Behavioral/Cognitive

Task-Related Modulation of Sensorimotor GABA+ Levels in Association with Brain Activity and Motor Performance: A Multimodal MRS–fMRI Study in Young and Older Adults

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Recent studies suggest an important role of the principal inhibitory neurotransmitter GABA for motor performance in the context of aging. Nonetheless, as previous magnetic resonance spectroscopy (MRS) studies primarily reported resting-state GABA levels, much less is known about transient changes in GABA levels during motor task performance and how these relate to behavior and brain activity patterns. Therefore, we investigated GABA+ levels of left primary sensorimotor cortex (SM1) acquired before, during, and after execution of a unimanual/bimanual action selection task in 30 (human) young adults (YA; age 24.5 ± 4.1, 15 male) and 30 older adults (OA; age 67.8 ± 4.9, 14 male). In addition to task-related MRS data, task-related functional magnetic resonance imaging (fMRI) data were acquired. Behavioral results indicated lower motor performance in OA as opposed to YA, particularly in complex task conditions. MRS results demonstrated lower GABA+ levels in OA as compared with YA. Furthermore, a transient task-related decrease of GABA+ levels was observed, regardless of age. Notably, this task-induced modulation of GABA+ levels was linked to task-related brain activity patterns in SM1 such that a more profound task-induced instantaneous lowering of GABA+ was related to higher SM1 activity. Additionally, higher brain activity was related to better performance in the bimanual conditions, despite some age-related differences. Finally, the modulatory capacity of GABA+ was positively related to motor performance in OA but not YA. Together, these results underscore the importance of transient dynamical changes in neurochemical content for brain function and behavior, particularly in the context of aging.

Key words: aging; fMRI; GABA; motor performance; MRS

Significance Statement

Emerging evidence designates an important role to regional GABA levels in motor control, especially in the context of aging. However, it remains unclear whether changes in GABA levels emerge when executing a motor task and how these changes relate to brain activity patterns and performance. Here, we identified a transient decrease of sensorimotor GABA+ levels during performance of an action selection task across young adults (YA) and older adults (OA). Interestingly, whereas a more profound GABA+ modulation related to higher brain activity across age groups, its association with motor performance differed across age groups. Within OA, our results highlighted a functional merit of a task-related release from inhibitory tone, i.e. lowering regional GABA+ levels was associated with task-relevant brain activity.

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Introduction

With advancing age, older adults (OA) are confronted with degraded motor performance, especially when task complexity is high (Voelcker-Rehage, 2008; Maes et al., 2017). These aging-induced motor performance deficits are proposed to partially result from alterations in the fine-grained balance between excitatory and inhibitory processes (Levin et al., 2014; Bhandari et al., 2016). Specifically, a plethora of evidence indicates an aging-induced disinhibition that contributes to a deficiency in flexibly adjusting neuronal resources to a particular task context. This leads to degraded performance across perceptual, cognitive and motor tasks (Mattay et al., 2002; Baliz et al., 2005; Levin et al., 2014; Steyvers et al., 2019; Heise et al., 2021). In this respect, the principal inhibitory neurotransmitter GABA is of particular interest because of its vital role in the discriminability and selectivity of neural activations which in turn may affect motor performance (Buzsáki et al., 2007; Boy et al., 2010; Bachtiar and Stagg, 2014; Levin et al., 2014). Indeed, resting-state baseline GABA levels seem to decrease with advancing age and lower GABA levels have been related to poorer motor performance, at least in OA (Hermans et al., 2018; Heise et al., 2021; Maes et al., 2021). Interestingly, to date most research has focused on resting-state GABA levels acquired at one or multiple timepoints before and/or after task execution. However, transient task-related alterations in GABA levels might thereby be missed. Indeed, a study by Kurcyus et al. (2018) demonstrated a visual stimulus-induced decrease of occipital GABA levels that regulated subsequent regional activity patterns. Additionally, motor GABA levels were found to be decreased during a hand clenching task (Chen et al., 2017). These task-induced alterations reflect dynamic metabolic processes that occur along with regional neuronal activity, thereby broadening the insights on task-related brain dynamics (Rae, 2014; Chen et al., 2017; Mullins, 2018). Indeed, decreased GABA levels seem to critically alter the equilibrium between excitatory and inhibitory processes, thereby lowering the threshold for neuronal activity to occur (Logothetis et al., 2001; Buzsáki et al., 2007; Donahue et al., 2010). This is especially relevant to aging research, as magnetic resonance spectroscopy (MRS) is independent of neurovascular effects that are known to alter with advancing age and thereby interfere with techniques that do depend on cerebral blood flow such as functional magnetic resonance imaging (fMRI; Stanley and Raz, 2018). Nonetheless, it is yet to be determined whether this phenomenon applies to an older population and/or more complex motor tasks. More importantly, the functional relevance of these task-related GABA modulations and the precise conditions under which such modulations occur remain elusive.

Additionally, the association of GABA with corresponding brain activity patterns in the context of motor performance has been understudied. Previous studies in the cognitive and perceptual domain typically linked higher baseline GABA levels to lower stimulus-induced brain activity within that particular region (Duncan et al., 2014). Hence, baseline GABA levels may serve as an indirect marker for the degree and spread of task-induced brain activity patterns. Importantly, it remains to be explored whether a transient decrease in GABA levels leads to an increase of (regional) brain activation. Furthermore, behavioral implications across age groups need to be addressed.

In summary, the task-induced modulatory capacity of regional GABA levels might be particularly relevant for brain activity patterns and in turn, motor performance. Therefore, we examined age-related differences in the modulation of GABA+ levels and brain activity patterns during a unimanual/bimanual action selection task. In addition to task-related fMRI data, GABA+ levels were acquired before, during, and after motor performance. We hypothesized that older as compared with young adults (YA) would perform poorer and exhibit overall lower GABA+ levels. Furthermore, we hypothesized that GABA+ levels would decrease during task performance in both YA and OA and that a more pronounced modulation would be linked to higher baseline GABA+ levels and thus better motor performance. Lastly, task-related decreases in GABA+ were hypothesized to be associated with higher levels of brain activity.

Materials and Methods

Participants

Sample size calculation was conducted a priori using G*Power (version 3.1.9.7). Considering an alfa level of 0.05 and a power of 0.9, a total sample size of 56 participants was recommended to detect small effect sizes (Cohen's $d = 0.2$) for a repeated measures ANOVA including two age groups and three time points (i.e., age-related differences in task-induced modulations of GABA, see below). To anticipate dropout or missing data, we recruited 60 right-handed participants of two distinct age groups, i.e., 30 YA (15 male, age range 19–35 years, mean ± SD 24.5 ± 4.1) and 30 OA (14 male, age range 61–79 years, mean ± SD 67.8 ± 4.9). The study protocol was approved by the Ethics Committee Research of universitair ziekenhuis/Katholieke Universiteit Leuven (study number S60428) and is in accordance with the declaration of Helsinki (1964). All participants reported to be in good physical and mental health and had no contraindications for MRI scanning. Informed consent was obtained from all participants before the experimental sessions. The Montreal Cognitive Assessment (MoCA), i.e., a screening tool for cognitive impairment, was performed in YA and OA and indicated a score below the cutoff of 23/30 for one YA who was therefore excluded from further analyses (Carson et al., 2018). Furthermore, one YA and one OA did not complete the experimental protocol because of an anatomic malformation in the brain and practical issues during MRI scanning, respectively. Age groups did not differ with respect to MoCA score (YA: mean ± SD = 28.6 ± 1.3; OA: mean ± SD = 28.4 ± 1.4; independent samples t test: $t_{(1,55)} = -0.53$, $p = 0.60$) or handedness, as defined by the Oldfield Handedness questionnaire [Oldfield, 1971; laterality quotient (LQ) YA: mean ± SD = 93.2 ± 11.3; LQ OA: mean ± SD = 95.4 ± 8.8; independent samples t test: $t_{(1,55)} = -0.83$, $p = 0.41$].

