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Age-related differences in task-related modulation of cerebellar brain inhibition

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ABSTRACT

Age-related reductions in cerebellar integrity predict motor impairments in older adults (OA), but the contribution of cerebro-cerebellar interactions to these impairments remains unclear. Understanding these interactions could reveal underlying mechanisms associated with age-related deficits in motor control. To explore this, twenty younger adults (YA) and twenty OA, all right-handed, participated in a dual-site transcranial magnetic stimulation protocol. Cerebellar brain inhibition (CBI) was measured at rest and during the anticipatory period of a bimanual tracking task (BTT). The results revealed that YA outperformed OA on the BTT. Both age groups demonstrated reduced CBI during the anticipatory period of the BTT compared to CBI at rest, with no differences in CBI levels between both groups. Notably, motor performance was influenced by CBI modulation, as learning progressed (early vs. slightly later short-term learning), and this influence differed between age groups. In summary, resting-state CBI and the task-related release of CBI were maintained in OA, challenging previous assumptions of reduced inhibitory function in OA. However, the modulation of CBI appears to influence short-term motor learning differently for both groups, suggesting potential functional reorganization of the cerebellar neural system.

1. Introduction

Overall life expectancy has been rising worldwide, with an increase of 6.6 years over the past 20 years (World Health Organisation, 2022). Likewise, the number of years lived without disease and/or injury, i.e., 'healthy life expectancy' increased. Yet, it grew at a slower rate as compared to the overall life expectancy (World Health Organisation, 2022). Hence, there is a growing interest in understanding the processes associated with age-related changes in human functioning.

Aging is characterized by changes in the structural (Chalavi et al., 2018; Inano et al., 2011), functional (King et al., 2018) and biochemical (Gong et al., 2022; Levin et al., 2014) integrity of the brain, often resulting in significant impairments in motor function and learning (Scherder et al., 2008; Seidler et al., 2010). These impairments, in turn, have a notable impact on quality of life and the ability to live independently (Ourry et al., 2021). Although age-related limitations in motor function have a multifactorial origin across various brain regions, cerebellar integrity has emerged as a prominent predictor of motor function in older adults (Bernard and Seidler, 2013; Raz et al., 2000; Woodruff-Pak et al., 2001). Specifically, the cerebellum has been identified as being significantly associated with task performance and motor learning (Beets et al., 2015; Debaere et al., 2004; Goble et al., 2010; Manto et al., 2012; Monteiro et al., 2017) and is deemed critical for determining the impact of aging on motor control and bimanual coordination in particular (Boisgontier et al., 2018; Debaere et al., 2001, 2004; Miyaguchi et al., 2022; Monteiro et al., 2019). Specifically, the cerebellum's role in bimanual coordination stems from its role in the feedforward model (D'Angelo, 2018) and its critical involvement in the coordination of movements and motor timing (Debaere et al., 2001, 2004). The latter is essential for bimanual coordination as the precise timing of motor commands allows for the controlled acceleration and deceleration of movements to achieve the desired spatiotemporal

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pattern (Debaere et al., 2004).

Several studies have linked age-related deteriorations in motor performance to cerebellar structure, revealing an overall volumetric decline and a reduction in white matter integrity in older adults (Bernard and Seidler (2013); Hoogendam et al. (2012); Jernigan et al. (2001); Ziegler et al. (2012); for a review see: Bernard and Seidler (2014)). Additionally, more recent functional magnetic resonance imaging (fMRI) studies identified an age-related decrease in cerebellar–cerebral network connectivity (Bernard et al., 2013; Monteiro et al., 2017). While fMRI can be employed to evaluate the temporal correlation between cerebellar and cerebral networks (Friston et al., 1993), neurophysiological tools with a high temporal resolution such as transcranial magnetic stimulation (TMS) enable researchers to unravel causal relationships (Ruohonen and Karhu, 2010). More specifically, TMS can reveal the influence of one neural system on another, i.e., effective connectivity, in a dual-site TMS (ds-TMS) paradigm (Seghier and Friston, 2013). Using ds-TMS, the modulatory impact of a motor-related brain region on the primary motor cortex (M1) is examined by stimulating both regions at a specific interstimulus interval (ISI) (Ferbert et al., 1992; Van Malderen et al., 2022). Consequently, ds-TMS provides a unique opportunity to identify the nature, strength, and context-specific modulations of effective connectivity between the cerebellum and contralateral M1 (Van Malderen et al., 2022). More specifically, it has been suggested that TMS can target the disynaptic dentato–thalamo–cortical pathway, which constitutes the connection between the cerebellum and M1 (Daskalakis et al., 2004; Grimaldi et al., 2014; Groiss and Ugawa, 2013; Reis et al., 2008). This disynaptic pathway is generally of facilitatory nature and originates from the dorsal part of the dentate nucleus. The Purkinje cells, a class of inhibitory neurons located more superficially in the cerebellar cortex, exert an inhibitory influence on this pathway (Grimaldi et al., 2014; Groiss and Ugawa, 2013; Na et al., 1997; Stoodley and Schmahmann, 2010). Since a TMS pulse over the cerebellum is postulated to activate these Purkinje cells, it leads to the inhibition of the dentate nucleus, subsequently resulting in a reduced excitatory influence of the dentato–thalamo–cortical pathway on M1 (Allen and Tsukahara, 1974; Daskalakis et al., 2004; Galea et al., 2009; Grimaldi et al., 2014; Groiss and Ugawa, 2013; Na et al., 1997; Shinoda et al., 1993). This reduction is manifested in a reduced M1 corticospinal excitability (CSE) when conditioning the cerebellum as compared to unconditioned TMS, which can be quantified through the measurement of motor evoked potentials (MEPs) and is referred to as cerebellar brain inhibition (CBI).

Numerous studies have used CBI as a marker for investigating the cerebellar contribution to motor learning in younger adults (Jayaram et al., 2011; Schlerf et al., 2015; Spampinato et al., 2017, 2020b; Tanaka et al., 2021). Specifically, these studies have shown a task-related modulation (reduction/release) of CBI during motor behaviors, such as the acquisition and adaptation of unimanual motor skills (Schlerf et al., 2012; Spampinato and Celnik, 2017). Furthermore, research suggests that this CBI modulation might facilitate the acquisition of new motor skills (Jayaram et al. (2011); Schlerf et al. (2015); Tanaka et al. (2021); for a review see: Van Malderen et al. (2022)). Notably, despite the importance of the cerebellum for bimanual motor control, interactions between the cerebellum and M1 have not yet been explored in this context.

Age-related declines in cortical inhibition and inhibitory modulation have been well-documented. Specifically, evidence indicates substantial changes in cortical inhibition with aging, including reduced baseline inhibition (Boudrias et al., 2012; Fujiyama et al., 2009; for reviews see: Dustman et al., 1996; Levin et al., 2014) and altered preparatory neural activity during motor tasks (Cuypers et al., 2013; Hillman et al., 2002; Sterr and Dean, 2008). Furthermore, alterations in task-related inhibitory modulation have been demonstrated across cortical brain regions. For instance, Heise et al. (2013) reported diminished task-related modulation of GABAergic inhibition in the left primary motor cortex in older adults, suggesting a reduced capacity to release inhibition during motor preparation. Similarly, Verstraelen et al. (2021) demonstrated reduced baseline M1–M1 inhibition and a smaller magnitude of disinhibitory modulation in older compared to younger adults. Finally, Fujiyama et al. (2016) observed that while inhibitory interhemispheric interactions between the dorsolateral prefrontal cortex (DLPFC) and M1 shift from inhibition to facilitation during the preparatory period of a bimanual tracking task in younger adults, this modulation is notably diminished in older adults. Importantly, impaired inhibitory control has been linked to declines in motor performance during aging (Levin et al., 2014). However, despite a wealth of research underscoring substantial changes in cortical inhibition as a consequence of aging (e.g., Boudrias et al. (2012); Fujiyama et al. (2009); for a review see: Dustman et al. (1996); Levin et al. (2014)) and studies suggesting a reduced task-related modulation of cortical inhibition (e.g., Fujiyama et al., 2016b; Heise et al., 2013; Verstraelen et al., 2021), only two studies have investigated CBI at rest in an aging population to date (Mooney et al., 2022; Rurak et al., 2022), and up to now no studies have investigated changes in task-related modulation of CBI with age. Rurak et al. (2022) reported a diminished CBI (i.e., less inhibition from the cerebellar hemisphere to contralateral M1) in older adults compared to their younger counterparts at rest. Intriguingly, the resting-state CBI magnitude was positively linked with 10-meter walk performance in younger adults but negatively associated with performance on this task in older adults, suggesting a functional reorganization during the aging process. In contrast, Mooney and colleagues demonstrated both a preservation or even a strengthening of CBI in older adults as compared to younger adults, depending on the ISI between the TMS stimulus to the cerebellum and M1 (Mooney et al., 2022). To the best of our knowledge, the impact of aging on task-related modulations in CBI remains unexplored. Therefore, investigating cerebellar–M1 interactions provides a unique window of opportunity to understand underlying processes of age-related deterioration in bimanual motor performance during short-term learning.

Given the marked structural and functional cerebellar alterations in aging and their suggested role in age-related declines of motor performance and motor learning on the one hand (Bernard and Seidler, 2013; Raz et al., 2000; Woodruff-Pak et al., 2001), and the scarcity of studies examining decline in bimanual motor function and skill acquisition with age on the other hand, this study seeks to better understand the impact of aging on cerebellar–M1 effective connectivity, and its consequences for bimanual motor control during short-term motor learning.

Firstly, it was hypothesized that (1) CBI is altered in older as compared to young adults at rest. Secondly, we hypothesized (2a) a reduction in the magnitude of CBI during the anticipatory period (i.e., from inhibition at baseline towards a release of inhibition prior to movement initiation) of a bimanual coordination task in young adults, however, less pronounced task-related modulation of CBI in older adults as compared to their young counterparts. Moreover, we hypothesized (2b) a positive association between the magnitude of task-related CBI modulation and bimanual motor performance during short-term motor learning, irrespective of age. To the best of our knowledge, this is the first study examining the task-related modulation of CBI during the anticipatory period of a motor task in the context of aging.

