GABA modulation

Predictors	*Estimates*	*Std. Error*	*t Ratio*	*p*
Model 1: GABA modulation × Age group				
Intercept	65,33	0,91	71,92	<0,0001
GABA modulation	-0,14	1,87	-0,07	0,9419
Age group [older]	-5,69	0,91	-6,27	<0,0001
GABA modulation × Age group [older]	-0,81	1,87	-0,43	0,6680

Effect Tests	*DF*	*Sum of Squares*	*F Ratio*	*p*
GABA modulation	1	0,21	0,0054	0,9419
Age group	1	1550,32	39,26	<0,0001
GABA modulation × Age group [older]	1	7,36	0,186	0,6680

Predictors	*Estimates*	*Std. Error*	*t Ratio*	*p*
Model 2: Age group				
Intercept	65,372443	0,8745	74,75	<0,0001
Age group [older]	-5,623846	0,8745	-6,43	<0,0001

Effect Tests	*DF*	*Sum of Squares*	*F Ratio*	*p*
Age group	1	1571,2611	41,3568	<0,0001

Table 2

Linear regression model results on GABA change

Predictors	*Estimates*	*Std. Error*	*t Ratio*	*p*
Model 1: GABA change × Age group				
Intercept	65,412013	0,901302	72,58	<0,0001
GABA change [decrease]	0,092149	0,901302	0,10	0,9190
Age group [older]	-5,559797	0,901302	-6,17	<0,0001
Age group [older] × GABA change [decrease]	-0,568789	0,901302	-0,63	0,5311

Effect Tests	*DF*	*Sum of Squares*	*F Ratio*	*p*
GABA change	1	0,4106	0,0105	0,9190
Age group	1	1494,6948	38,0520	<0,0001
Age group × GABA change	1	15,6436	0,3983	0,5311

Predictors	*Estimates*	*Std. Error*	*t Ratio*	*p*
Model 2: Age group				
Intercept	65,372443	0,8745	74,75	<0,0001
Age group [older]	-5,623846	0,8745	-6,43	<0,0001

Effect Tests	*DF*	*Sum of Squares*	*F Ratio*	*p*
Age group	1	1571,2611	41,3568	<0,0001

4. Discussion

This study investigated the relationship between changes in GABA levels in the SMA and bimanual coordination in younger and older adults. Results revealed no significant difference in resting GABA levels in the SMA between younger and older adults. Alongside, no significant relationship between GABA modulation and BTT score was found in either younger or older adults. The same can be said for the GABA change: no significant interaction between GABA change and age was found, indicating no difference in the effect of the direction of GABA modulation on task performance in the young and elderly. However, age and BTT score did have a significant relationship, with older adults tending to score lower on the task than younger adults.

4.1. Age-related differences in GABA rest levels

According to the results, the hypothesis of lower GABA rest levels in the SMA in older adults can be disproven. Prior studies on GABA levels in the SMA among the elderly have reported mixed findings. Maes et al. (2021) found no significant difference in GABA levels in the SMA in younger and older adults. Conversely, a significant difference in GABA levels was found in the pre-SMA by Liu et al. (2024) and Hermans et al. (2018), where older adults tended to have lower GABA levels. A potential explanation for these discrepancies between studies could be that the age of the elderly group affects resting GABA levels. The elderly group in Maes et al. had a mean age of 67.8 years, which is comparable to the mean age of this study (68.4 years). However, the study by Porges et al. (2017), which found significantly lower GABA levels in the frontal lobe, included an older group with a mean age of 73.1 years. This suggests that age-related GABA reductions may only become apparent at more advanced ages, which can be an interesting subject for further research. In addition, there is variability in the brain regions in which GABA levels were measured in the studies mentioned above. Thus, it could be possible that different brain regions show greater or smaller fluctuations in
GABA, possibly due to the function of different brain regions or their GABA concentration.

4.2. GABA modulation and its direction in relation to bimanual coordination task

This study found no significant relationship between GABA modulation and BTT score in either younger or older adults. As far as the current literature extends, this is the only study in which this has been specifically examined in the SMA.

For the direction of GABA modulation, it was hypothesized that a greater GABA modulation in the SMA is associated with a better score on the BTT test in older adults. According to the results of this study, no significant interaction between GABA change and age was found. This indicates no difference in the effect of the direction of GABA modulation on task performance in younger and older adults. These findings reject the hypothesis. Previous research by Maes et al. (2022) found that in older adults, a more substantial decrease in GABA levels in SM1 during the task was associated with better performance. The opposite was found in younger adults, where a stronger decrease in GABA levels during the task was associated with lower performance. This suggests that a negative modulation of GABA in older adults is associated with better bimanual coordination. Conversely, a study by Rasooli et al. (2024) showed no significant task-related changes in GABA levels, measured in SM1 and middle temporal visual area (MT/V5). However, this study was only conducted on younger adults between 18 and 35 years old, with no older adults included.