Study outline

During a first experimental session, participants completed questionnaires and a behavioral task battery. Within that same session, participants were introduced to an MRI environment by the use of a mock scanner in which they performed a familiarization run of the multidigit task to-be-performed in the MRI scanner (a description of the task is presented below, Multidigit task). In a second experimental session, participants performed the multidigit task in the MRI scanner while both MRS of the left primary sensorimotor cortex (SM1) and task-related fMRI data were obtained (Fig. 1*A*). To examine the time course of task-induced modulations of GABA+ levels, participants were randomly assigned to one of two scanning paradigms in which the order of task-related MRS and fMRI data were altered. Specifically, in half of the participants task-related GABA+ levels were acquired before the task-related fMRI data acquisition (task-related MRS first: 14 YA and 14 OA), whereas task-related GABA+ levels were acquired subsequent to fMRI data in the other half of participants (task-related fMRI first: 14 YA and 15 OA). This enabled us to investigate whether task-induced changes in GABA+ levels occurred in the early (i.e., first 8 min of task execution) or later phase (i.e., after 23 min of task execution) of practice or both (Fig. 1*A*). In addition to the MRS assessment of GABA+ levels during task execution, GABA+ levels were acquired before and after

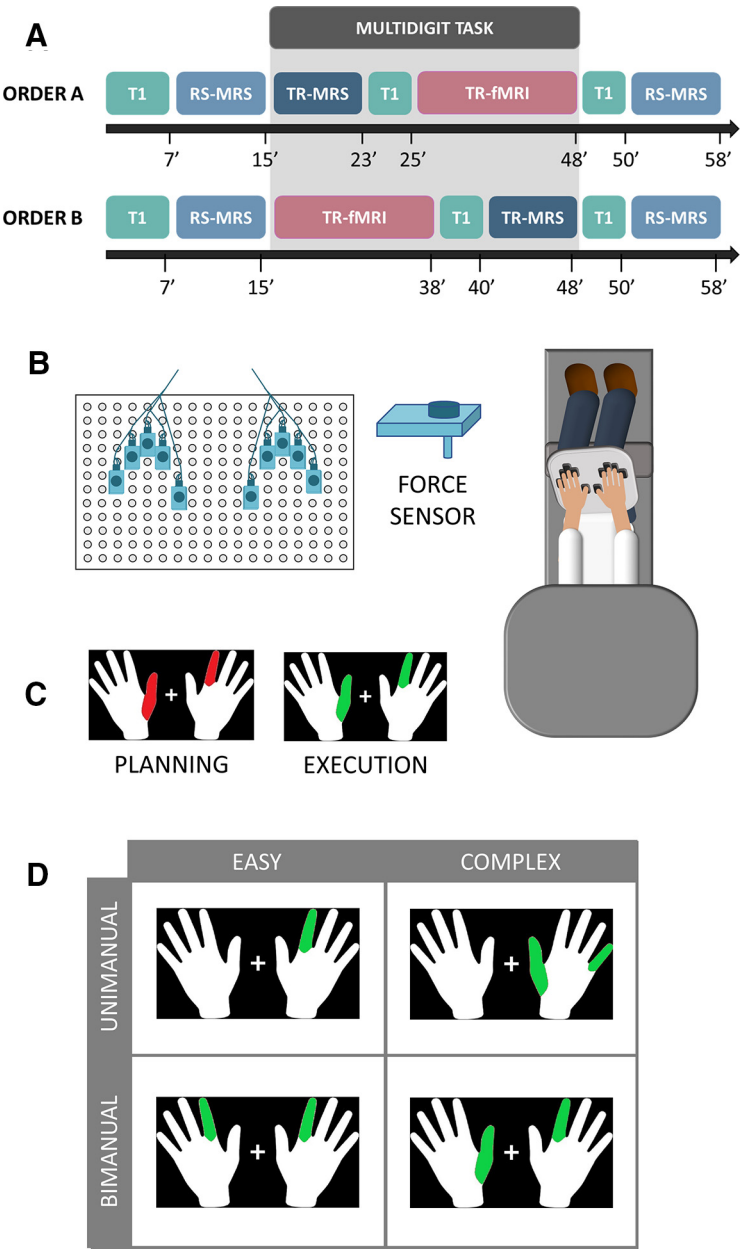

Figure 1. Experimental protocol and the multidigit task. ***A***, Experimental protocol. GABA+ levels were quantified within left SM1 before, during, and after performance of an action selection task. Furthermore, during task performance, task-based fMRI data were acquired as well. The order at which task-related MRS and fMRI data were acquired was counterbalanced across participants: whereas task-related MRS was acquired during the first one third of task execution in half of the participants, task-related MRS data were acquired during the last third of task performance in the other half of participants. During the remaining time (66%) of task performance, fMRI data were acquired. To confirm that participants did not move during the course of scanning, short T1-weighted anatomic images were acquired in between MRS and fMRI scans. In case of head motion, the position of the MRS VOI was recalibrated based on the short T1 image. RS-MRS: resting-state MRS; TR-MRS: task-related MRS; TR-fMRI: task-related fMRI. ***B***, Task apparatus. The task apparatus consisted of a board on which 10 force sensors, i.e., one for each finger, were attached. The position of these sensors could be adapted based on the shape of the hand of each individual participant. This board was positioned on the participant's lap while lying supine in the MR scanner. ***C***, Task visualization. During scanning, participants performed an action selection task that required them to lift a specific set of fingers. The prescribed movement pattern was presented on a screen by coloring the to-be-moved fingers. During the first 2 s of each trial, fingers were colored red such that participants could plan the upcoming movement. A change of color to green marked the beginning of the execution phase (2 s) during which participants were instructed to lift those colored fingers while inhibiting (the co-movement of) others. ***D***, Task variants. Four different task variants were presented, i.e., two unimanual and two bimanual conditions that each consisted of an easy and complex task variant. During the easy unimanual condition, one finger of the right hand had to be moved while the left hand remained positioned on the force sensors. During the complex unimanual condition, two to three fingers of the right hand were moved. The easy and complex bimanual task conditions required the coordinative movement of homologous or nonhomologues fingers, respectively. During these bimanual conditions, either one or two fingers per hand were lifted.

task completion when the participant was at rest, i.e., not performing a task.

Multidigit task

Experimental setup

A newly-designed action selection task was used to assess the selectivity of unimanual/bimanual motor responses. The task apparatus consisted of 10 nonferromagnetic force sensors (FS03, Honeywell), i.e., one for each finger, attached to a board with holes ~1 cm apart (Fig. 1*B*). Each force sensor was accommodated with a custom-made plastic housing including a pin at the bottom that could be positioned in the holes of the board. Before task execution, force sensors were positioned on the board to maximize comfort during task execution; this position was dependent on the individual hand size and shape. During task performance, participants were positioned supine in the MR scanner with a cushion underneath the knees such that the task apparatus could be placed on their lap (Fig. 1*B*). The task apparatus was positioned such that participants flexed their elbows at ~135°, allowing the upper arms to rest on the MRI table. If needed, cushions were provided underneath the arms or apparatus to ensure maximal comfort. The pressure exerted on the force sensors was saved at a sampling rate of 1000 Hz. Before and after task completion, a baseline pressure measurement was performed within the MR scanner when participants had lifted their fingers from the sensors. The task was projected with an LCD projector (NEC PA500U, 1920 × 1200 pixels) onto a mirror positioned in front of the participant's eyes. Specifically, two white hands were presented on a black background and the to-be-moved fingers of these hands were cued during task performance (Fig. 1*C*).

Task description

Participants were instructed to place each finger on its corresponding force sensor. The aim of the task was to lift specific finger(s) of the left and/or right hand, as cued on the screen. Each trial consisted of a planning phase (2 s) and an execution phase (2 s; Fig. 1*C*). During the planning phase of movement, the to-be-moved fingers were precued by visualizing them in red, enabling the participant to prepare the desired movement pattern while keeping all fingers on the force sensors. The start of the execution phase was marked by the color of the cued fingers changing from red to green, which served as the trigger for the participant to lift the corresponding fingers while keeping all other fingers on the force sensors. Considering that regional GABA levels are more closely related to the precision rather than speed of motor execution (Boy et al., 2010; Kurcyus et al., 2018; Maes et al., 2021), participants were instructed to prioritize movement accuracy over speed of execution. Furthermore, to assure similar levels of motor activity across all task variants, participants were instructed to keep their fingers lifted for the entire duration of the execution phase. The beginning of a subsequent trial was marked by the start of the planning phase of the new trial, i.e., a new set of fingers would be colored

Table 1. MRS Tissue-corrected GABA levels, quality metrics, and tissue composition of the voxel