2. Methods

2.1. Participants

Recruitment took place in Flanders, Belgium, on community and university level via social media, posters, an article in the newspaper, and flyers. Additionally, older adults listed in the database of the rehabilitation research group (University of Hasselt) were contacted via e-mail/telephone. Adults were eligible for the study when they were aged 20–40 years (younger adults; YA) or 60–80 years (older adults; OA), right-handed, and had a normal or corrected to normal eyesight. To define their handedness, participants completed the Edinburgh Handedness Inventory (EHI; lateralization quotient ranging from −100 to

+100, with values > +50 indicating right-handedness) (Oldfield, 1971). The Montreal cognitive assessment (MoCA (Nasreddine et al., 2005); cut-off score ≤ 23/30 (Carson et al., 2018)) was used to assess cognitive and executive functioning. Additionally, the Beck depression inventory (BDI; a 21-item questionnaire to assess depressive symptoms, with higher scores corresponding to more depressive symptoms; cut-off score: >13) (Beck et al., 1961; Van der Does, 2002) and symptom checklist (SCL; 90-item questionnaire assessing physical and psychological symptoms; cut-off score: >81) (Derogatis, 1975) were used to screen participants, ensuring they were in a good mental and physical health. The scores of each questionnaire for all included participants are shown per group (younger vs. older adults) in Table 1. Furthermore, participants were excluded if they self-reported any central nervous system diseases, psychiatric disorders, medication intake affecting the central nervous system (sedatives, anti-depressants, etc.), history of brain surgery or injury, or health conditions that, either directly or through their treatment, potentially impact the central nervous system, history of drug or alcohol abuse, or presence of contraindications for TMS (assessed using the TMS screening questionnaire (Rossi et al., 2021; Wassermann, 1998)). Finally, participants were excluded from the study if it was not possible to elicit CBI at rest (after the first ds-TMS block), i.e., if they showed an average percentage of CSE of the unconditioned (single--pulse) motor-evoked potentials (MEPs), i.e., $\%CSE_{unconditioned}$, of 95 % or more (corresponding to 5 % inhibition) as described in detail in section 2.5.1. In addition, the international physical activity questionnaire (IPAQ; assessing the self-reported physical activity levels over 5 domains, with higher scores corresponding to a higher physical activity level) (Craig et al., 2003) was administered to evaluate physical activity over the past seven days. All participants gave written informed consent prior to study participation according to the latest amendment of the Declaration of Helsinki (World Medical Association, 2013). The study was approved by the medical ethics committee of Hasselt University (B11520211000011).

Twenty-two participants (11 YA and 11 OA) were excluded due to the inability to elicit CBI at rest. One younger adult was excluded from the study due to the presence of persistent cervical root activity. This activity was observed bilaterally and at a short latency (±14 ms) upon visual inspection of the electromyographic (EMG) signals (Martin et al., 2009). Three younger adults dropped out due to discomfort associated with cerebellar stimulation. Finally, one older adult dropped out because of the noise of the double-cone (DC) coil, which induced a transient tinnitus-like ringing/whizzing sound, despite wearing earplugs. In total, 20 younger adults (12 female; age mean ± SD: 24 ± 4 years) and 20 older adults (13 female; age mean±SD: 69 ± 6 years) completed the entire procedure. An overview of initial participant recruitment, reasons for exclusion, and dropout can be found in Fig. 1.

Table 1
Participant demographics.

Characteristic	YOUNGER ADULTS*N = 20 (12 F, 8 M)*		OLDER ADULTS*N = 20 (13 F, 7 M)*		Group comparison
	Median (Mean▽)	*IQR (SD▽)*	*Median (Mean▽)*	*IQR (SD▽)*	*WRST (p-value t-test ▽)*
Age (years)	24.35▽	4.01▽	69.10▽	5.78▽	
Questionnaires					
EHI LQ (%)	100.00	11.63	100.00	0.00	0.1600
MoCA (score /30)	29.00	2.00	26.50	3.75	**0.0026***
SCL (score /360)	9.00	14.75	10.00	11.75	1.0000
BDI (score /63)	5.00	5.50	4.00	4.00	0.6822
IPAQ (MET/h)	3854.85	7426.00	4239.50	4376.63	0.9246
TMS measures					
SP MEPs rest (mV)	1.19	1.27	1.03	1.11	0.4570
SP MEPs BL (mV)	2.34	1.47	2.94	2.13	**0.0013***
SP MEPs Prep (mV)	2.27	1.57	2.84	2.32	**0.0004***
rMT (%MSO)	39.80▽	5.98▽	44.85▽	10.68▽	0.0750▽

Variables denoted by ▽ represent normally distributed data, for which the mean and standard deviation are reported. These variables were analyzed using Welch's *t*-test. Statistical analyses of parameters with non-normal distributions were performed using the 2-sample Wilcoxon test. Significant group differences are indicated with an asterisk (*) and written in bold.

Abbreviations: BDI = Beck's depression inventory; BL = baseline timing during task-related measurement; EHI LQ = Edinburgh handedness inventory's lateralization quotient; F = female; IPAQ = International physical activity questionnaire; IQR = Interquartile range; M = male; MoCA = Montreal cognitive assessment; %MSO = Percentage of maximum stimulator output; mV = millivolt; Prep = preparatory timepoint during task-related measurement; rMT = resting motor threshold; SCL = Symptom checklist; SD = standard deviation; SP MEPs = single-pulse motor evoked potentials; TMS = transcranial magnetic stimulation; WRST = Wilcoxon Rank sum Test.

2.2. EMG recording

EMG signals were recorded from the left and right first dorsal interosseus (FDI) muscle using surface Ag-electrodes (Bagnoli™ DE-2.1 EMG Sensors, DELSYS Inc, Boston, MA, USA) attached to the mildly exfoliated (3M™ Red Dot™ Trace Prep 2236, 3M Health Care, St. Paul, MN, USA) skin using double-sided adhesive skin interfaces (Bagnoli Sensor Adhesive Interface, DELSYS Inc, Boston, MA, USA). Grounding electrodes (5×5 cm, 3444057; EN-Trode, Enraf-Nonius, Rotterdam, NL) were placed on the distal ulnar bony protuberance.

50 Hz mains noise was eliminated using Humbug (HumBug, Quest Scientific, North Vancouver, BC, Canada), amplified (gain = 1000), bandpass filtered (20–2000 Hz), digitalized at 2500 Hz (CED 1401 micro, CED Limited, Cambridge, UK), and stored on the computer for offline analysis.

Throughout the experimental TMS session, participants were seated in a comfortable chair with both hands supported on the table. EMG signals from bilateral FDI were continuously monitored, and participants were encouraged to relax their hand muscles (Pinto and Chen,

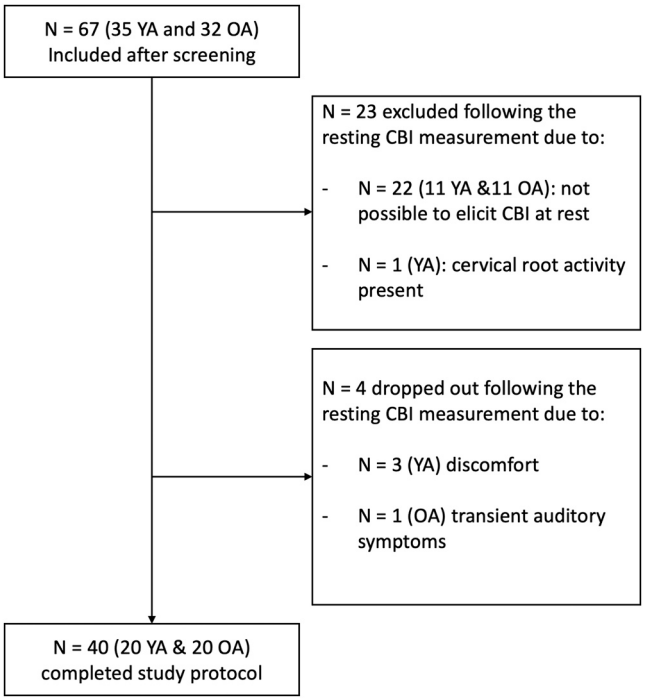

Fig. 1. Participant flow diagram.
Abbreviations: CBI = Cerebellar brain inhibition; N = Number; OA = Older adults; YA = Younger adults.

2001), to keep the background EMG signal to a minimum.

2.3. Transcranial magnetic stimulation

For CBI assessment, a ds-TMS paradigm was adopted (see Fig. 2). The test stimulus (TS) over the hotspot for the left M1 was delivered using a 70-mm figure-of-eight (Fig-8) coil (3190–00; Magstim, Whitland, Dyfed, UK) connected to a monophasic Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK). For mapping the hotspot of the right FDI, a standardized procedure based on the method of Hehl et al. (2020) was conducted. Specifically, using the Brainsight® software (Brainsight®2, Rogue Research Inc, Montreal, Quebec, Canada) and a Montreal Neurological Institute (MNI)-based participant template, a 1-cm spaced rectangular 19x19 grid, centered around the vertex (determined in accordance with the EEG 10–20 system (Klem et al., 1999)) was created over the approximated brain surface and projected to the scalp. The TMS coil was placed perpendicular to the scalp and oriented 45° relative to the mid-sagittal line, with the handle pointing posterolateral, inducing a monophasic posterior–anterior-directed current in the brain. Optically tracked neuronavigation (Brainsight®2, Rogue Research Inc, Montreal, Quebec, Canada) was used to ensure stable and accurate coil placement throughout the experiment (Brasil-Neto et al., 1992; Julkunen et al., 2009; Mills et al., 1992). The resting motor threshold (rMT) was determined with the Fig-8 coil placed over the left M1 hotspot. The rMT is defined as the minimal TMS intensity, expressed as percentage of maximum stimulator output (%MSO), that elicits an MEP amplitude $\geq$ 50 μV in at least five out of ten successive trials (Chen et al., 2008). Stimulation intensity of the TS over left M1 was set to evoke an average MEP amplitude of F1 mV peak-to-peak in five consecutive trials (Fernandez et al., 2018a).

The conditioning stimulus (CS) over the right cerebellum was delivered using a 90-mm double cone (DC) coil (4610–00, Magstim, Whitland, Dyfed, UK), connected to a second Magstim 200 stimulator. Due to its angled circular windings, the DC coil can be used to target deeper brain structures such as the cerebellum (Deng et al., 2013). Moreover, this coil type has been proven to elicit CBI in a reliable manner (Hardwick et al., 2014; Spampinato et al., 2020a). The coil was positioned over the right cerebellar hemisphere. Specifically, the coil was placed 3 cm lateral and 1 cm inferior relative to the palpated inion, since this location is assumed to target the motor areas of the cerebellar cortex in lobes V and VIII (Hardwick et al., 2014), and was positioned to induce an upward-directed current in the brain (Fernandez et al., 2018a). The stimulation intensity of the CS was set at 65 % of the MSO, as this intensity has been demonstrated to elicit the most reliable results while minimizing participant discomfort (Fernandez et al., 2018b). In the dual-pulse conditions (CS+TS), the CS preceded the TS by an ISI of 5 ms (e.g., Baarbé et al., 2014; Daskalakis et al., 2004; Fernandez et al., 2018b; Hardwick et al., 2014; Spampinato and Celnik, 2017; Spampinato et al., 2017; Tanaka et al., 2021).

Ds-TMS measurements

Fig. 3 shows an overview of the experimental protocol.

2.3.1. Ds-TMS at rest

Prior to the resting-state ds-TMS measurement, a short familiarization block for TMS over the right cerebellar hemisphere was performed, as cerebellar stimulation is often perceived as unpleasant (Fernandez et al., 2018a, b) due to the concomitant activation of the deeper neck muscles. Piloting has shown that a familiarization enhances protocol adherence by minimizing discomfort due to muscle tension caused by unpredictable expectations. More specifically, a total of 5–7 pulses were applied by the DC coil over the right cerebellar cortex. The stimulation intensity was gradually ramped up with increments of ± 5–10 % per pulse, starting at 25 %MSO. One pulse was delivered every five seconds until 65 %MSO was reached. Following this TMS familiarization, each participant underwent a ds-TMS block to assess CBI at rest. Participants were instructed to keep their eyes open and to position their hands on the table surface in a relaxed posture. This resting-state ds-TMS block consisted of 20 single-pulse (TS only) and 20 dual-pulse (CS+TS) trials, which were administered in pseudo-randomized order.