This study measured GABA modulation in the SMA, whereas previous studies that found a link (e.g., Maes et al., 2022, and Rasooli et al., 2024) have focused on other areas, such as the left primary sensorimotor cortex (SM1). It could be that the role of GABA in the SMA is more subtle in bimanual tasks and more difficult to detect with MRS. GABA levels measured with MRS are believed to indicate tonic inhibition, while phasic inhibition at the synaptic level may be more closely linked to motor function. (Maes et al., 2021). In addition, methodological differences in MRS data acquisition may explain these inconsistencies in findings. This study used a HERMES sequence, whereas, for example, the study by Maes et al. (2022) used MEGA-PRESS. Another possible explanation is that the BTT involves not only motor coordination but also executive functions, such as attention, timing, and planning. Given this complexity, performance is likely mediated by multiple neural systems, making it challenging to attribute variance in performance to GABA modulation in a single region.

4.3. Age-related decline in bimanual coordination task

This research found an age-related decline in BTT-score, consistent with previous research. (Stelmach et al., 1988; Lin et al., 2014; Krehbiel et al., 2017; Maes et al., 2017; Danuta & Tokarski, 2021). A decrease in bimanual motor performance with age is a phenomenon that has been confirmed several times by research. A review by Maes et al. (2017) found that with increasing task complexity, age-related differences become more pronounced and that a more

complex version of the task has revealed more and/or larger errors in the elderly. A subsequent study by the same research group reaffirmed these findings. (Maes et al., 2022). Danuta & Tokarski (2024) confirm that older adults exhibit higher mean coordination error and greater variability. Another explanation could be that age-related structural degeneration of motor-related cortical regions contributes to diminished motor performance. Seidler et al. (2010) reported that older adults show pronounced gray matter atrophy, particularly in the prefrontal cortex, with milder effects observed in primary motor and somatosensory areas (M1 and S1). In addition, white matter integrity is compromised, most notably in the corpus callosum, a key structure for interhemispheric communication. Such degradation likely disrupts the coordination between hemispheres, which is essential for effective bimanual movement.