	$GABA+_{pre}$			$GABA+_{task}$			$GABA+_{post}$		
	YA (mean ± SD)	OA (mean ± SD)	*p*	YA (mean ± SD)	OA (mean ± SD)	*p*	YA (mean ± SD)	OA (mean ± SD)	*p*
Tissue-corrected GABA levels	2.88 ± 0.24	2.75 ± 0.27	NA	2.11 ± 0.25	1.93 ± 0.23	NA	2.85 ± 0.26	2.72 ± 0.19	NA
Quality metrics									
GABA fit error (%)	3.05 ± 0.61	3.34 ± 0.66	0.10	3.12 ± 0.61	3.49 ± 0.83	0.07	3.19 ± 0.64	3.24 ± 0.52	0.77
GABA SNR	24.25 ± 3.24	22.31 ± 4.10	0.06	23.60 ± 3.77	21.82 ± 3.16	0.071	23.54 ± 3.23	21.47 ± 3.53	0.029
NAA linewidth (Hz)	9.59 ± 1.16	9.93 ± 0.90	0.24	9.53 ± 1.13	9.79 ± 0.74	0.33	9.65 ± 1.08	9.82 ± 0.74	0.51
Frequency drift (Hz)	0.004 ± 0.003	0.005 ± 0.006	0.79	0.003 ± 0.004	0.002 ± 0.005	0.51	0.002 ± 0.004	0.003 ± 0.006	0.56
Tissue composition									
Gray matter fraction	0.33 ± 0.02	0.27 ± 0.03	<0.001	0.33 ± 0.02	0.26 ± 0.03	<0.001	0.32 ± 0.02	0.26 ± 0.03	<0.001
White matter fraction	0.59 ± 0.04	0.62 ± 0.04	0.005	0.59 ± 0.04	0.62 ± 0.04	0.006	0.60 ± 0.04	0.63 ± 0.04	0.004
CSF fraction	0.09 ± 0.03	0.11 ± 0.03	0.001	0.08 ± 0.02	0.11 ± 0.03	<0.001	0.08 ± 0.02	0.11 ± 0.03	<0.001

NA: not applicable; SD: standard deviation.

red. The change of color from green to red served as a cue for participants to place all fingers back on the force sensors and prepare for the next trial. If all fingers on the screen where colored white, this indicated a resting period during which participants kept all fingers on the force sensors.

In total, four different task variants were implemented, i.e., two unimanual and two bimanual conditions examining intramanual and intermanual coordination abilities, respectively (Fig. 1*D*). These task variants were presented to the participants in a blocked order starting with the easy unimanual condition, followed by the complex unimanual, easy bimanual and the complex bimanual condition. During the unimanual conditions, only fingers of the right hand were cued while fingers of the left hand remained at rest on the force sensors. One finger was cued per trial in the easy unimanual condition, whereas a set of multiple fingers (two or three) were cued at the same time during the more complex unimanual condition. During the bimanual conditions, participants had to lift one or two homologous (i.e., easy bimanual condition) or nonhomologous (i.e., complex bimanual condition) fingers of the left and right hand at the same time. Each block (20 s) consisted of five trials of the same task variant followed by a rest period. During in-scanner task performance, both MRS and fMRI data were acquired. During the task-related MRS acquisition, four blocks of each task variant were presented, resulting in a total of 80 trials, i.e., 20 trials per task variant. During task-related fMRI acquisition, two runs of six blocks per task variant were acquired, resulting in a total of 240 trials, i.e., 60 trials per task variant across both fMRI runs. For the purpose of fMRI data acquisition, the duration of the rest period varied between 7.5 and 10.5 s (mean of 9 s). During task-related MRS acquisition, rest periods were similar to those during the task-related fMRI acquisition.

Data analysis

Behavioral data were analyzed using in-house developed MATLAB (R2018b, The MathWorks Inc) scripts and Microsoft Excel 2013. First, behavioral data of each force sensor were filtered using the medfilt 1 option in MATLAB, averaging the signal across a 10-ms time window. Second, to identify when participants lifted a finger from the force sensor, the baseline pressure on each force sensor was subtracted from the corresponding pressure levels exerted during task performance. Thus, a finger was considered lifted if the pressure exerted on the force sensor approximated the baseline pressure. A correct response was marked by all fingers correctly positioned on their corresponding force sensors during the planning phase, followed by correctly lifting the cued finger(s) and not lifting the noncued fingers during the course of the execution phase.

Because of data registration problems, data of three YA and seven OA were excluded completely from data analysis and three YA and five OA had incomplete datasets. Of those participants that were included, 12% of trials (1808 out of 15,040 trials) were removed before data analysis. For each task variant, the percentage of correctly executed responses was calculated and used as a dependent variable. Because data deviated significantly from a normal distribution

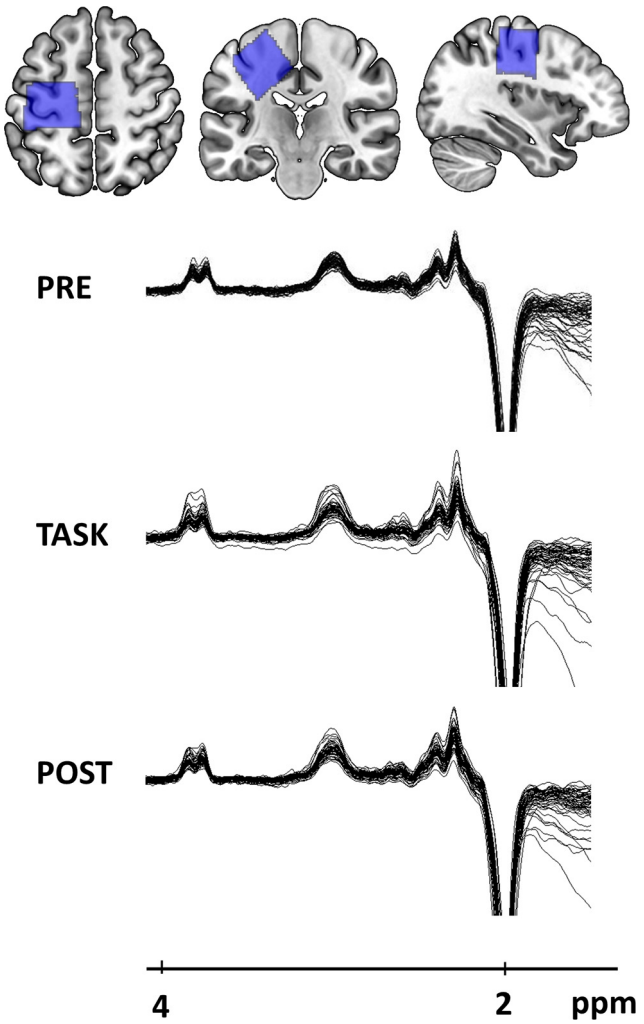

Figure 2. MRS-derived GABA+ levels within the left SM1. The MRS VOI was positioned over the hand knob within the left motor cortex. Individual spectra, acquired before, during, and after task performance, are visualized with the GABA peak situated at 3 ppm.

demonstrating a negative skew, an exponential transformation was applied to data of all four task variants. To verify whether performance levels differed across the acquisition order and/or runs, a 2 (age: YA, OA) × 3 (run: Run 1, Run 2, Run 3) repeated measures ANOVA was conducted. When task-related MRS was acquired first, Run 1 corresponded to the task-related MRS run and Run 2 and 3 corresponded to the first and second task-related fMRI run, respectively. In contrast, when task-related fMRI was acquired first, Runs 1 and 2 corresponded to the first and second task-related fMRI run,

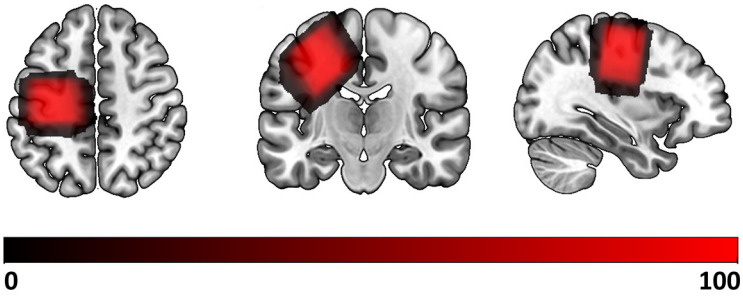

Figure 3. MRS mask used for fMRI analyses. fMRI analyses were restricted to the left SM1 by creating a mask based on the sum of all MRS VOI acquired before task execution ($GABA+_{pre}$). The figure includes a heatmap (0–100% overlap) to illustrate the overlay across the participant's VOIs.

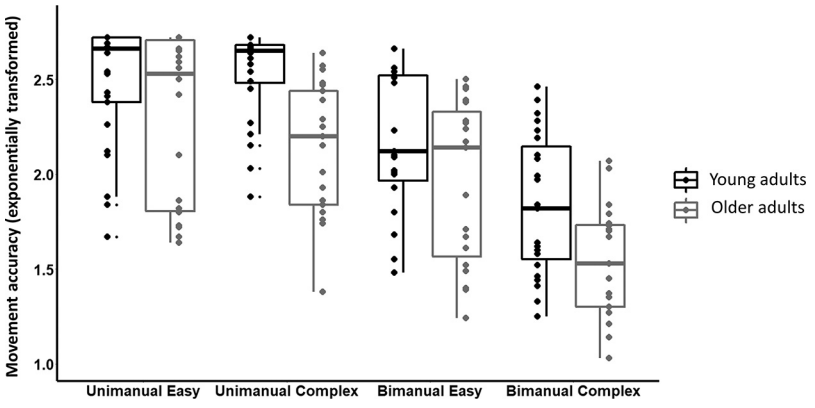

Figure 4. Behavioral results. Performance differed across complexity levels and coordination modes, with better performance in the easy as compared with the complex and the unimanual as compared with the bimanual conditions, respectively. Furthermore, OA performed significantly worse as opposed to YA, especially when task complexity was high. The figure shows boxplots with individual datapoints superimposed.