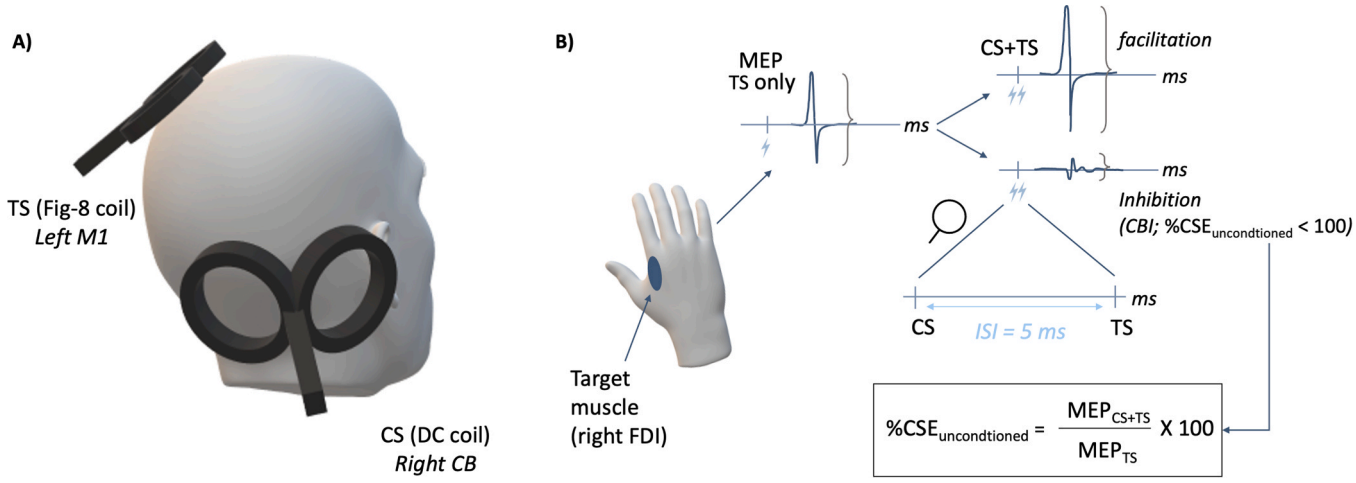

Fig. 2. Transcranial magnetic stimulation (TMS) set-up and ds-TMS principle for CBI. Panel A represents the coil placement. The test stimulus (TS) coil, a 70 mm figure-of-eight (Fig-8) coil, was oriented tangentially to the scalp over the left primary motor cortex (M1) and rotated 45° away from the mid-sagittal line with the handle facing posterolateral (Brasil-Neto et al., 1992; Mills et al., 1992). The conditioning stimulus (CS) coil, a 90 mm double-cone (DC) coil, was oriented horizontally, inducing an upward-directed current in the right cerebellar hemisphere. Panel B provides an overview of the basic principle of dual-site transcranial magnetic stimulation (ds-TMS) over the cerebellum. The TS over left M1 is preceded by a CS over the right cerebellar hemisphere at an interstimulus interval (ISI, i.e., the time between CS and TS application) of 5 ms. By dividing the motor-evoked potential (MEP) amplitude of the CS+TS condition by the MEP amplitude of the TS only condition, a quantification of the influence of the cerebellum (CB) on corticospinal excitability (CSE) is provided. This influence can be expressed as a percentage of the unconditioned corticospinal excitability (%CSE). Larger MEPs in the 'CS+TS' relative to the 'TS only' condition can be interpreted as facilitation, whereas smaller MEPs represent inhibition, referred to as cerebellar brain inhibition (CBI).

Abbreviations: CB = cerebellum; CBI = cerebellar brain inhibition; CS = conditioning stimulus; CSE = corticospinal excitability DC = double-cone; ds-TMS = dual-site transcranial magnetic stimulation; FDI = first dorsal interosseus; Fig-8 = figure-of-eight; ISI = interstimulus interval; M1 = primary motor cortex; MEP = motor evoked potential; TS = test stimulus.

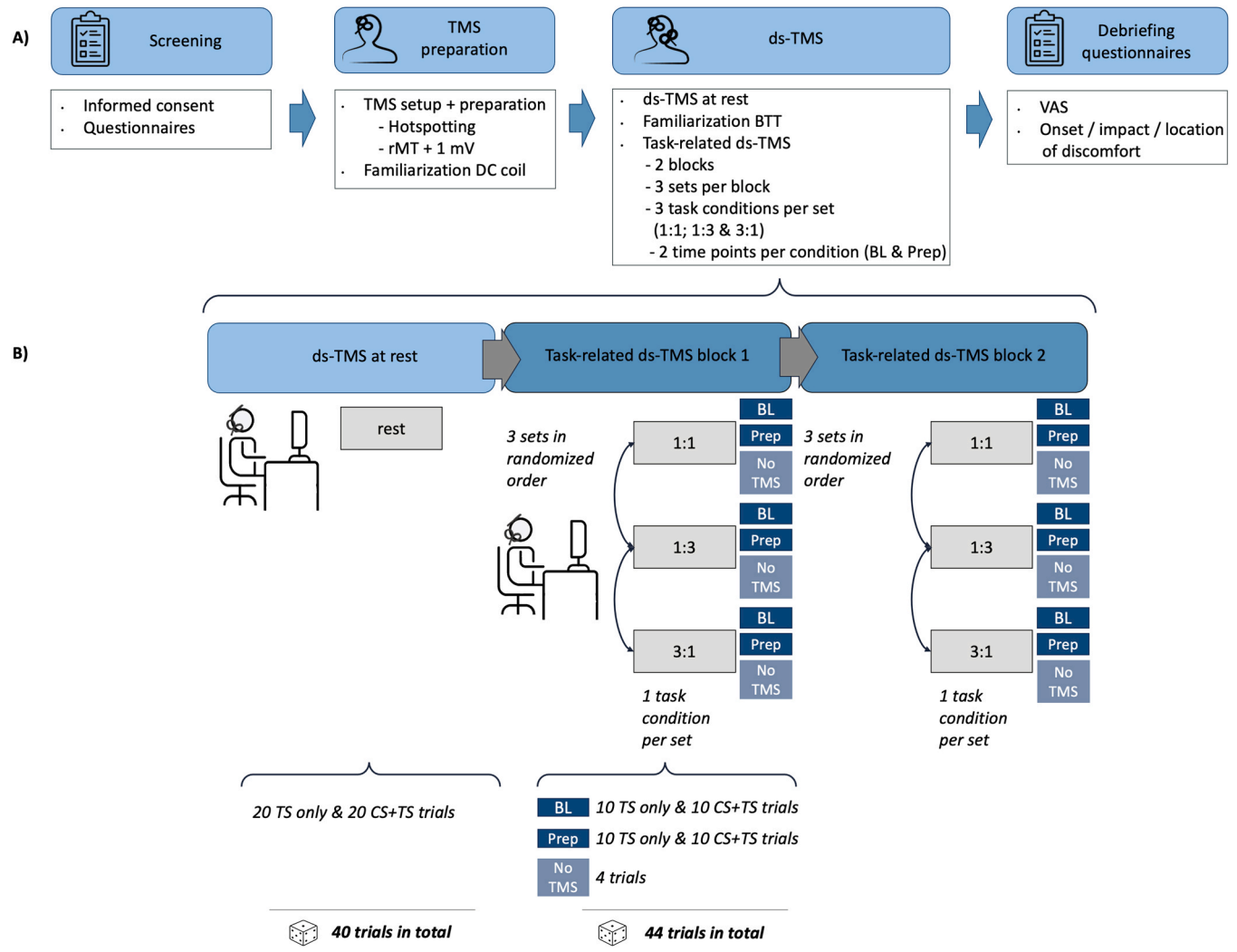

Fig. 3. Overview experimental protocol. The entire protocol was conducted in a single session. A) Following an initial screening, the TMS measurements were prepared. First, the hotspot and the resting motor threshold (rMT) were determined with the figure-of-eight coil positioned over the left M1. Then, a brief familiarization session followed for TMS over the right cerebellar cortex using the double cone (DC) coil. B) The ds-TMS protocol comprised two phases: a resting-state ds-TMS block, and two task-related ds-TMS blocks. During the resting-state ds-TMS block, 40 trials were administered in a pseudo-randomized order: 20 single-pulse (TS only) and 20 dual-pulse (CS+TS) trials. Subsequently, participants underwent a BTT familiarization session to ensure comprehension of the task requirements before administering task-related ds-TMS. Following familiarization, two task-related ds-TMS blocks were conducted, implementing the ds-TMS paradigm during the anticipatory period of the BTT. Each block consisted of three sets of 44 trials, with each set corresponding to a specific task condition (1:1, 1:3, or 3:1). The order of these sets was pseudo-randomized. The composition of each 44-trial set was as follows: Baseline (BL): 10 TS only trials and 10 CS+TS trials; Preparation (Prep): 10 TS only trials and 10 CS+TS trials, with TS applied 50 ms prior to movement onset (see Fig. 4); No TMS: 4 trials without TMS.
Abbreviations: BL = baseline timepoint during task-related measurement; CS = conditioning stimulus; ds-TMS = dual-site transcranial magnetic stimulation; Prep = preparatory timepoint during task-related measurement; TMS = Transcranial magnetic stimulation; TS = test stimulus; VAS = visual analogue scale.

2.3.2. *Bimanual tracking task*

The bimanual tracking task (BTT) allows for the assessment of bimanual coordination based on real-time control of complex bimanual movement patterns. This task was developed by our group (e.g., Fujiyama et al., 2016b; Monteiro et al., 2019; Sisti et al., 2011) and the set-up was further optimized for the TMS procedures used in this study. Fig. 4A provides an overview of the experimental setup.

The aim of this task was to track a white target dot, shown on a monitor in front of the participant, as accurately as possible as it progressed at a constant speed along a blue target line by coordinating movements of the two index fingers. For this purpose, participants positioned the palm of each hand on a handle, while simultaneously placing each index finger within the circular groove of a rotatable dial. While maintaining contact with the handle, only their index fingers were able to move. Each trial started with a black screen (see Fig. 4C). After 1000 ms, the blue target line appeared with a big yellow dot covering the smaller white target dot, which was located at the right end of the blue line. This indicated the start of the anticipatory period. This period had a duration of 2000 ms, after which the movement phase started, indicated by the disappearance of the large yellow dot. Tracing the white dot was performed by simultaneously rotating the left and right dial to control the vertical (y-axis) and horizontal (x-axis) movements, respectively. The real-time trajectory of the participant's cursor was visualized by a red line. The movement period had a constant duration of 5 s, and ended when the white target dot reached the other end of the blue target line. Hence, a full trial lasted for 8 s in total, separated by 3 s of rest (intertrial interval). See Fig. 4C for the course of a single trial.