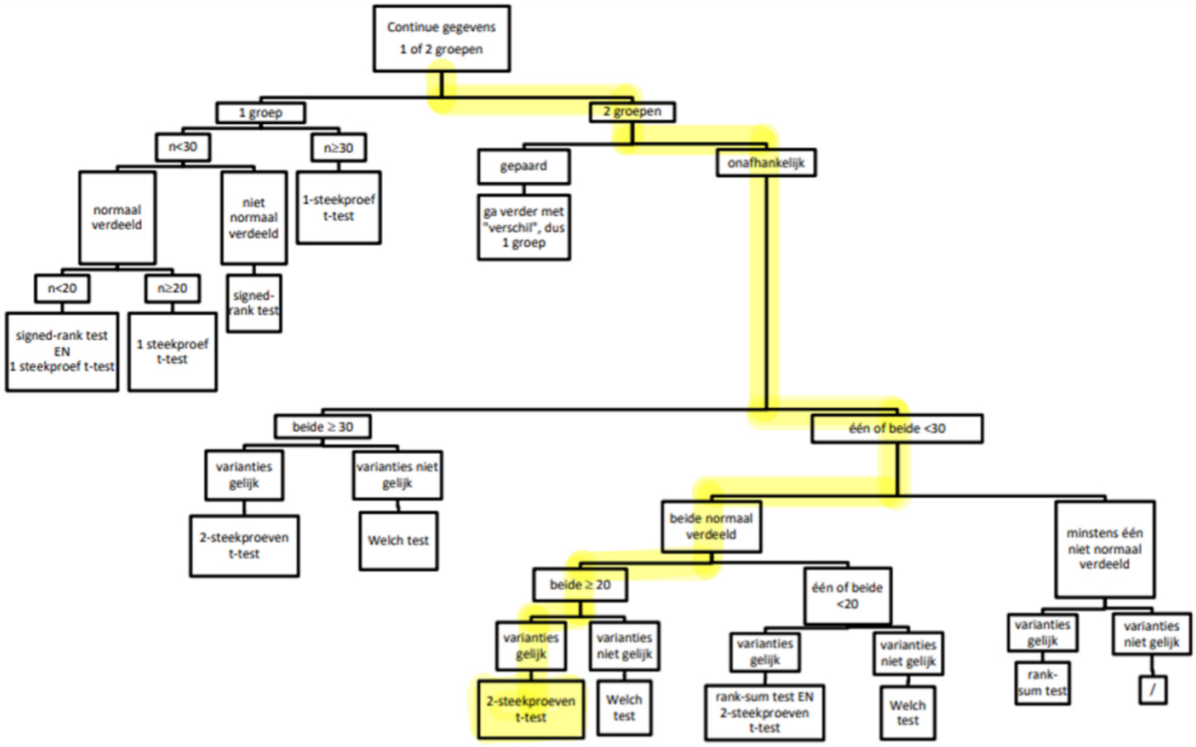
4.4. Limitations

Despite the methodological accuracy of this study, several limitations must be considered when interpreting the findings. First, the relatively small sample size per age group may have limited the statistical power to detect subtle effects or interactions. Furthermore, the MRS method provides an average measurement over the entire task block (approximately 11 minutes), which does not account for dynamic changes in neurochemical activity between task conditions. This limits the ability to capture fluctuations related to different levels of task complexity, which, unfortunately, are indistinguishable within this block design. Although standardized, individual anatomical variability may have affected the voxel placement in the SMA, particularly in older adults with age-related atrophy. Alongside, the BTT engages not only motor control but also higher-order cognitive functions, including attention and planning, suggesting that performance may depend on distributed neural systems beyond the SMA. Lastly, the use of a single task limits the generalizability of the findings to broader motor functioning. Together, these factors highlight the complexity of studying GABA modulation in the aging brain and point to the need for future multimodal, longitudinal studies.

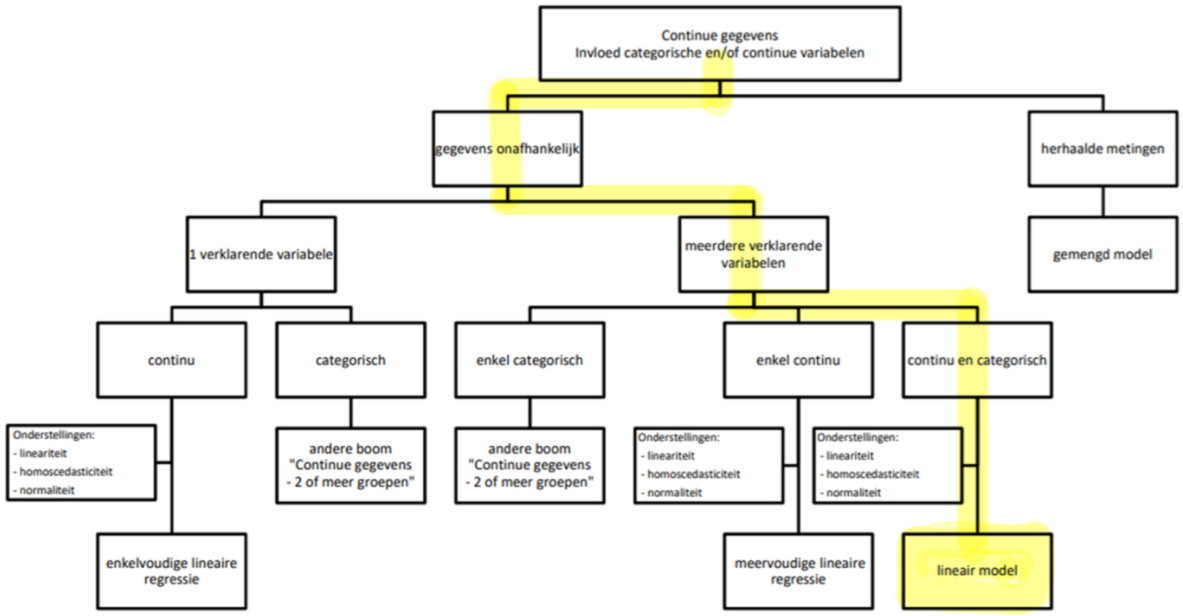
5. Conclusion

This study examined age-related changes in GABA concentrations in the SMA and their relationship to bimanual coordination. Although older adults performed significantly worse on the BTT, no significant differences were found in resting GABA levels between younger and older participants. Also, the degree of GABA modulation during the task did not appear to be a predictor of motor performance regardless of age group. These findings suggest that, despite a clear effect of age on coordination ability, changes in GABA levels in the SMA may not fully explain this difference. Further research is needed to explore other brain regions and more comprehensive, multimodal explanatory models.

Attachments



Attachment 1: Decision tree 1



Attachment 2: Decision tree 2

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