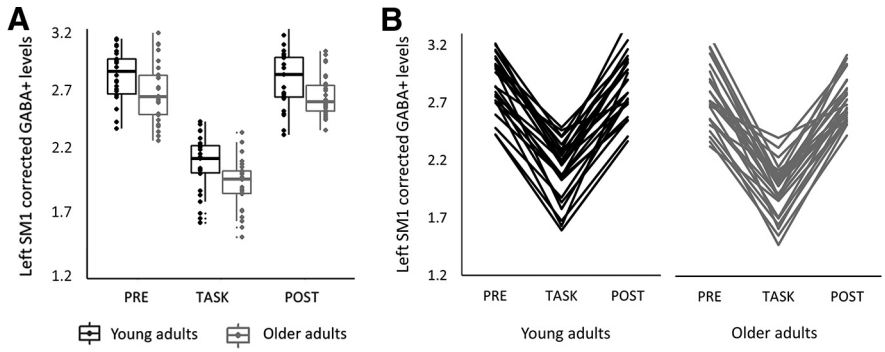

Figure 5. MRS results. ***A***, Overall, GABA+ levels were lower in older as opposed to YA. Furthermore, GABA+ levels were found to decrease in response to task performance and returned to baseline after task completion. This transient decrease of GABA+ levels was observed across both age groups. The figure shows boxplots with individual datapoints superimposed. ***B***, Visualization of the individual datapoints in YA and OA to illustrate that the task-related decrease of GABA+ levels was consistently observed across all participants. i.u.: institutional units.

whereas Run 3 corresponded to the task-related MRS run. As results revealed no significant effect of Run nor significant interaction effects (all $ps > 0.30$), performance on each task variant was averaged across runs for subsequent analyses.

Neuroimaging data

Data acquisition

Neuroimaging data were acquired at the University Hospital Leuven using a 3 Tesla Philips Achieva dstream MRI scanner equipped with a 32 channel receive only head coil. An overview of the overall scanning protocol is presented in Figure 1*A*. At the beginning of the session, a high-resolution T1 weighted image was acquired using a chemical shift 3D turbo field echo [3DTFE; TE = 4.6 ms, 1 × 1 × 1 mm voxel size, field of view (FOV) = 256 × 242 × 182 mm, 182 sagittal slices, scan duration ± 7 min] to capture the anatomic features of the brain. MRS data were acquired within the dominant left SM1 in a 3 × 3 × 3 cm voxel of interest (VOI) that was placed over the hand knob of the motor cortex and in line with the cortical surface in the coronal plane (Yousry et al., 1997; Fig. 2). To quantify GABA levels within the VOI, identical acquisition parameters were used for the quantification of GABA levels before, during, and after task execution. Specifically, a MEGA-PRESS sequence (TE = 68 ms, TR = 2 s, 2-kHz spectral width, 112 averages, scan duration ± 8 min) was used. ON and OFF spectra were acquired in an interleaved fashion and sixteen unsuppressed water spectra were acquired in the same region using identical acquisition parameters. With respect to fMRI, two identical task-related fMRI runs were acquired of ~11.5 min each. Specifically, a gradient echo-planner sequence was performed that consisted of multislice T2-weighted fMRI images that covered the whole brain and were acquired in an ascending order along the *z-axis* (TE = 30 ms, TR = 2 s, 90° flip angle, 60 parallel axial slices with a slice thickness of 2 mm, interslice gap 0.2 mm, in-plane resolution 2 × 2 mm). Furthermore, to account for local distortions, four multislice T2-weighted fMRI images with identical acquisition parameters, yet a reversed phase encoding direction, were acquired. To allow for equilibration of tissue magnetization, four dummy scans were acquired at the start of each scan and consecutively discarded. To account for possible head movement, a short T1 anatomic image (TE = 4.6 ms, 1.5 × 1.5 × 1.5 mm voxel size, FOV = 256 × 244 × 182 mm, 182 sagittal slices, ± 1.5 min) was acquired in between task-related MRS and fMRI as well as before the acquisition of GABA levels after task completion.

Data analysis

MRS. An overview of the acquired spectra at all three timepoints is presented in Figure 2. For data analysis, the GABA analysis toolkit Gannet (version 3.1.4) was used (Edden et al., 2014). First, spectral registration was applied for frequency-correction and phase-correction (Near et al., 2015). Subsequently, the GABA signal was fitted between 4.2 and 2.8 parts per million (ppm) using a three-Gaussian function, whereas the water signal was fitted using a Gaussian–Lorentzian model. Next, considering that CSF does not contain GABA and assuming that GABA levels are twice as high in gray as compared with white matter, GABA levels were corrected for tissue fractions within the VOI (Harris et al., 2015). To this end, MRS voxels were co-registered to the anatomic images that were used to correctly position the VOI. If correct VOI positioning was confirmed on a low-resolution short T1 image acquisition (i.e., for VOIs acquired after task performance and VOIs acquired during task performance when task-

Table 2. Regression analyses including GABA+$_{task}$

Predictors	Estimates	SE	CI	Statistic	*p*	*F* (df)	*p*
(Intercept)	2.03	0.65	0.75 to 3.31	3.13	**0.002**		
Age group						16.54 (1,3)	**<0.001**
YA	Reference						
OA	0.84	0.93	−0.99 to 2.67	0.91	0.367		
GABA+	0.21	0.30	−0.39 to 0.80	0.69	0.491	0.16 (1,3)	0.69
Age group × GABA+						9.43 (1,3)	**0.002**
Age group OA: GABA+	−0.48	0.46	−1.38 to 0.42	−1.05	0.294		
Task variant						34.53 (3149)	**<0.001**
Unimanual easy	Reference						
Unimanual complex	−0.09	0.92	−1.90 to 1.72	−0.10	0.920		
Bimanual easy	−0.78	0.97	−2.69 to 1.13	−0.81	0.420		
Bimanual complex	−0.45	0.97	−2.35 to 1.46	−0.46	0.644		
Age group × task variant						0.59 (3149)	0.62
Age group OA: task variant UC	−0.38	1.37	−3.07 to 2.32	−0.27	0.784		
Age group OA: task variant BE	2.37	1.46	−0.52 to 5.26	1.62	0.107		
Age group OA: task variant BC	0.41	1.40	−2.35 to 3.18	0.29	0.769		
GABA+ × task variant						0.39 (3149)	0.76
GABA+ : task variant UC	0.07	0.43	−0.78 to 0.91	0.16	0.875		
GABA+ : task variant BE	0.23	0.45	−0.66 to 1.12	0.51	0.612		
GABA+ : task variant BC	−0.09	0.45	−0.97 to 0.80	−0.19	0.850		
Age group × GABA+ × task variant						1.26 (3149)	0.29
Age group OA: GABA+ : task variant UC	0.09	0.67	−1.24 to 1.41	0.13	0.895		
Age group OA: GABA+ : task variant BE	−1.22	0.72	−2.65 to 0.20	−1.69	0.093		
Age group OA: GABA+ : task variant BC	−0.29	0.69	−1.64 to 1.07	−0.42	0.675		
Observations	165						
R^2 Nagelkerke	0.51						
AIC	134.88						

Significant *p* values are indicated in bold. CI: confidence interval; YA: young adults; OA: older adults; UC: unimanual complex; BE: bimanual easy; BC: bimanual complex.