In all task conditions, the left and right dial had to be rotated clockwise and counterclockwise, respectively (i.e., inward rotation) to trace the target dot. There were three different task conditions, which varied based on the inter-hand frequency ratios. Specifically, three different inter-hand movement frequency ratios were presented (i.e.,

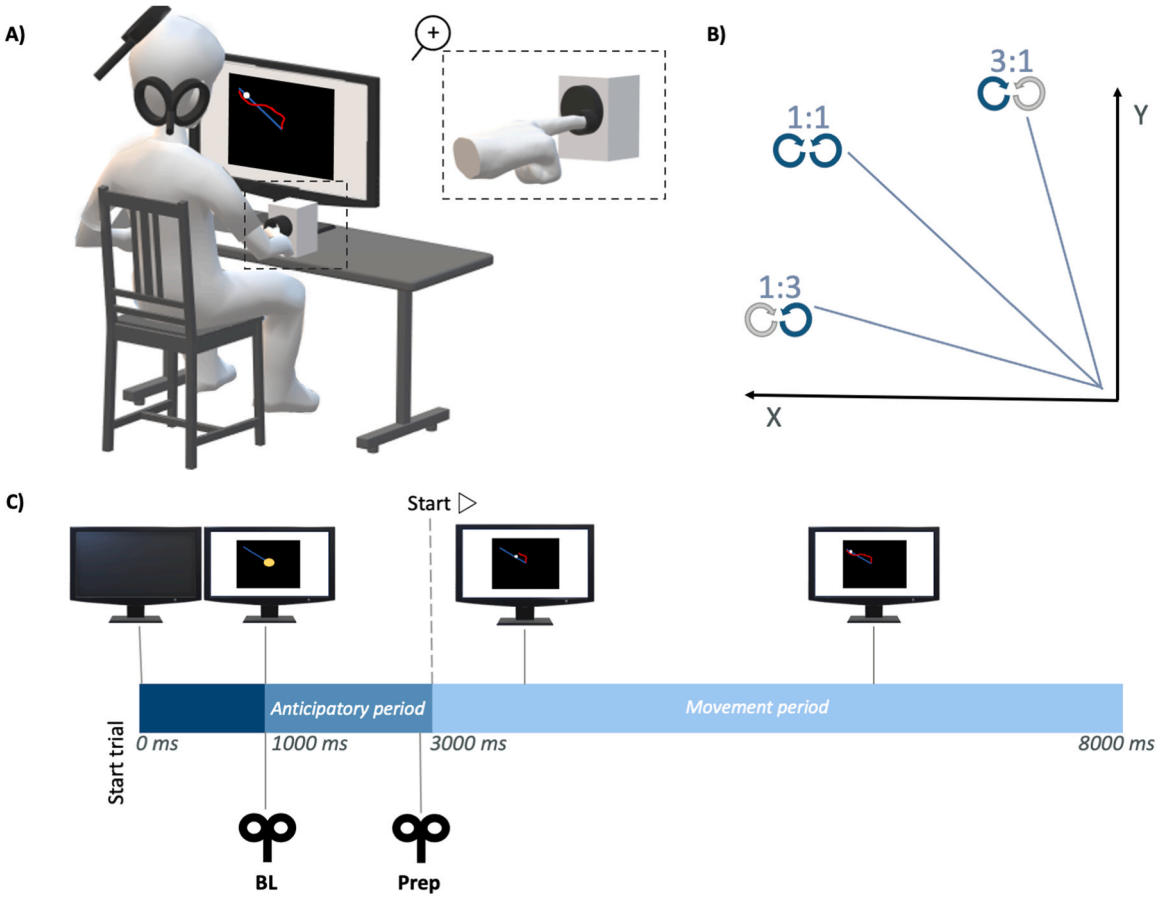

Fig. 4. Experimental setup of the bimanual tracking task (BTT). A) Overview of the experimental setup of the dual-site transcranial magnetic stimulation (ds-TMS) during the performance of the visuomotor bimanual tracking task (BTT). Participants were seated on a chair facing a monitor, resting each palm on a handle and placing each index finger in a circular groove of a dial. The aim of this task was to follow a white target dot, shown on a monitor in front of the participant, as accurately as possible as it progressed at a constant speed over a blue target line. To do so, participants had to make cyclical movements with their index fingers to rotate the dials. B) Schematic image of the three possible task conditions during the BTT. Rotating the left dial controlled the vertical movements (y-axis) and the right dial controls the horizontal movements (x-axis). Participants had to rotate the left and right dial clock- and counterclockwise respectively (i.e., inward rotation), with similar or different inter-hand movement frequency ratios (indicated by the inclination of the target line). Specifically, three different frequency ratios were presented (i.e., 1:1, 1:3, 3:1). For the 1:1 condition, both hands had to move at the same speed, which is considered an easier movement. However, for the 1:3 and 3:1 condition, the right or left index finger had to move three times faster than the other finger, respectively, which is considered a more complex movement. C) Course of a single task-related ds-TMS trial, and the two different timings of ds-TMS application (i.e., baseline [BL] and preparatory timepoint [Prep]). For 'BL' the test stimulus was delivered at the onset of the anticipatory period (i.e., the exact moment at which the target template appeared on the screen, i.e., at 1000 ms after starting the trial) while for 'Prep', it was delivered at the end of the anticipatory period, 50 ms prior to the imperative signal to start the movement period (i.e., 2950 ms after starting the trial).

Abbreviations: BL = Baseline timepoint during task-related measurement; ms = millisecond; Prep = Preparatory timepoint during task-related measurement; TMS = Transcranial magnetic stimulation.

[left:right] 1:1, 1:3, 3:1). During the 1:1 condition both fingers had to move at the same speed (i.e., iso-frequency condition), which is considered an easier movement (e.g., Sisti et al., 2011; Swinnen et al., 1997; Swinnen and Wenderoth, 2004). In the two more difficult non-iso-frequency conditions, 3:1 implied that the left index finger had to move three times faster than the right finger, and vice versa for the 3:1 ratio (see Fig. 4B).

2.3.3. *Task-related ds-TMS*

Prior to the task-related ds-TMS block participants completed a BTT familiarization to rule out possible discrepancies in task comprehension. More specifically, every BTT task condition was practiced five times in a row and this sequence was repeated twice, resulting in a total of ten practice trials per task condition.

Subsequently, two task-related CBI blocks (assessing early vs. slightly later short-term motor learning) were administered, during which the ds-TMS paradigm was applied during either a relative rest (baseline; BL) or towards the end of the anticipatory period (Prep) of each BTT trial. Specifically, for 'BL' the test stimulus was delivered at the onset of the anticipatory period (i.e., the exact moment at which the target template appeared on the screen, i.e., at 1000 ms after starting the trial). This timing provides a measure of relative task-related rest, since participants had their hands positioned to perform the BTT but had not yet had sufficient time to react to the visual input. In contrast, ds-TMS was applied at Prep, 50 ms before the imperative signal to start moving was given (i.e., 2950 ms after starting the trial). This timing reflected the immediate preparation to perform the BTT (Fujiyama et al., 2016a; Verstraelen et al., 2020) (see Fig. 4C). Each block consisted out of three sets of 44 trials of the same BTT condition (i.e., a frequency ratio of 1:1, 1:3 or 3:1). For each participant, the order of these three sets within a block was pseudo-randomized but kept constant between task-related ds-TMS block 1 and 2. Within each set, 10 TS only trials and 10 CS+TS trials were administered at BL, 10 TS only trials and 10 CS + TS trials were administered at Prep, and 4 trials without TMS (noTMS) (see Fig. 3B). These 44 trials were presented in pseudo-random order within a set, mitigating anticipation effects associated with cerebellar TMS. The

trials without TMS were included to evaluate the participant's performance without the influence of TMS on motor output.

Finally, after the participant completed all task-related CBI blocks, the tolerability of cerebellar stimulation was assessed in a debriefing using a visual analog scale (VAS; a continuous scale ranging from 0 (no pain or discomfort) to 10 (extreme amount of pain and/or discomfort)). Apart from the VAS, participants were asked at what time of the protocol they began to feel the pain/discomfort; to what extent possible pain/discomfort had an influence on their general well-being, and where the discomfort was located.

2.4. Data processing

Custom-made MATLAB scripts (MATLAB R2021a (version 9.10.0.1684407)) were used for EMG and behavioral analyses.

2.4.1. TMS outcome measures

To quantify CBI at a specific time point, the ratio of the average right FDI MEP peak-to-peak amplitude in dual-pulse conditions (MEP_{CS+TS}) to single-pulse conditions (MEP_{TS}) was calculated and multiplied by 100 to obtain a percentage of the unconditioned CSE:

$\%CSE_{unconditioned} = \frac{MEP_{CS+TS}}{MEP_{TS}} \times 100$. Values below 100 can be interpreted as an inhibitory interaction between the right cerebellar hemisphere and the left M1, representing CBI (see Fig. 2B). Conversely, values surpassing 100 suggest a facilitatory interaction between these regions. Hence, the term "$\%CSE_{unconditioned}$" refers to the absolute magnitude of cerebellum–M1 interaction, encompassing both inhibitory and facilitative influences exerted by the cerebellum. In contrast, 'CBI' specifically denotes the inhibitory effect of the cerebellum on the contralateral primary motor cortex.

In order to quantify the task-related modulation of CBI, the $\%CSE_{unconditioned}$ at Prep was subtracted from the $\%CSE_{unconditioned}$ at BL: $Modulation = (\%CSE_{unconditioned})_{Prep} - (\%CSE_{unconditioned})_{BL}$. Therefore, a positive modulation indicates a higher value and hence less CBI during Prep as compared to relative rest (BL), whereas a negative modulation indicates a lower value and hence more CBI during Prep as compared to BL.

Due to the proximity of the cerebellum to the corticospinal tract, there is a significant concern that TMS delivered to the caudal posterior head might elicit potential cervicomedullary evoked potentials (CMEPs) or cervical root activity resulting from a direct activation of the corticospinal tract initiated at the cervical level (Fisher et al., 2009; Renaud and Kelly, 1974; Ugawa et al., 1995). Latencies of approximately 14.6 ms are commonly attributed to cervical root activity, whereas latencies around 21 ms correspond to MEPs elicited by single-pulse TMS or cerebellar–M1 interactions (Martin et al., 2009). To ensure that the CS intensity did not trigger cervical root activity, the latency of MEP EMG traces was carefully examined. This examination was conducted both online and offline, with each individual trace visually inspected, following the methodology described by Baarbé et al. (2014). In instances where cervical root activity was detected online, the coil placement was adjusted and the respective resting-state ds-TMS or task-related ds-TMS set was repeated. In one case, a younger adult was excluded from the study due to persistent cervical root activity despite these adjustments. The protocol for offline analysis stipulated the exclusion of affected data points; however, it is noteworthy that no such exclusions were necessary.

Individual TMS trials were additionally excluded from analysis (i.e., averaging) if the EMG root mean square within the 50 ms window preceding the first TMS pulse exceeded 30 μV to ensure absence of muscle pre-activation [percentage deleted trials (mean±SD) YA: 13.22 ± 20.00 %; OA: 33.60 ± 29.00 %]. In one older adult, this resulted in the removal of numerous trials of the second block of the 3:1 task condition. As there were insufficient data points (<5) remaining to calculate an average single pulse for analysis, this task block was excluded from further analysis [min/max/mean±SD of data points per condition in one set: 5; 44; 33.16 ± 10.51].