Table 3. Regression analyses including GABA+$_{mod}$

Predictors	Estimates	SE	CI	Statistic	*p*	*F* (df)	*p*
(Intercept)	2.62	0.29	2.03 to 3.20	8.87	**<0.001**		
Age group						20.70 (1,3)	**<0.001**
YA	Reference						
OA	−0.47	0.39	−1.24 to 0.30	−1.20	0.231		
GABA+	0.60	1.10	−1.58 to 2.78	0.54	0.587	2.27 (1,3)	0.13
Age group × GABA+						17.72 (1,3)	**<0.001**
Age group OA: GABA+	−1.23	1.40	−4.00 to 1.55	−0.87	0.384		
Task variant						36.29 (3141)	**<0.001**
Unimanual easy	Reference						
Unimanual complex	0.16	0.42	−0.67 to 1.00	0.39	0.697		
Bimanual easy	0.14	0.46	−0.77 to 1.04	0.30	0.765		
Bimanual complex	−0.19	0.46	−1.09 to 0.71	−0.42	0.676		
Age group × task variant						0.74 (3141)	0.53
Age group OA: task variant UC	−0.41	0.56	−1.52 to 0.70	−0.73	0.469		
Age group OA: task variant BE	−1.42	0.61	−2.63 to −0.21	−2.32	**0.022**		
Age group OA: task variant BC	−1.06	0.59	−2.22 to 0.10	−1.80	0.074		
GABA+ × task variant						0.34 (3141)	0.59
GABA+ : task variant UC	0.41	1.57	−2.69 to 3.52	0.26	0.794		
GABA+ : task variant BE	1.70	1.72	−1.71 to 5.10	0.99	0.326		
GABA+ : task variant BC	1.75	1.72	−1.66 to 5.16	1.02	0.311		
Age group × GABA+ × task variant						2.31 (3141)	0.08
Age group OA: GABA+ : task variant UC	−0.71	2.03	−4.73 to 3.30	−0.35	0.725		
Age group OA: GABA+ : task variant BE	−5.07	2.21	−9.45 to −0.69	−2.29	**0.024**		
Age group OA: GABA+ : task variant BC	−3.56	2.15	−7.81 to 0.69	−1.66	0.100		
Observations	157						
R^2 Nagelkerke	0.56						
AIC	116.24						

Significant *p* values are indicated in bold. CI: confidence interval; YA: young adults; OA: older adults; UC: unimanual complex; BE: bimanual easy; BC: bimanual complex.

related fMRI data were acquired first, see Fig. 1*A*), the high-resolution T1 image acquired at the beginning of the session was co-registered to this short anatomic image to assure proper resolution of the to-be-segmented data. The fraction of gray matter, white matter and CSF within the VOI was calculated by segmentation of the data using statistical parametric mapping (SPM) software (version 12). In a last step, GABA levels were normalized to the average voxel composition of the corresponding age group (Harris et al., 2015; see their

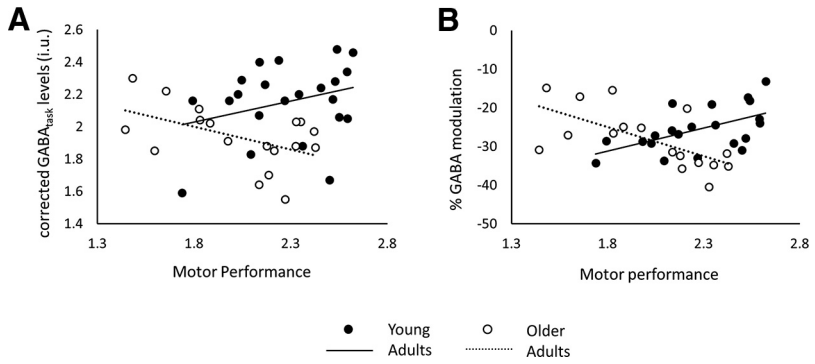

Figure 6. GABA+ levels in association with bimanual action selection performance. Regression analyses between GABA+ levels (*y*-axis) and action selection performance (*x*-axis). Exponentially transformed performance scores are presented, i.e., higher values represent better performance. Results revealed that, for both $GABA+_{task}$ and $GABA+_{mod}$, the association between GABA+ and motor performance was age-dependent. ***A***, Lower $GABA+_{task}$ levels were related to better performance in OA, whereas no significant association was observed within YA. ***B***, A more pronounced modulation of GABA+ (i.e., more negative $GABA+_{mod}$ value) was significantly related to better performance in OA, yet poorer performance in YA.

Table 4. Relationship between brain activity and GABA+ levels within the MRS VOI

	$GABA+_{task}$					$GABA+_{mod}$				
Brain region	*x*	*y*	*z*	Z_{max}	*p*	*x*	*y*	*z*	Z_{max}	*p*
Negative association between BOLD and GABA+ levels across age groups										
Unimanual complex										
S1, S2, IPL	/					−48	−18	27	4.00	0.011
PMC, M1	/					−26	−17	68	3.55	0.013
Bimanual easy										
S1, S2, IPL	/					−48	−19	27	3.9	0.028
PMC, M1	/					−27	−18	65	3.52	0.034
Bimanual complex										
S1, S2, IPL	/					−47	−19	28	4.58	0.010
PMC, M1	/					−26	−17	68	3.65	0.028

Coordinates are presented in MNI space. S1: primary somatosensory cortex; S2: secondary somatosensory cortex; M1: primary motor cortex; PMC: premotor cortex; IPL: inferior parietal lobule.

Equation 6). Considering that macromolecules are co-edited together with the GABA signal, we will refer to it as GABA+. In agreement with previous work from our group and others (Chalavi et al., 2018; Hermans et al., 2018; Cassady et al., 2019), water was used as a reference compound.

Data quality was assessed in a qualitative manner by visual inspection for lipid contamination of the spectra and quantitatively by means of GABA+ SNR, frequency drift and full-width half-maximum (FWHM) of the modeled NAA signal (for an overview, see Table 1). Overall, 7% of the acquired MRS voxels were excluded because of practical issues during scanning ($GABA+_{pre}$: 1 YA, $GABA+_{task}$: 2 YA, $GABA+_{post}$: 2 YA) or lipid contamination ($GABA+_{pre}$: 1 YA and 2 OA, $GABA+_{task}$: three OA, $GABA+_{post}$: 1 OA). Thus, analyses are based on 53 spectra for $GABA+_{pre}$ (26 YA and 27 OA), 52 spectra for $GABA+_{task}$ (26 YA and 26 OA), and 54 spectra for $GABA+_{post}$ (26 YA and 28 OA). To verify whether task-induced modulations of GABA+ levels were already present at the beginning of task execution or only emerged over time, the effect of scan order (i.e., task-related GABA+ levels acquired before or after task-related fMRI data) was investigated using a 2 (order: task-related MRS first, task-related fMRI first) × 3 (time: $GABA+_{pre}$, $GABA+_{task}$, $GABA+_{post}$) repeated measures ANOVA. As results revealed no significant main or interaction effect including order (all $ps > 0.40$), this factor was not included in further analyses. In addition, the individual level of GABA+ modulation from baseline $GABA+_{pre}$ to $GABA+_{task}$ levels was examined by subtracting $GABA+_{pre}$ from $GABA+_{task}$ levels and subsequently correcting for baseline GABA+ levels [formula: ($GABA+_{task}$ – $GABA+_{pre}$)/$GABA+_{pre}$]. Considering that $GABA+_{post}$ levels were primarily acquired to verify whether the reduced GABA+ levels returned to baseline after task completion and because the modulation between $GABA+_{pre}$ and $GABA+_{task}$ levels was highly correlated with the modulation between $GABA+_{task}$ and $GABA+_{post}$ levels (Pearson's correlation: $r = 0.837$, $p < 0.001$), we focused on the modulation of GABA+ levels from baseline $GABA+_{pre}$ to task performance in subsequent analyses ($GABA+_{mod}$).

fMRI. The FMRIB Software Library (FSL) version 7 was used for fMRI data analysis. First, the Brain Extraction Tool (BET) was used on the T1-weighted anatomic images to extract the brain from the dura and skull. Furthermore, fMRI runs were corrected for local distortions using the Topup command. Next, preprocessing steps were conducted using the FMRI Expert Analysis Tool (FEAT). Here, a high-pass filter cutoff of 65 s was used and MCFLIRT motion correction was applied. EPIs were co-registered to their corresponding T1 anatomic image using the nonlinear registration tool FNIRT. Subsequently, the resulting image was co-registered (linear registration, 12 degrees of freedom) to an age-appropriate template based on 555 participants with an age range from 20 to 86 as derived from the Information Extracted from Medical Images (IXI) database (brain-development.org/ixi-dataset; Ericsson et al., 2008). Co-registration was visually checked by inspecting the overlap of gyri, sulci, and ventricles between the input and resulting image. Subsequently, a general linear model was performed in which the planning and execution phase of all four task variants (unimanual easy, unimanual complex, bimanual easy, bimanual complex) were included as conditions of interest. For these eight conditions, regressors and their first temporal derivatives were defined and added to the general linear model. The number of digits involved in the required movement pattern was incorporated in the regressor files as parametric modulators by using a three-column format in which trial onset, trial duration and number of fingers involved corresponded to the first, second and third column, respectively. Each ensuing vector was convolved with the canonical hemodynamic response function. Using the FSL motion outliers command, a confound matrix was created including timepoints and their six motion parameters and derivatives that were corrupted by large motion. This was included in the GLM as confound explanatory variable together with a CSF and WM mask that was created using the FMRIB's automated segmentation tool (FAST). From the 28 YA and 29 OA that completed the full experimental protocol, data of four YA and three OA were discarded because of excessive motion (motion > 1.5* voxel size, 1 YA and 1 OA), incomplete field of view (1 YA and 1 OA), poor registration quality (1 YA and 1 OA) or data export issues (1 YA). Therefore, fMRI results are based on 24 YA and 26 OA. For these participants, a fixed-effect model was conducted to collapse across the two fMRI runs. The resulting contrast images were entered in a higher-level group analysis, i.e., a random effects model that used Gaussian random field theory. Group analyses were done to investigate the effect of age on task-related brain activity patterns (i.e., task vs rest) for each task variant separately. First, to investigate the association between MRS-derived GABA+ levels and task-based brain activity patterns, cluster-based fMRI regression analyses were conducted by including demeaned GABA+ values as a covariate of interest within these fMRI group analyses (i.e., two models including either $GABA+_{task}$ or $GABA+_{mod}$ as a covariate). Considering that MRS-derived GABA+ levels were acquired within left SM1, these analyses were restricted to a mask that was created based on the sum of all individual MRS VOIs acquired before task execution (i.e., $GABA+_{pre}$; Fig. 3). Second, to examine the relationship between motor performance and brain activity, fMRI group analyses were performed per task variant including demeaned