2.4.2. BTT performance

Scores on the BTT (S) could range from 0 to 100, where 100 represents perfect performance. First, a preliminary score P was calculated according to Zivari Adab et al. (2020) (see their Figure 1D) and reflects the proportion of the target line 'covered' in the right order by the participant's actual movement trajectory. This preliminary score P was multiplied by a distance correction factor D that additionally takes the distance between the target line and participants track into account:

$$S = P \bullet D$$

More specifically, the P was calculated as the total number of unique 'completed' points (i.e., points on the target template with a minimal Euclidean distance from the trajectory) divided by the total number of points forming the target template, multiplied by 100. Using this method (Zivari Adab et al., 2020), participants achieve a high success score when a participant's red feedback line is on top of but also parallel to the goal line, due to the correct inter-hand frequency (Zivari Adab et al., 2020). To impose a penalty on participants who maintained a trajectory predominantly parallel to the target line but exhibited substantial deviations from it, this preliminary score was corrected using the distance factor D. This factor takes the distance (averaged over the trial) between the participants' track and the target line ($\bar{d}$) into account, ensuring that staying closer to the target line yields a higher score. Specifically, D was calculated using the following formula with 1 unit being the distance that can be covered in 200 ms:

$$D = (1 - \frac{\bar{d}}{5})$$

D could range from 1, i.e., no distance between the track traveled and the target line, to theoretically 0, i.e., maximal distance between the track traveled and the target line. However, the lower limit of D was set at 0.1 rather than 0 in order not to discourage participants during the familiarization with the task.

2.5. Statistical analyses

All statistical analyses were performed using JMP® software (version 17 SAS Institute Inc., Cary, NC) and the significance level was set at $\alpha = 0.05$. All values are presented as mean±SD unless stated otherwise.

Where linear mixed models (LMMs) were employed, all models included sex (female and male) as a covariate of no interest. Starting from a full-factorial model, the final model was obtained through a series of models using backward selection. Specifically, starting from the initial model, this involved iteratively removing fixed effects that lacked significance. The normality and homoskedasticity of conditional residuals of all models were visually checked using the Q-Q plot and the residual-by-predicted plot, respectively. Where adequate, post hoc pairwise comparisons adjusting for multiple testing were performed using Tukey honestly significant difference (HSD) tests or Benjamini-Hochberg correction (False Discovery Rate threshold (q) 0.05).

Effect sizes were estimated using both the estimated fixed effects and standardized coefficients for LMMs. Standardized coefficients were calculated using R (R Core Team, 2024) using the 'LME4' (Bates et al., 2014) and 'effectsize' (Ben-Shachar et al., 2020) packages. For the Wilcoxon rank-sum test, the Wilcoxon effect size (r) (Rosenthal, 1986) and Cohen's d are provided. All effect size estimates can be found in the supplementary materials (Supplement 5. Estimated fixed effect coefficients and standardized effect sizes).

Differences in baseline characteristics. Potential differences in the baseline characteristics between both age groups were examined using the Wilcoxon two-sample test for non-normally distributed parameters (EHI, SCL, BDI, IPAQ, MoCA, and SP MEPs), while a Welch's t-test was applied for the normally distributed parameter rMT.

Task performance. Only the 'noTMS' trials were used to quantify the BTT performance to prevent TMS-related motor effects from affecting the task performance outcome. BTT scores were averaged for each task condition within each set. An LMM, with average BTT score (*S* score) as Y-variable, age group (YA and OA), condition (1:1, 1:3, and 3:1), and block (task-related ds-TMS block 1 and block 2; to look at the influence of early vs. slightly later short-term motor learning) as main fixed effects and subject as a random intercept, was employed to investigate differences in task performance on the BTT between the two age groups.

Group-differences in CBI at rest. For the resting-state data, potential differences in CBI_{rest} between both age groups were investigated using a two-sample Wilcoxon test.

CBI at rest differs from a hypothesized value of 100. A one-sample Wilcoxon signed-rank test was used to determine if the sample median in the younger adult group differed significantly from the hypothesized value of 100 (i.e., no CBI), as the data did not meet the normality assumption. Conversely, a one-sample *t*-test was conducted to assess whether the sample mean in the older adult group was significantly different from 100, given the normal distribution of the data in this group.

Group-differences in task-related CBI. To investigate CBI during task anticipation, an LMM analysis was used, with CBI_{task} used as a Y-variable and age group (YA and OA), condition (1:1, 1:3 and 3:1), block (task-related ds-TMS block 1 and block 2), and timing (BL and Prep) as fixed effects and subject as a random intercept.

Task-related CBI differs from a hypothesized value of 100. A one-sample Wilcoxon signed-rank test was used to determine if the sample median in both age-groups differed significantly from the hypothesized value of 100 (i.e., no CBI), as the data did not meet the normality assumption.

Difference in CBI between rest and task-related CBI. CBI was also directly compared between resting-state and the Prep timepoint, using an LMM with CBI as a Y-variable. Age group (YA and OA) and state (rest and task) were used as fixed effects and subjects as a random intercept.

Association between CBI modulation and task performance. The association between CBI modulation from BL to Prep and performance on the BTT was analyzed using an LMM analysis, with the averaged BTT score (S score) as the Y-variable. Age group (YA and OA), condition (1:1, 1:3 and 3:1), block (1 and 2), and CBI modulation (i.e., difference between Prep and BL) were added as fixed effects and subject as a random intercept.

Group-differences in VAS score (debriefing questionnaire). Finally, a Wilcoxon 2-sample test was used to analyze potential age group differences in perceived discomfort.

3. Results

3.1. Baseline characteristics

As reported in Table 1, age groups did not significantly differ in basic characteristics such as handedness (EHI), physical activity (IPAQ), and mental well-being (SCL, BDI), and the TMS characteristics rMT and single-pulse MEPs at rest (all, $p > 0.05$). However, there was a significant difference in MoCA scores between the age groups ($z = 3.02$, $p = 0.0026$), with older adults demonstrating lower MoCA scores as compared to the younger adults (OA / YA: 26.85 ± 2.03 / 28.85 ± 1.08). There was also an age group difference for single-pulse MEPs applied during the task-related ds-TMS blocks (BL: z = -3.22, $p = 0.0013$; Prep: z = 3.54, $p = 0.0004$) with older adults demonstrating higher single-pulse MEPs as compared to younger adults (single-pulse MEPs BL for OA / YA: 3.24 ± 1.48 / 2.68 ± 1.34; single-pulse MEPs Prep for OA / YA: 3.24 ± 1.64 / 2.57 ± 1.33).

3.2. Task performance

There was a significant effect of age group ($F(1,38) = 27.79$, $p < 0.0001$) (OA / YA: 39.28 ± 13.37 / 54.22 ± 11.44), condition ($F(2195) = 59.37$, $p < 0.0001$), and the condition*block interaction ($F(2195) = 17.29$, $p < 0.0001$) on BTT performance (see Fig. 5). The remaining effects were not significant ($p > 0.05$). The mean scores on the BTT per age group are visualized in Fig. 5A.

Post-hoc pairwise comparisons of the condition*block interaction effect (Table 2) showed no performance difference between blocks for the conditions 1:1 ($t(195) = -2.13$, $p = 0.28$) and 1:3 ($t(195) = -1.81$, $p = 0.46$), whereas for condition 3:1, performance was better in block 1 than in block 2 ($t(195) = 5.23$, $p < 0.0001$). Within each block, the 1:1 condition was consistently better executed than the 1:3 condition (block 1: $t(195) = 6.35$, $p < 0.0001$; block 2: $t(195) = 6.68$, $p < 0.0001$), and the 3:1 condition (block 1: $t(195) = 3.14$, $p = 0.0235$; block 2: $t(195) = 10.50$, $p < 0.0001$). Notably, the 1:3 was executed worse than the 3:1 condition in block 1 ($t(195) = -3.21$, $p = 0.0190$), whereas an opposite pattern was observed in block 2 ($t(195) = 3.82$, $p = 0.0024$). The condition*block interaction is visualized in Fig. 5B.

3.3. TMS results

3.3.1. CBI at rest

There was no significant effect of age group on CBI_{rest} ($\%CSE_{unconditioned}$ OA / YA: 66.93 ± 16.55 / 67.88 ± 21.33; z = 0.61, $p = 0.5428$) (Fig. 6). As expected, based on the inclusion criteria, the $\%CSE_{unconditioned}$ was significantly smaller than 100 in both younger (S = −105.00; $p < 0.0001$) and older (t = -8.73; $p < 0.0001$), indicating significant CBI at rest.

3.3.2. Task-related CBI

Women demonstrated significantly more CBI_{task} (lower $\%CSE_{unconditioned}$) during task anticipation as compared to men [$F(1,38) = 4.51$; $p = 0.04$]. Since sex was only included as a covariate and was not of primary interest to the study, these results are discussed further in the supplementary materials (See Supplement 1 Fig. 1.A). There was no significant relationship between age group and CBI_{task} (Figure 7), or any other effects (all, $p > 0.05$). Interestingly, $\%CSE_{unconditioned}$ was significantly smaller than 100 in both younger ($\%CSE_{unconditioned}$ 94.30 ± 28.95; S = −5558.00; $p < 0.0001$) and older ($\%CSE_{unconditioned}$ 91.43 ± 35.22; S = −5575.00; $p < 0.0001$), indicating that CBI was not completely disinhibited during the anticipatory period of a motor task.

3.3.3. Difference in CBI between rest and task-related CBI

$\%CSE_{unconditioned}$ was significantly lower at rest compared to the anticipatory period of a motor task, indicating enhanced CBI at rest relative to task-related CBI [$F(1, 238.8) = 37.80$, $p < 0.0001$].

The covariate sex was found to be significant [$F(1,41.7) = 6.43$; $p = 0.0150$], indicating that women demonstrated more CBI both at rest ($\%CSE_{unconditioned}$ female / male: 60.71 ± 19.04 / 78.56 ± 14.23) as well as during the anticipatory period ($\%CSE_{unconditioned}$ female / male: 87.01 ± 30.09 / 78.56 ± 14.23) (see supplementary materials, Supplement 1). However, this variable was not of primary interest in our study. None of the remaining effects were significant (all, $p > 0.05$). The difference between CBI at rest relative to task-related CBI for young and older adults is illustrated in Figure 8.

3.3.4. Association between bimanual motor control and CBI modulation

The results indicate that age group [$F(1, 36.8) = 28.15$, $p < 0.0009$], condition [$F(2, 185.1) = 61.89$, $p < 0.0009$], condition*block [$F(2, 185.3) = 18.33$, $p < 0.0009$], block*CBI modulation [$F(1, 189.6) = 13.31$, $p = 0.0009$], age group*block*CBI modulation [$F(1, 189.7) = 6.02$, $p = 0.0270$] have a significant effect on BTT performance. The remaining effects were all non-significant (all, $p > 0.05$). After adjustment using the Benjamini-Hochberg method, all significant comparisons

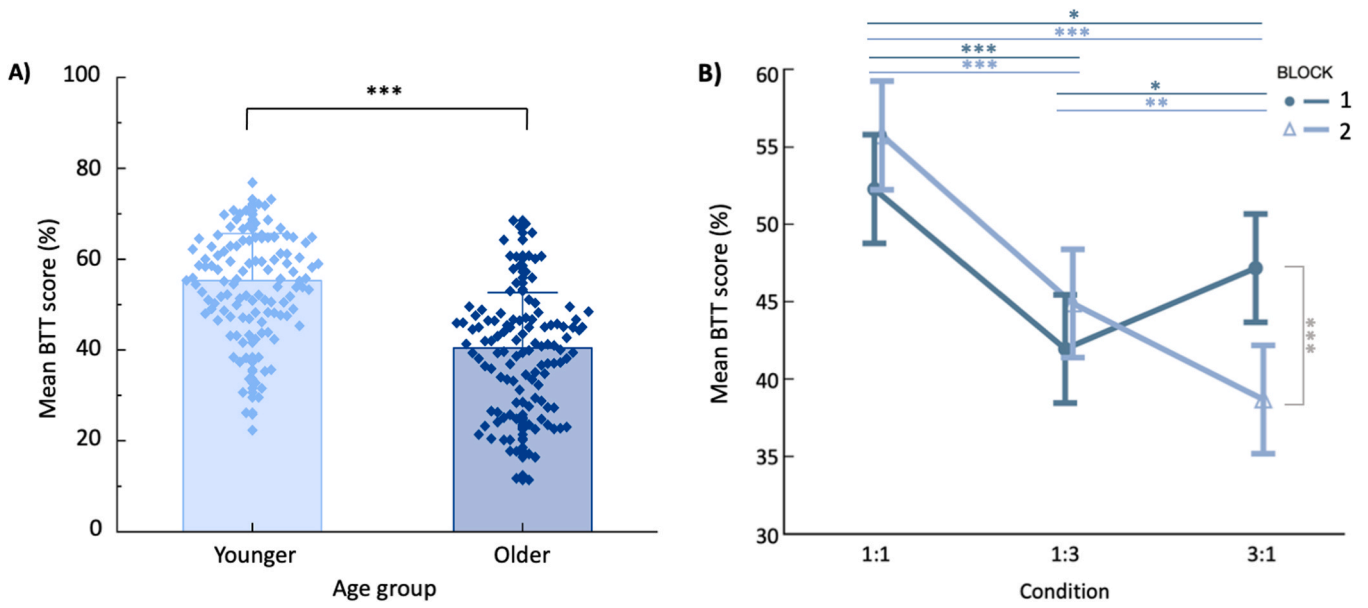

Fig. 5. Behavioral results. Panel A) Younger adults have higher mean BTT scores as compared to older adults. This figure shows a bar graph with SD (whiskers) and individual data points (pooled for all conditions and task blocks) superimposed. Panel B) Visualization of the significant condition*block interaction. Whiskers visualize the SD. There was no performance difference between task blocks for conditions 1:1 and 1:3, whereas for condition 3:1, BTT performance was better in block 1 than in block 2. Within each block, the iso-frequency 1:1 condition was significantly better executed compared to the non-iso-frequency 1:3 and 3:1 conditions. Notably, the 1:3 was executed worse than the 3:1 condition in block 1, whereas an opposite pattern was observed in block 2. Significant differences are indicated using: * for $p < 0.05$; * * for $p < 0.01$; * ** for $p < 0.001$.

Table 2
Tukey HSD all pairwise comparison analysis of the condition*block effect on BTT score.

Condition	Block	-Condition	-Block	Difference	t Ratio	Lower 95 % CI	Upper 95 % CI	p-value
1:1	1	1:1	2	−3.47	−2.13	−8.16	1.22	0.2756
1:1	1	1:3	1	10.35	6.35	5.66	15.04	**< 0.0001** *
1:1	1	1:3	2	7.40	4.54	2.72	12.09	**0.0001** *
1:1	1	3:1	1	5.12	3.14	0.43	9.81	**0.0235** *
1:1	1	3:1	2	13.63	8.37	8.94	18.32	**< 0.0001** *
1:1	2	1:3	1	13.82	8.48	9.13	18.51	**< 0.0001** *
1:1	2	1:3	2	10.88	6.68	6.19	15.57	**< 0.0001** *
1:1	2	3:1	1	8.59	5.27	3.9	13.28	**< 0.0001** *
1:1	2	3:1	2	17.10	10.50	12.41	21.79	**< 0.0001** *
1:3	1	1:3	2	−2.95	−1.81	−7.64	1.74	0.4626
1:3	1	3:1	1	−5.23	−3.21	−9.92	−0.54	**0.0190** *
1:3	1	3:1	2	3.28	2.01	−1.41	7.97	0.3384
1:3	2	3:1	1	−2.29	−1.40	−6.98	2.40	0.7248
1:3	2	3:1	2	6.23	3.82	1.54	10.92	**0.0024** *
3:1	1	3:1	2	8.51	5.23	3.82	13.20	**< 0.0001** *

Significant p-values are written in bold and indicated with an asterisk.

remained significant at $p < 0.05$. The p-values reported here are adjusted (Yekutieli and Benjamini, 1999).

The age group*block*CBI modulation interaction suggests that the relationship between performance on the BTT and CBI modulation (from BL to Prep timepoint) depends on the task-related ds-TMS block and age group. In order to facilitate interpretation of the age group*block*CBI modulation interaction, the relationship between BTT score and CBI modulation was visualized. Separate plots were created for each age group, with each plot further subdivided to represent both task-related ds-TMS blocks (i.e., block 1 and block 2). The predicted BTT score (Y) per age group (YA vs. OA) and block (block 1 [B1] vs. block 2 [B2]) can be calculated using the following (marginal model) equations, with x being the CBI modulation (from BL to Prep): $Y_{OA,\ B1} = 40.07–0.03x$; $Y_{OA,\ B2} = 38.08 + 0.1x$; $Y_{YA,\ B1} = 53.91 + 0.06x$; $Y_{YA,\ B2} = 54.78 + 0.05x$. Modulation from BL to Prep for all task conditions and corresponding BTT scores were plotted and indicated as dots per age group, see Fig. 9.

3.4. Perceived discomfort of cerebellar stimulation

Participants reported their degree of discomfort (VAS score) to be 3.13 (± SD: 2.22), which can be interpreted as 'mild' (Collins et al., 1997). Furthermore, there was no significant difference in reported VAS score between both age groups ($z = 0.73$, $p = 0.46$). Additionally, 63 % of the participants reported that cerebellar stimulation did not affect their subjective well-being. About 32 % of the participants experienced a mild influence on their subjective well-being, while only two participants (5 %) reported a moderate or strong influence. Regarding the perceived location of cerebellar stimulation, 75 % of all participants indicated a localized sensation located close to the right cerebellar hemisphere targeted with the DC coil (i.e., slightly lateral at the lower back of the head), while 15 % indicated a more widespread sensation (i.e., most referred to a sensation in their jaw and/or clenching their teeth during cerebellar pulses). Finally, one participant reported a localized feeling in the tongue during cerebellar stimulation. No adverse events were reported after finalizing study participation.

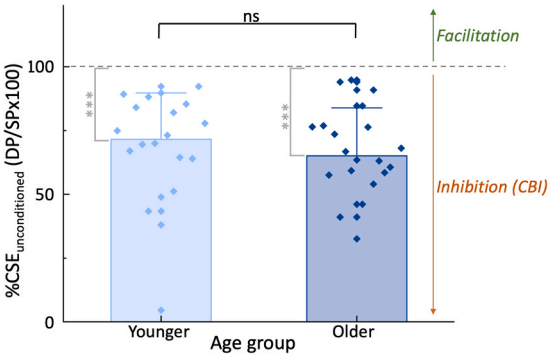

Fig. 6. CBI at rest. No difference in CBI_{rest} between younger and older adults. Bar graphs with SD (whiskers) and individual data points superimposed. The gray dashed line indicates no CBI, i.e., a $\%CSE_{unconditioned}$ [DP (MEP_{CS+TS}) to SP (MEP_{TS}) x 100] of 100. Values below 100 are interpreted as an inhibitory interaction (i.e., CBI), with lower values indicating more CBI, whereas ratios above 100 would be interpreted as facilitation. Both groups demonstrated significant CBI at rest as the $\%CSE_{unconditioned}$ at rest was significantly lower than 100. * ** indicates a significant difference of $p < 0.001$.
Abbreviations: CBI = cerebellar brain inhibition; CSE = corticospinal excitability; DP = double-pulse; ns = not significant; Older = older adults; SP = single-pulse; Younger = younger adults.

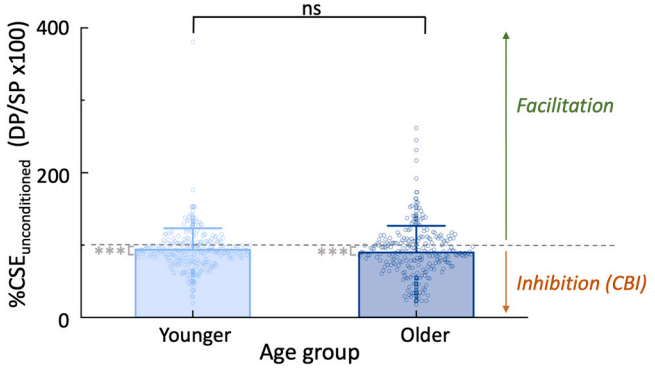

Fig. 7. Task-related CBI. There was no significant difference in CBI_{task} between younger and older adults. Bar graphs with SD (whiskers) and individual data points (for each condition, task-related ds-TMS block, and timepoint) superimposed. The gray dashed line indicates no CBI, i.e., a $\%CSE_{unconditioned}$ [DP (MEP_{CS+TS}) to SP (MEP_{TS}) x 100] of 100. Values below 100 are interpreted as an inhibitory interaction (i.e., CBI), whereas ratios above 100 are interpreted as facilitation Interestingly, mean $\%CSE_{unconditioned}$ from both age groups are significantly below 100, indicating no disinhibition during the anticipatory period of a motor task. * ** indicates a significant difference of $p < 0.001$.
Abbreviations: CBI = cerebellar brain inhibition; CSE = corticospinal excitability; DP = double-pulse; ns = not significant; Older = older adults; SP = single-pulse; Younger = younger adults.

4. Discussion

This study aimed to examine the differences in effective cerebellar–M1 connectivity between younger and older adults and explore whether these differences contribute to age-related motor deficits and potential deficits in short-term motor learning by measuring CBI using a ds-TMS paradigm.

On a behavioral level, the results revealed an overall better bimanual motor performance in young adults as compared to their older counterparts. Both age groups performed generally better on the 1:1 condition compared to 1:3 and 3:1, with no difference between the latter non-iso-frequency task variants. In contrast to our hypothesis, CBI at rest and a task-related release of CBI (i.e., increased $\%CSE_{unconditioned}$; less inhibition) were maintained in older as compared to younger adults.

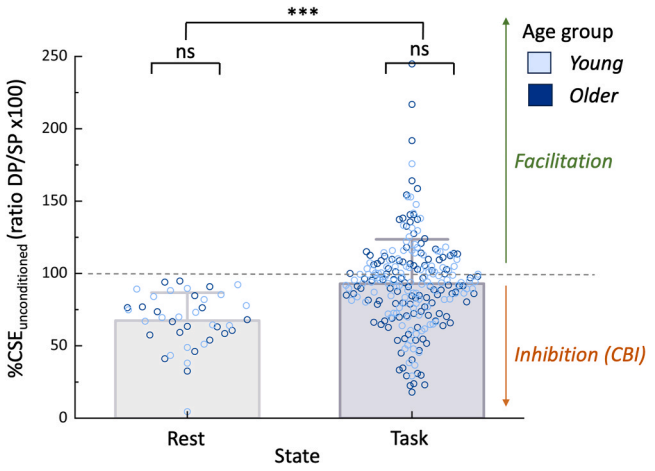

Fig. 8. Difference between $\%CSE_{unconditioned}$ at rest and during a motor task. $\%CSE_{unconditioned}$ was lower at rest as compared to during the anticipatory period of a motor task i.e., there was more CBI at rest relative to task-related CBI. However, there was no age-related difference in $\%CSE_{unconditioned}$ at rest and during the anticipatory period of a bimanual motor task. Bar graphs with SD (whiskers) and individual data points (all task conditions and blocks were pooled) superimposed. The gray dashed line indicates no CBI, i.e., a $\%CSE_{unconditioned}$ [DP (MEP_{CS+TS}) to SP (MEP_{TS}) x 100] of 100. Values below 100 are interpreted as an inhibitory interaction (i.e., CBI), whereas ratios above 100 are interpreted as facilitation. * ** indicates a significant difference of $p < 0.001$ (rest vs. task, pooled age groups), while ns indicates no significant differences.
Abbreviations: CBI = cerebellar brain inhibition; CSE = corticospinal excitability; DP = double-pulse; ns = not significant; Older = older adults; SP = single-pulse; Young = younger adults.