performance scores of the corresponding task variant as a covariate of interest. Similar to the fMRI analyses incorporating GABA+ as a covariate, these analyses were restricted to brain regions that were covered by the MRS VOI mask. In Results, the location and local maxima of each cluster are reported. For all fMRI analyses, cluster-based thresholding was applied using a probability threshold of $p < 0.05$ and $Z > 2.3$.

Statistical analyses

First, age-related differences in action selection performance (% correct trials) were examined using a 2 (age group: YA, OA) × 2 (complexity: easy, complex) × 2 (coordination mode: unimanual, bimanual) mixed model repeated measures ANOVA in which age group was treated as between-subject factor and complexity and coordination mode as within-subject factors. Second, to investigate the modulatory capacity of GABA+ levels within left SM1 in the context of aging, a 2 (age group: YA, OA) × 3 (time: $GABA+_{pre}$, $GABA+_{task}$, $GABA+_{post}$) mixed model repeated measures ANOVA was conducted. Here, age group and time served as a between-group and within-group factors of interest, respectively. To assure that our results were not driven by differences in frequency drift, the mean difference between the nominal water frequency at 4.68 ppm and the observed frequency of the residual water signal in the prefrequency-corrected spectra was included as a covariate in the above mentioned repeated measures ANOVA (Mikkelsen et al., 2017). Third, to verify whether baseline GABA+ levels (i.e., $GABA+_{pre}$) were related to the modulatory capacity of GABA+ levels (i.e., $GABA+_{mod}$), Pearson correlations were performed within age groups. Finally, linear regression analyses were conducted to investigate whether GABA+ was indicative of action selection performance and whether the association was dependent on the age group (YA, OA) and/or task variant (unimanual easy, unimanual complex, bimanual easy and bimanual complex). These analyses were performed for $GABA+_{task}$ and $GABA+_{mod}$ separately. In case of significant age group × GABA+ level interaction effects, *post hoc* linear regression analyses were performed within age groups to further characterize the age-related differences in the association between $GABA+_{task}$/$GABA+_{mod}$ and motor performance. Cook's distance was used to verify the presence of influential datapoints, i.e., bivariate outliers that highly influence the correlation observed across both variables (Cook, 1977). The following criteria were used: Cook's distance > 0.5, Cook's distance > 3*mean Cook's distance, and visual inspection showing a large difference between the Cook's distance of the influential datapoint as compared with the other values. For all except the unimanual easy task variant, influential datapoints of the same young and older participant were removed. In the bimanual easy task variant, data of one additional OA were excluded. For both repeated measures ANOVAs, the threshold for statistical significance was set to $p < 0.05$ and the Greenhouse–Geisser correction was applied when the sphericity assumption was violated. Within the linear regression analyses, Holm corrections were used to account for multiple comparisons (Holm, 1979).

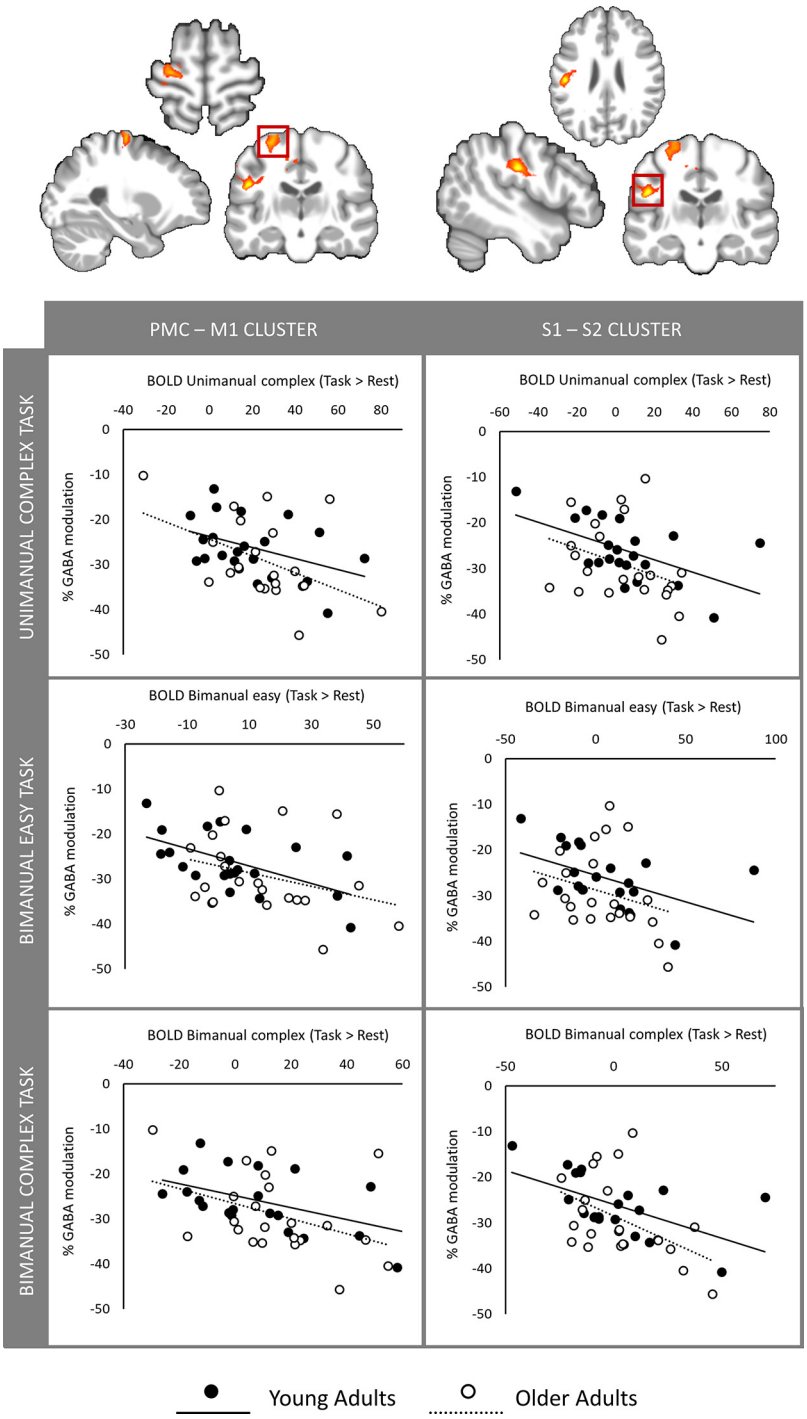

Figure 7. Associations between task-related GABA+ modulation and SM1 brain activity patterns. Except for the unimanual easy task variants, a more pronounced modulation (task-induced decrease) of left SM1 GABA+ was related to higher task-related brain activity in two clusters within the SM1 mask, i.e., a cluster covering PMC and M1 and a cluster covering S1 and S2. Scatterplots are used to illustrate the association between the modulation of GABA+ and brain activity within each cluster per task variant. Indicated BOLD values represent percent signal change.

Results

Behavioral performance

Behavioral results are based on the complete datasets of 23 YA and 22 OA and are illustrated in Figure 4. The 2 (age group: YA, OA) × 2 (complexity: easy, complex) × 2 (coordination mode: unimanual, bimanual) mixed model ANOVA revealed a main effect of complexity ($F_{(1,43)} = 63.56$, $p < 0.001$, $\eta_p^2 = 0.60$) and coordination mode ($F_{(1,43)} = 184.98$, $p < 0.001$, $\eta_p^2 = 0.81$).