Interestingly, the relationship between CBI modulation and bimanual motor control varied by age group and learning stage, as revealed by a significant age group*block*CBI modulation interaction.

Specifically, in older adults, the relationship shifted from a slight negative association in block 1 (Y = 40.07–0.03x) to a positive association in block 2 (Y = 38.08 + 0.1x) where increasing levels of inhibition were associated with a better motor performance during the early stage of short-term motor learning (Prep vs. BL timepoint), while less inhibition (i.e., modulation towards facilitation or facilitation) led to a better performance during the later stage of short-term motor learning. In contrast, in younger adults this relationship remained relatively stable across blocks with a slight positive association between CBI modulation and performance (Block 1: Y = 53.91 + 0.06x; Block 2: Y = 54.78 + 0.05x) where less inhibition is associated with better motor performance during this immediate movement preparation, irrespective of the training stage.

4.1. Older adults perform less well on bimanual coordination

Bimanual motor performance was decreased in the older age group as compared to the young adults, and depended on task complexity (i.e., better motor performance on iso-frequency as compared to non-iso-frequency task variants), consistent with previous literature (e.g., Boisgontier et al., 2018; Maes et al., 2022; Swinnen and Wenderoth, 2004; Van Hoornweder et al., 2022; Van Ruitenbeek et al., 2023).

4.2. No age-related difference in the amount of CBI at rest

Despite the assumption that there are fewer Purkinje cells (Childs et al., 2021; Zhang et al., 2010) or that they would be less excitable due to degenerative changes (Zhang et al., 2010) with increasing age, which would result in reduced inhibition of the dentato–thalamo–cortical pathway (i.e., reduced CBI), there was no difference in CBI at rest between the two age groups. In contrast to the present findings, Rurak

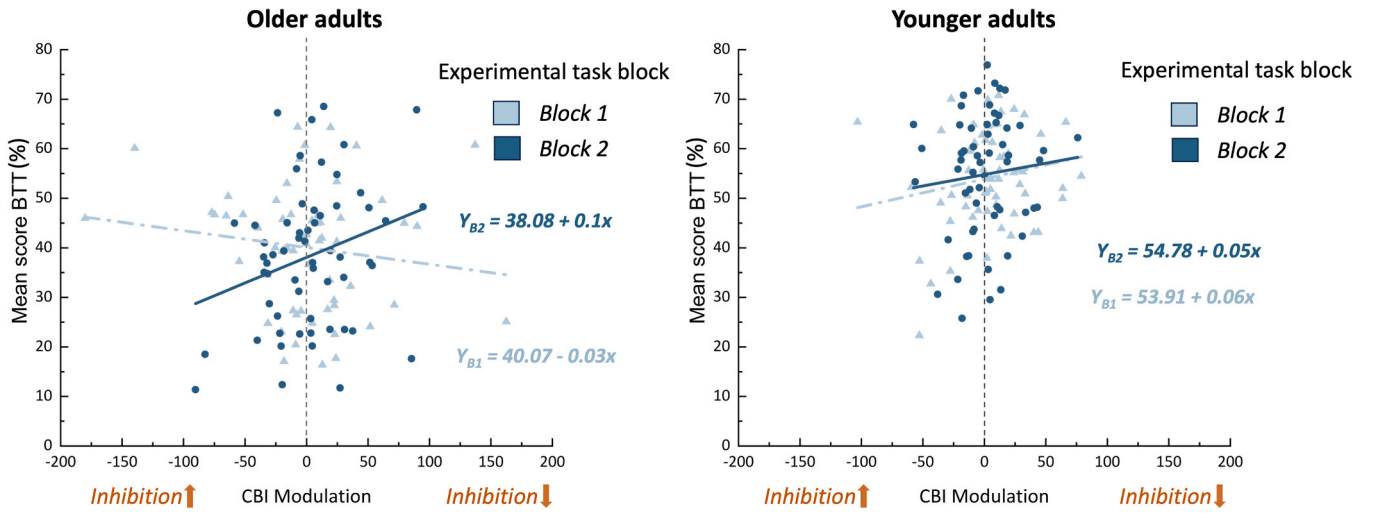

Fig. 9. Interaction effect of age group, block and CBI modulation on task performance. The effect of the CBI modulation (from BL to Prep, x) on the mean BTT score (Y) was plotted separately for each age group (OA and YA plotted in panel A and B, respectively) and block (block 1 [B1] and block 2 [B2]) to facilitate interpretation of the three-way interaction effect. Each graph shows the plot of both equations (B1 and B2) with the individual data points (BTT scores) superimposed. The gray dashed lines indicate no modulation. CBI modulation was quantified as the $\%CSE_{unconditioned}$ at the Prep timepoint subtracted from the $\%CSE_{unconditioned}$ at the BL timepoint.

Abbreviations: BTT = Bimanual tracking task; CBI = cerebellar brain inhibition; CSE = corticospinal excitability.

et al. (2022), the first study looking at age-related differences in CBI at rest, found that the amount of CBI was reduced in older as compared to younger adults. A critical factor potentially explaining the conflicting results between studies is the choice of coil used for cerebellar stimulation. (Rurak et al., 2022) used a Fig-8 coil rather than the conventional DC coil typically used for cerebellar stimulation, which could have resulted in suboptimal stimulation of Purkinje cells. More specifically, previous work showed that coil design significantly impacts stimulation depth and efficacy. The large and angled DC coil possesses greater efficacy in stimulating deeper structures, such as the cerebellar Purkinje cells, while the flat and smaller Fig-8 coil is mainly restricted to superficial target areas (Deng et al., 2014; Fernandez et al., 2018b; Grandori and Ravazzani, 1991; Hardwick et al., 2014). Note that chances of ineffective stimulation of Purkinje cells, resulting from limited stimulation depth using a Fig-8 coil, might be even higher in older as compared to younger adults, since (cerebellar) atrophic changes are more likely to occur with increasing age (Bernard and Seidler, 2014; Jernigan et al., 2001; Raz and Rodrigue, 2006), which might explain the decreased CBI found by Rurak et al. (2022). In addition to this difference in pure stimulation efficacy due to differences in stimulation depth, the depth of stimulation also potentially influences distinct populations of neurons within the cerebellum. Specifically, the more local and superficial stimulation obtained with a Fig-8 coil presumably targets the more superficial cells located in the molecular layer which are inhibiting Purkinje cell activity (Andersen et al., 2003; D'Angelo, 2018; Fernandez et al., 2020), reducing their inhibitory influence on the dento–thalamo–cortical pathway and, hence, possibly resulting in less CBI. While the DC coil is presumed to target the Purkinje cells, it might potentially stimulate the deeper cells located in the granular layer, forming excitatory synapses with Purkinje cells (Fernandez et al., 2018a). This differential stimulation could activate distinct neural populations, potentially explaining conflicting findings between studies. Furthermore, the age-related reduction in Purkinje cell density (Andersen et al., 2003; Zhang et al., 2010) might increase reliance on other cerebellar layers. Consequently, these distinct neuronal pathways might exhibit varying age-related alterations (Fernandez et al., 2020; Rurak et al., 2022). It should be noted that although stimulation of Purkinje cells supports most of the evidence (Daskalakis et al., 2004; Pinto and Chen, 2001; Ugawa et al., 1997, 1995), there is no clear consensus on which structures are stimulated during cerebellar TMS. Moreover, the question remains whether Purkinje cells are stimulated directly or indirectly via the parallel or climbing fibers of surrounding layers (Siebner et al., 2022).

Our results were in line with another study that reported no difference in resting CBI between younger and older adults when using an ISI of 5 ms and a DC coil to stimulate the cerebellum, identical to the present study (Mooney et al., 2022). In addition to a preservation of CBI at rest in the older group when using a 5 ms ISI, Mooney et al. (2022) even showed an age-related strengthening of CBI with an ISI of 7 ms. Mooney and colleagues proposed that this enhancement might reflect an increased excitability of Purkinje cells in older adults, serving as a compensatory mechanism to counteract the age-related cerebellar volumetric decline and maintain dexterous movement (Mooney et al., 2022). The authors' support their compensatory hypothesis by their observation that CBI at 5 ms ISI was similar between young and older groups, despite using lower CS intensities in older adults due to their lower brainstem active motor threshold (Mooney et al., 2022). This is noteworthy because previous studies have shown that higher CS intensities correlate with greater CBI (Panyakaew et al., 2016; Schlerf et al., 2015). Thus, achieving comparable levels of CBI with lower CS intensities in older adults suggests an age-related enhancement of Purkinje cell excitability. Conversely, the current study used a fixed CS intensity and did not show an age-related increase in CBI at rest, indicating merely an age-related preservation rather than enhancement of CBI. In keeping with Mooney et al. (2022)'s line of thought, this preservation of CBI, using a fixed CS combined with a 5 ms ISI, could be a mechanism to compensate for age-related Purkinje cell loss and degeneration and might reflect an increased excitability of the remaining Purkinje cells in older adults to achieve a similar level of CBI (Childs et al., 2021; Zhang et al., 2010) in an attempt to preserve motor function.

4.3. *Task-related modulation of CBI is maintained in older adults*

The findings of this study might substantiate the claim that the cerebellum plays a crucial role in integrating visual information with precise motor responses, as well as in updating and refining the internal temporal and spatial control mechanism (Spampinato et al., 2017; Tanaka et al., 2021), inherent to adaptive motor learning and tracking task learning. Particularly, in accordance with earlier research findings regarding the modulation of CBI in the context of unimanual motor

learning in younger adults [e.g., Schlerf et al. (2015); Spampinato (2020b); Spampinato et al. (2017); Tanaka et al. (2021); for a review see Van Malderen et al. (2022)], this study reveals a reduction in the amount of CBI during the anticipatory period of a bimanual motor task as compared to rest [i.e., from significant inhibition at rest towards a (partial) release of inhibition or even a facilitation during the anticipatory period (Prep timepoint) of a motor task]. This decrease in CBI during short-term learning might be interpreted as an information exchange promoting successful task performance (Serrien et al., 2006) and has been suggested to facilitate the acquisition of novel motor skills since a positive relationship between a disinhibitory/facilitatory modulation and performance on the task has been demonstrated (Jayaram et al., 2011; Schlerf et al., 2015; Tanaka et al., 2021).

This study marks the first investigation of task-related modulation of CBI in older adults. We hypothesized that older adults might exhibit impaired task-related modulation of effective cerebellar–M1 connectivity. Specifically, we expected less release of inhibition during short-term learning. Remarkably, the results of this present study interestingly present evidence for a similar CBI modulation in the older as compared to the younger age group, challenging the notion of age-related disparities in cerebellar–M1 interactions, contrasting with the earlier findings about alterations in cortico–cortical interactions.