Table 5. Relationship between brain activity and motor performance within the MRS VOI

Brain region	*x*	*y*	*z*	Z_{max}	*p*
Positive association between BOLD and performance levels across age groups					
Bimanual complex					
Corticospinal tract	−23	−21	27	3.70	0.005
Interaction of age group with the association between BOLD and performance levels					
Unimanual easy					
Corticospinal tract	−18	−21	42	3.34	0.045
Bimanual easy					
SM1	−47	−15	43	3.61	0.021

SM1: primary sensorimotor cortex.

Moreover, a significant complexity × coordination mode interaction effect ($F_{(1,43)} = 42.95$, $p < 0.001$, $\eta_p^2 = 0.50$) indicated a larger difference between easy and complex task conditions during bimanual task variants as compared with unimanual task variants. Furthermore, there was a main effect of age group ($F_{(1,43)} = 5.53$, $p = 0.023$, $\eta_p^2 = 0.11$) and a significant age group × complexity interaction effect ($F_{(1,43)} = 5.85$, $p = 0.020$, $\eta_p^2 = 0.12$) implying that the age-related decline in performance was more prominent in the complex as compared with the easy task variants. The age group × coordination mode and the age group × coordination mode × complexity level interaction effects were not significant ($F_{(1,43)} = 0.01$, $p = 0.93$, $\eta_p^2 = 0.00$ and $F_{(1,43)} = 1.28$, $p = 0.26$, $\eta_p^2 = 0.03$, respectively).

GABA+ levels

MRS results of the 2 (age group: YA, OA) × 3 (time: $GABA+_{pre}$, $GABA+_{task}$, $GABA+_{post}$) mixed model repeated measures ANOVA including frequency drift as a covariate included complete datasets of 25 YA and 25 OA and are summarized in Figure 5. Results indicated a significant main effect of age group ($F_{(1,45)} = 5.95$, $p = 0.019$, $\eta_p^2 = 0.12$) such that GABA+ levels were lower in OA as compared with YA. Furthermore, a significant main effect of time was observed ($F_{(2,90)} = 196.30$, $p < 0.001$, $\eta_p^2 = 0.81$). *Post hoc* analyses revealed that GABA+ levels during task execution were significantly lower as compared with GABA+ levels measured at rest during the pre-task and post-task execution phase ($p < 0.001$). $GABA+_{pre}$ and $GABA+_{post}$ levels did not differ ($p = 0.68$). Remarkably, as illustrated in Figure 5*B*, this transient decrease in GABA+ levels in response to task performance was consistently observed across all participants. There was no significant time × age group interaction effect ($F_{(2,90)} = 0.50$, $p = 0.61$, $\eta_p^2 = 0.01$), indicating that the modulation of GABA+ levels from rest to task execution was independent of age group. Indeed, an independent samples *t* test on $GABA+_{mod}$ data revealed no significant difference between both age groups ($t_{(1,48)} = 1.20$, $p = 0.236$). Finally, correlation analyses revealed that higher resting-state $GABA+_{pre}$ levels were related to a more pronounced task-induced modulation of GABA+ levels ($GABA+_{mod}$) in OA ($r = -0.424$, $p = 0.035$), whereas no significant association was observed within YA ($r = -0.019$, $p = 0.93$).

GABA+ levels in association with motor performance

Results of the regression analyses are summarized in Tables 2, 3 as well as in Figure 6. Regression analyses including $GABA+_{task}$ levels (complete datasets for both measures in 21 YA and 18 OA) revealed that age group as well as task variant were significant predictors of performance. Furthermore, a significant age group × $GABA+_{task}$ interaction effect was observed suggesting that the association between $GABA+_{task}$ levels and motor performance was age-dependent. *Post hoc* analyses within age groups revealed that higher $GABA+_{task}$ levels were related to poorer motor performance in OA ($F_{(1,3)} = 6.42$, $p = 0.01$), whereas no significant association between $GABA+_{task}$ levels and performance was observed in YA ($F_{(1,3)} = 2.84$, $p = 0.10$; Fig. 6*A*). Regression analyses including $GABA+_{mod}$ (complete datasets for both measures in 20 YA and 16 OA) revealed similar results, i.e., a main effect of age group and task variant as well as a significant age group × $GABA+_{mod}$ interaction effect. Here, *post hoc* analyses within age groups revealed a significant association between the task-induced modulation of GABA+ levels and action selection performance for both age groups, yet in opposite directions. Specifically, a more profound GABA+ modulation (i.e., more negative $GABA+_{mod}$ value) related to poorer performance in YA ($F_{(1,3)} = 5.80$, $p = 0.02$), whereas a more profound GABA+ modulation related to better performance in OA ($F_{(1,3)} = 13.97$, $p < 0.001$; Fig. 6*B*).

Brain activity patterns in association with GABA+ levels

Results of the fMRI analyses per task variant including $GABA+_{task}$ or $GABA+_{mod}$ as a covariate of interest are reported in Table 4. The analyses including $GABA+_{task}$ as a covariate included data of 22 YA and 23 OA, whereas the analysis including $GABA+_{mod}$ as a covariate included 21 YA and 22 OA. For all except the unimanual easy task variant, fMRI activity patterns within SM1 were negatively associated with task-related $GABA+_{mod}$ across age groups. Specifically, a larger decrease of left SM1 inhibitory tone, as reflected by a more pronounced task-induced decrease of left SM1 GABA+ levels, was associated with higher brain activity (Fig. 7).

Brain activity patterns in association with motor performance

Results of the fMRI analyses within the MRS VOI mask per task variant including performance scores as a covariate of interest included data of 21 YA and 19 OA and are summarized in Table 5 and Figure 8. For the unimanual easy task variant, we found an age-dependent association between brain activity and motor performance such that higher brain activity related to poorer motor performance in YA as opposed to OA (Fig. 8*A*). However, as multiple participants reached maximal performance scores (i.e., 100% correct trials), these results should be interpreted with caution. No association between brain activity and performance on the unimanual complex task variant was observed. With respect to brain activity and motor performance on the bimanual easy task variant, age affected the direction of the association such that higher BOLD related to better motor performance in YA but not in OA (Fig. 8*B*). Lastly, in the complex bimanual task variant, higher brain activity related to better motor performance, regardless of age group (Fig. 8*C*).

Discussion

We examined the modulation of GABA+ during performance of an action selection task and its association with stimulus-induced BOLD changes in the context of aging. On a behavioral level, OA performed poorer as compared with YA, especially when task complexity was high. On a neurochemical level, GABA+ levels were found to decrease during task performance and returned to baseline when

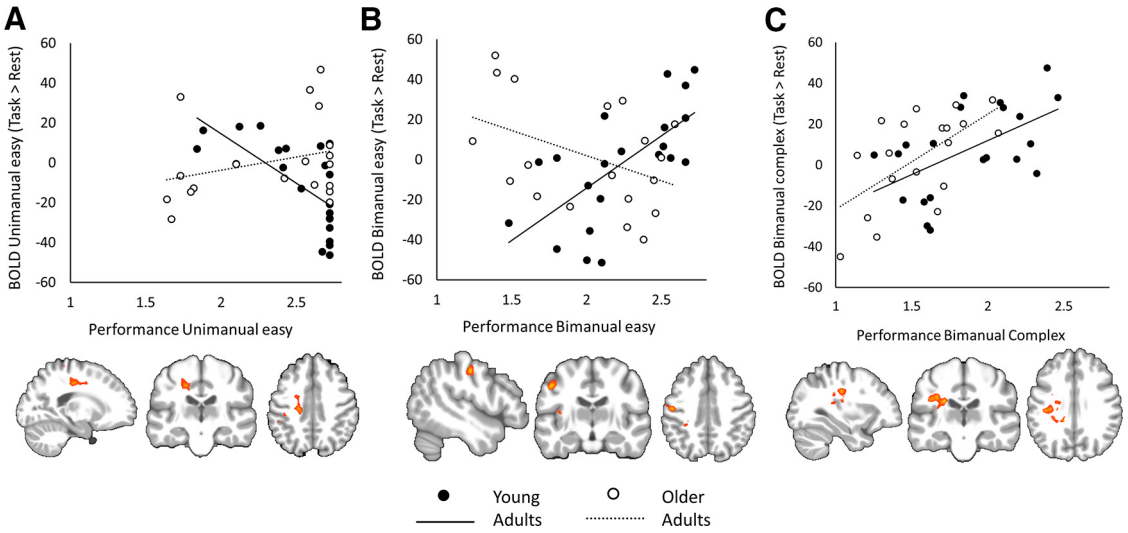

Figure 8. Association between task-related brain activity and motor performance. ***A***, Higher task-induced brain activity was associated with poorer performance on the unimanual easy task variant in YA but not OA. However, as multiple participants achieved the maximal score, this result should be interpreted with caution. ***B***, The association between brain activity and performance on the bimanual easy task variant was age-dependent such that higher brain activity related to better motor performance in YA but not OA. ***C***, Irrespective of age, higher task-related brain activity related to better performance on the bimanual complex task variant. Exponentially transformed performance scores are presented, with higher scores indicating better motor performance. Indicated BOLD values represent percent signal change.

measured after task completion at rest. This held up for both YA and OA, although OA as compared with YA exhibited overall lower GABA+ levels. Furthermore, higher task-induced decreases of GABA+ levels (higher modulation) were associated with higher SM1 brain activity across age groups. Additionally, higher brain activity related to better bimanual performance, albeit partially mediated by age. Interestingly, in OA, a more profound task-related decrease of GABA+ levels was related to better bimanual performance, whereas an opposite association was observed in YA. Together, these results provide new insights into the dynamical properties of GABA+ and their importance for motor performance and corresponding brain activity patterns across age groups.

Age-related decrease in the selectivity of motor output

Performance levels on the action selection task were dependent on task complexity level as well as coordination mode. As expected, we also observed an aging-induced motor deficit that was dependent on task complexity such that OA had disproportionately more difficulty than YA with the complex as compared with the easier task variants. Our results suggest that OA encounter more difficulties in overcoming interference among the movements of different effectors, presumably facing more task-irrelevant motor overflow and thus decreased manual precision.

A transient task-related decrease of SM1 GABA+ levels

This is the first study to detect a decrease of GABA+ levels in response to the execution of an effector selection task. Considering that task-related GABA+ levels acquired either during the first or last third of in-scanner task execution did not differ, these results suggest a rapid decrease in GABA+ levels that is maintained over the course of task execution. Notably, resting-state GABA+ levels measured during baseline ($GABA+_{pre}$) or immediately after task completion ($GABA+_{post}$) did not differ, suggesting a quick postperformance recovery of GABA+ levels. As previous work reported no alterations in task-related GABA+ in response to the execution of a random tapping sequence (Kolasinski et al., 2019), we suggest that transient dynamical changes in $GABA+_{task}$ content might depend on the nature and load of the task. This is supported by previous work demonstrating GABA+ content to increase/decrease depending on the task paradigm of interest as well as the timing of MRS measurements (Floyer-Lea et al., 2006; Chen et al., 2017; Chalavi et al., 2018; Van Vugt et al., 2020).

Indeed, successful performance of the multidigit task employed in our study required distinctive movements while suppressing task-irrelevant finger movements and this may have resulted in temporary depletion of the GABA+ pool (Griffin and Strick, 2020). Moreover, alterations in corticospinal excitability have been documented particularly for tasks that require high levels of manual precision (Liepert et al., 1998; Hasegawa et al., 2001; Pearce and Kidgell, 2009). Hence, the higher the task load, the more the equilibrium between excitatory and inhibitory processes is challenged, resulting in dynamic neurochemical changes.

Importantly, despite the observed lower resting-state left SM1 GABA+ levels in older as compared with YA in agreement with previous work (Chalavi et al., 2018; Cassady et al., 2019; Cuypers et al., 2020), we observed a preserved task-related modulatory capacity of GABA+ in OA. Likewise, previous studies that investigated alterations in resting-state GABA+ levels in response to learning or brain stimulation also demonstrated preserved GABA+ modulations within OA (Antonenko et al., 2017; Chalavi et al., 2018; King et al., 2020). Although more research is required, these results suggest that the modulatory capacity of GABA+ levels is not necessarily restricted by an age-related decrease of (baseline) GABA+ levels. Together, these results underscore an eminent role for task-related MRS in unfolding transient dynamical GABA+ changes across both age groups. Future work should invest in determining (transient) neurochemical dynamics across different brain regions and distinct motor tasks for revealing differential behavioral functions.

The modulatory capacity of GABA+ levels is associated with motor performance

Although literature is rather limited, previous studies consistently associated higher resting-state GABA levels with better performance in OA (Hermans et al., 2018; Cassady et al., 2019;

Lalwani et al., 2019; Simmonite et al., 2019; Heise et al., 2021; Maes et al., 2021). Conversely, our task-induced results revealed that, in OA, lower $GABA+_{task}$ was associated with better performance. At first sight, these findings appear contradictory but it is important to realize that resting-state GABA+ and task-related GABA+ modulation reflect different features of GABA tone. Specifically, OA exhibiting a more pronounced task-induced decrease in GABA+ levels showed a better performance. Moreover, OA with higher baseline $GABA+_{pre}$ levels generally demonstrated a more pronounced task-related decrease of GABA+. Hence, a release from inhibitory tone during task performance, as reflected by a task-induced lowering of GABA+ levels, was linked with better motor performance in OA. In YA, however, an opposite association was observed such that a task-induced release of inhibitory tone was related to poorer performance. Previous work also identified age as well as the task paradigm of interest as factors that influenced the direction of the association between GABA+ levels and motor performance (Heise et al., 2021; Maes et al., 2021). Furthermore, in YA, higher resting-state GABA levels were previously related to better performance on discrimination tasks (Boy et al., 2010; Puts et al., 2011; Kurcyus et al., 2018). Potentially, YA benefit from higher task-related GABA+ levels to uphold the specificity of neural responses, whereas lowering GABA+ during task performance may support the recruitment of additional neuronal resources in OA. The specific reasons underlying this differential age effect remain to be studied in further detail. Nonetheless, our study is the first to underscore the behavioral relevance of transient task-induced modulations of GABA+ levels within the sensorimotor cortex, providing an exciting avenue for future scientific research endeavors.

Task-related brain activity is associated with the modulatory capacity of GABA+ levels and motor performance

The information available about the interrelationship between fMRI-derived brain activity levels and task-related GABA+ levels, let alone the task-induced modulation of GABA+ levels, is scarce. Therefore, we investigated whether the negative association between GABA+ and stimulus-induced BOLD changes, as observed in the perceptual and cognitive domain (Duncan et al., 2014; Kolasinski et al., 2017; Thielen et al., 2018; Lalwani et al., 2019), could be extended to the motor domain across age groups. Here, we identified an important role for the modulatory capacity of SM1 GABA+ levels in relation to SM1 brain activity. Specifically, a more pronounced task-induced lowering of GABA+ levels was associated with higher task-induced brain activity. Although seemingly contradictory, this finding is consistent with the previous observation that higher baseline GABA+ levels are associated with lower brain activity in that reducing GABA+ via experimental manipulation paves the way for higher BOLD responses. These findings corroborate previous work that suggests an important role for GABA+ in defining the threshold at which signal processing occurs (Logothetis et al., 2001; Buzsáki et al., 2007; Donahue et al., 2010). Thus, a decrease of or release from inhibitory tone seems essential to the occurrence of elevated task-related BOLD signals. Moreover, in line with the observation of a more pronounced task-related modulation (decrease) of GABA+ being related to better bimanual motor performance in OA, higher task-induced brain activity was also related to better bimanual performance (particularly during the complex bimanual condition). Together, these results suggest that GABA+ modulation enables enhanced recruitment of the sensorimotor cortex, which may be relevant to task performance in OA.

Limitations and future directions

First, we acknowledge the behavioral data loss because of wearing of the force sensors that impacted the power of our study. Nonetheless, our results underscore that the experimental setup is sensitive to anticipated coordination mode-dependent, complexity-dependent, and age-dependent performance differences. Moreover, the intended modulation of GABA+ levels was consistently achieved. Second, GABA+ levels were acquired within a relatively large voxel to assure proper data quality, whereas clusters of brain activity can be located at much smaller scale. Third, it should be noted that, as the macromolecules co-edited with the GABA signal are known to increase with advancing age (Noworolski et al., 1999; Aufhaus et al., 2013; Marjańska et al., 2018), the observed age-related decrease of GABA levels might be underestimated. Furthermore, although some studies suggest macromolecular contamination to be functionally irrelevant (Harris et al., 2015; Duncan et al., 2019), the strength of the observed associations between GABA+ levels and behavior might increase when using macromolecule-suppressed GABA measurements (Mikkelsen et al., 2018). Fourth, although the present study provides initial evidence on the role of the modulatory capacity of left SM1 GABA+ levels in relation to BOLD changes, the role of functional connectivity patterns needs to be addressed in future research. To this end, methodological advancements that increase the resolution of MRS [i.e., higher field strength (7T)] are indispensable.

In conclusion, although GABA+ levels at rest were lower in OA as compared with YA, we identified a transient decrease in left SM1 GABA+ during motor performance, independent of age. Moreover, this release of inhibitory tone was related to higher SM1 brain activity patterns across YA and OA. Furthermore, a more pronounced task-induced modulation (decrease) of GABA+ levels was related to better bimanual action selection performance in OA only. Together, these results underscore the potential of studying GABA+ levels not only during resting-state but also during task-related conditions to determine behaviorally relevant task-induced modulations of GABA+ levels, especially in the context of aging.

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