This preservation of task-related cerebellar–M1 modulation capacity observed in our study aligns with recent fMRI research on age-related effects on cortical brain regions (Van Ruitenbeek et al., 2023). Specifically, Van Ruitenbeek et al. (2023) showed that both younger and older adults exhibit similar increases in brain activation in the motor/visuospatial network, including the cerebellar hemispheres, as task complexity increased during a BTT similar to the one used in the current study. Along the same line, Heuninckx et al. (2008) reported preserved cerebellar activity (i.e., heightened activity in both age groups), in older relative to younger adults during iso- and non-isodirectional movements. These findings are particularly noteworthy given the documented age-related changes in cerebellar structure and function, including atrophic changes in cerebellar gray matter (Bernard and Seidler, 2013), alterations in the integrity of cerebellar white matter (Abe et al., 2008; Bennett et al., 2010; Giorgio et al., 2010) and decreased cerebellar resting-state connectivity (Bernard et al., 2013). Despite these changes, effective cerebellar–cortical connectivity and cerebellar activity in the context of task performance appears to be preserved or even increased in older individuals (Heuninckx et al., 2008; Mooney et al., 2022; Van Ruitenbeek et al., 2023; Wu and Hallett, 2005). Hence together with the present study's findings, this might suggest the notion of a (functional and/or neural) cerebellar reserve that counteracts the effects of aging on the cerebellum to preserve motor function (Kawato et al., 1987; Mitoma et al., 2020, 2022).

4.4. *Age group-dependent relationship between short-term motor learning, bimanual motor control, and CBI modulation in short-term motor learning*

This study examined task-related modulation of CBI during short-term motor learning of the BTT, a bimanual coordination task. Our results demonstrated an interaction effect between task block (early vs. slightly later short-term motor learning), bimanual motor performance and age group. In older adults, during early short-term learning (i.e., the first task block), a negative CBI modulation (i.e., increased inhibition from BL to Prep) corresponded to better bimanual motor performance. During slightly later short-term learning (i.e., the second task block), this relationship inverted: a positive CBI modulation (i.e., reduced inhibition / facilitation from BL to Prep) corresponded to better motor performance. In younger adults, the latter disinhibitory/facilitatory modulation was observed consistently in both task blocks, yet generally less pronounced than in older adults.

While the functions of the cerebellum extend well-beyond motor processes (e.g., Koziol et al., 2014; Van Overwalle et al., 2020), it is known to play an important role in motor control and learning through acquisition and updating of inverse and (feed-)forward models, enabling the prediction of movement trajectories and, subsequently, facilitating swift online corrections (Ito, 2008; Penhune and Steele, 2012). As described in the previous paragraph, an explanation for the decrease in CBI (less inhibition) during the motor anticipatory period might be that it promotes an exchange of information underlying successful motor coordination and the acquisition of a novel motor coordination skill (Serrien et al., 2006). This disinhibitory modulation appears to be a key mechanism in facilitating novel motor skill acquisition, as evidenced by its positive correlation with task performance (Jayaram et al., 2011; Schlerf et al., 2015; Tanaka et al., 2021).

The differential CBI modulation observed between younger and older adults during motor task performance may indicate functional reorganization with age. Motor learning encompasses diverse processes, including error-based, reinforcement, use-dependent, and strategic learning, each associated with distinct neuronal substrates functioning within a broader network (Haith and Krakauer, 2013; Krakauer and Mazzoni, 2011; Shadmehr and Krakauer, 2008; Spampinato and Celnik, 2021; Taylor and Ivry, 2014). Error-based learning, characterized by adjustment-making, is assumed to be predominantly cerebellum-dependent, while reinforcement, use-dependent and, strategic (cognitive) learning are thought to depend mainly on the striatum, M1 and the (pre-)frontal cortex, respectively (Spampinato and Celnik, 2021; Taylor and Ivry, 2014). These processes collectively contribute to motor learning, with their relative weights fluctuating throughout the acquisition of new behaviors.

The present study's results suggest that older adults may demonstrate a differential weighting of these motor learning components and their neural correlates, potentially reflecting age-related adaptations in neural plasticity and motor skill acquisition strategies. This is consistent with previous research showing that older adults typically demonstrate a shift towards recruiting more (pre)frontal areas as compared to younger adults (Goble et al., 2010; Heuninckx et al., 2005, 2008; Monteiro et al., 2017). This increased frontal activity might reflect greater reliance on cognitive control rather than automatic processing of movement, as demonstrated using fMRI (Heuninckx et al., 2005). Notably, such increased activity in frontal brain regions has been associated with performance improvement during motor learning in older adults, whereas more activity in posterior and cerebellar regions was linked to improved motor performance in younger adults (Monteiro et al., 2017).

This initial reliance on (pre-)frontal brain regions, reflecting an increased relative weight on the strategic (cognitive) learning process, might be a compensatory mechanism in older adults to enhance accuracy and control before the motor task becomes more automated and less dependent on conscious regulation. This assumption aligns with the positive task-related CBI modulation (i.e., release of inhibition) in successful older adults in the slightly later as compared to the early short-term learning stage.

It should be noted that motor learning was not behaviorally established since there was no significant performance improvement during the second task block in both age groups. For the non-iso-frequency 3:1 condition (left hand rotating three times faster than the right) performance was, in fact, better during the first task block compared to the second. Given the pseudo-randomized order of conditions, this effect is unlikely attributable to fatigue. The observed interaction between task block, age group, CBI modulation, and motor performance in short-term motor learning may instead reflect a habituation process rather than skill acquisition.

4.5. *Limitations*

Apart from the limitations that are inherent to ds-TMS research (Van Malderen et al., 2022), there were some limitations specific to this study. One of the limitations of this study is the use of a single ISI of 5 ms. Although this ISI is commonly employed in CBI research (e.g., Hardwick

et al., 2014; Schlerf et al., 2015; Spampinato et al., 2020a; Spampinato and Celnik, 2017; Spampinato et al., 2017), an ISI of 7 ms has been suggested to reflect a discrete cerebellar–M1 pathway (Spampinato et al., 2020b). Hence, additionally employing a 7 ms ISI might have yielded different results and interpretations of cerebellar inhibitory modulation. Another constraint is the use of a fixed CS intensity. While the chosen intensity may have been appropriate for most participants (Fernandez et al., 2018b), individual variability in cortical excitability and cerebellar responsiveness could influence the outcomes. However, testing the active motor threshold with the DC coil placed over the inion before starting the experimental protocol and the fairly high stimulation intensities causes discomfort (e.g., Baarbé et al., 2014; Martin et al., 2009; Fernandez et al., 2018a). Therefore, we opted for a fixed intensity in the present study. A final limitation is the statistical power. The sample size for this study was determined based on the effect size reported in a clinical study comparing CBI between individuals with schizophrenia and healthy controls (Daskalakis et al., 2005) since no prior research on CBI in older populations was available during the study's development. A G*Power analysis (two-tailed independent samples t-tests, Cohen's $d = 1.02$, $\alpha = 0.05$, power $= 0.90$) indicated that 17 participants per group would be required. Even though 20 participants per group were included, the study may still have been underpowered due to the use of linear mixed models instead of simple t-tests. Notably, interactions can require a larger sample size compared to detecting group differences (da Silva Frost and Ledgerwood, 2020). While the study provides valuable insights into age-related differences in CBI modulation and its relationship to behavior, the findings—particularly regarding interaction effects—should be interpreted cautiously and considered exploratory rather than confirmatory.

4.5.1. Considerations for future CBI studies

A first consideration is the number of participants that had to be excluded because of the inability to elicit CBI. This inability might be caused by methodological constraints such as fixed CS intensities, fixed target locations and, in some participants, the coil-to-cortex distance or the scalp-to-cortex distance (Van Hoornweder et al., 2023). A greater protocol flexibility tailored to the (neuro)anatomical features of the individual, based on a priori electric field modeling (Thielscher et al., 2015), might mitigate the number of non-responders. A detailed comparative analysis of potential factors influencing CBI elicitation is provided in Supplement 6.

Yet, not only the non-individualized design of the study, but also the fact that some participants tense up in anticipation of the TMS pulse or startled in response to cerebellar stimuli could be responsible for the lack of CBI in some participants. Future studies should report the number of non-responders as this will aid in refining and optimizing the methodology, ensuring a more consistent and effective application of the CBI technique.

A final important aspect to consider is the proximity of the cerebellum to the corticospinal tract. Instead of stimulating the cerebellum and thus the dentato–thalamo–cortical pathway, it is also possible to directly activate the corticospinal tract, which will result in CMEPs rather than MEPs (Fisher et al., 2009; Renaud and Kelly, 1974; Ugawa et al., 1995). While it is possible to visually discriminate between cervical root activity and MEPs based on the latency, this is very hard for CMEPs given the small difference in latencies [mean±SD: 14.6 ± 1 ms (cervical root activity); 18.1 ± 1.3 ms (CMEPS); 21.2 ± 1.6 ms (MEPs)] (Martin et al., 2009). Moreover, antidromic effects, which propagate in a direction opposite to the typical orthodromic signal transmission, present a methodological limitation that cannot be adequately controlled for in ds-TMS paradigms. Therefore, it cannot be guaranteed that there are no CMEPs or antidromic effects present, and their potential presence must be considered.

5. Conclusion

Firstly, the current work revealed no age-related difference in the amount of CBI at rest, challenging previous assumptions of reduced (cerebellar) inhibitory function in older adults. Secondly, this study demonstrated a state dependent release of inhibition in the context of a bimanual tracking task, which was similar for both age groups. This preservation of CBI modulation in the context of a motor task in older adults might suggest the existence of neural mechanisms that counteract the effects of aging on the cerebellum to maintain dexterous movement control, i.e., cerebellar reserve. Finally, this study revealed age-related differences in CBI modulation during short-term motor learning of a bimanual coordination task. In older adults, increased inhibition was associated with better motor performance during early learning, followed by a shift towards disinhibition/facilitation in successful task performers during slightly later learning. In contrast, successful younger adults demonstrated a consistent disinhibition/facilitation during both early and slightly later short-term motor learning. This could imply a functional reorganization, characterized by a delayed transition from prefrontal-dominant learning to a greater reliance on cerebellum-dependent processes in older adults, potentially reflecting compensatory mechanisms and a prolonged reliance on cognitive control during motor skill acquisition.

CRediT authorship contribution statement

Hardwick Robert M.: Writing – review & editing, Methodology. **Swinnen Stephan P.:** Writing – review & editing, Resources, Methodology, Conceptualization. **Cuypers Koen:** Writing – review & editing, Resources, Methodology, Conceptualization. **Hehl Melina:** Writing – review & editing, Methodology, Formal analysis. **Nuyts Marten:** Writing – review & editing, Investigation. **Verstraelen Stefanie:** Writing – review & editing, Formal analysis. **Heemels Robin E.:** Writing – review & editing, Investigation. **Van Malderen Shanti:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Shanti Van Malderen reports financial support was provided by Research Foundation Flanders. Melina Hehl reports financial support was provided by Research Foundation Flanders. Marten Nuyts reports financial support was provided by Research Foundation Flanders. Shanti Van Malderen reports financial support was provided by UHasselt Special Research Fund. Marten Nuyts reports financial support was provided by UHasselt Special Research Fund. Robert M. Hardwick reports financial support was provided by Belgian National Fund for Scientific Research. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the

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