Distinct roles of brain network flexibility in motor learning across age

Kazumasa Uehara[1, 2], Makoto Hagihara[3, 2], and Keiichi Kitajo[2, 3]

1) Neural Information Dynamics Laboratory, Department of Computer Science and Engineering, Toyohashi University of Technology, Toyohashi, Japan
2) Division of Neural Dynamics, National Institute for Physiological Sciences, Okazaki, Japan
3) Department of Physiological Sciences, School of Life Science, The Graduate Institute for Advanced Studies, SOKENDAI, Okazaki, Japan

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Correspondence to: Kazumasa Uehara, Ph.D., Associate Professor
Neural Information Dynamics Laboratory,
Department of Computer Science and Engineering,
Toyohashi University of Technology, Toyohashi
1-1 Hibarigaoka, Tempaku-cho, Toyohashi, Aichi, 441-8580, JAPAN
Tel/Fax: +81-532-44-1215
E-mail: uehara.kazumasa.so@tut.jp

Keiichi Kitajo, Ph.D, Professor
Division of Neural Dynamics,
National Institute for Physiological Sciences
38 Nishigonaka, Myodaiji, Okazaki, Aichi, 444-8585, JAPAN
Tel: +81-564-55-7751, Fax: +81-564-55-7754
E-mail: kkitajo@nips.ac.jp

Abstract

Motor learning is a lifelong process, from infancy through old age. Acquiring new motor skills through repetitive practice requires adjusting motor output in response to sensory input and integrating them to facilitate learning. For this to occur, the central nervous system must flexibly predict and adapt to the dynamic interplay between sensory inputs and motor outputs. Although overall brain function changes with age, it remains unclear how neural flexibility evolves and influences motor learning ability with aging. To address this, we designed a motor learning paradigm involving both younger and older adults and quantitatively assessed neural flexibility from the perspective of functional brain networks, leveraging multichannel electroencephalography (EEG) in humans. Here we found age-related differences in motor learning properties, brain network flexibility, and their neural relationships. In younger adults, motor learning retention was associated with brain network flexibility during the preparatory period of the task. However, this association was not observed in older adults. Together, our findings establish that brain network flexibility plays a crucial role in acquiring and maintaining new motor skills in younger adults, but this relationship becomes less effective with age.

Introduction

More recently, many people live well beyond the age of 60 and maintain good health. In our current reality, various learnings related to motor and cognition occur throughout a lifetime, spanning from early infancy to old age. Notably, acquiring new motor skills, such as playing musical instruments, remains feasible even in older adulthood. The definition of high skill emphasizes reducing variability in action outcomes and this variability progressively decreases throughout the learning process. However, the relationships between motor learning and movement variability remain a subject of debate, both behaviorally and neurally. At the behavioral level, the crucial ability to adapt motor output flexibly in response to multisensory inputs is pivotal throughout the motor learning process (Ranganathan and Newell, 2010; Uehara et al., 2019; Ranganathan et al., 2020). This strategy allows for a trial-and-error approach, effectively promoting motor exploration to achieve better outcomes (Wu et al., 2014). Furthermore, it is not solely about learning a new action but also about adeptly modifying well-learned actions while maintaining a high skill level, even amidst sudden changes in the surrounding environment.

At the neural level, flexible brain networks that reconfigure moment-to-moment play a crucial role in motor learning and skilled actions, particularly in younger individuals (Bassett et al., 2011; Reddy et al., 2018; Uehara et al., 2023). Analyzing brain network flexibility involves examining the time-varying properties of functional connectivity networks and characterizing their dynamics through graph-based community structures. The advent of this analysis has significantly advanced our understanding of how neural dynamics relate to motor learning. Using scalp electroencephalogram (EEG) recordings, we have found that overall brain network flexibility can predict the skill of musical performance in proficient brass players. Notably, brain network flexibility primarily contributed to feedback control in skilled musical performance, rather than feedforward control (Uehara et al., 2023). This observation implies that brain network flexibility is likely leveraged in adapting well-learned behaviors.

With advancing age, elderly people undergo widespread changes in neuromuscular function even during healthy aging, which can disrupt the interplay between sensory input, motor output, cognition, and their neural integrations (Goble et al., 2009; Coxon et al., 2014; Serbruyns et al., 2015; Frolov et al., 2020; Zapparoli et al., 2022; Goelman et al., 2023). These age-related changes in sensorimotor function often lead to a gradual decline in motor learning ability and hinder the adaptation of previously learned behaviors to accommodate changing environmental and task demands. These physiological changes stem from reductions in white and gray matter volumes (Courchesne et al., 2000; Good et al., 2001; Jernigan et al., 2001), alterations in brain activity, and networks (Garrett et al., 2013; Monteiro et al., 2019; Frolov et al., 2020; Goelman et al., 2023), and declines in dopaminergic and gamma-aminobutyric acid (GABA) neurotransmission (Kaasinen and Rinne, 2002; Guitart-Masip et al., 2016; Hermans et al., 2018) even in healthy aging. These factors collectively disrupt the orchestrated brain network at multiple levels leading to changes in behavior. A human functional magnetic resonance imaging (fMRI) study demonstrated that the strength of brain network flexibility correlated with age-related changes in motor function in elderly people (Monteiro et al., 2019). The reduction of brain responses in response to various tasks was observed and this reduction was associated with lower behavioral performance (Coxon et al., 2014; Damoiseaux, 2017). These findings relate directly to a research question in this study whether age-related changes in brain network flexibility could hinder motor learning in the elderly. The majority of studies to date have explored specific changes in brain activity or connectivity with age and their relationship to behavioral performance. However, age-related differences in brain network flexibility and motor learning ability have yet to be thoroughly investigated, and yet mechanisms within brain network flexibility responsible for acquiring and retaining new skills through motor learning remain unclear.

Here we aimed to investigate whether age-related changes in brain network flexibility impact the motor learning abilities of elderly people. We utilized multichannel scalp EEG recordings while participants from both young adults (YA) and older adults (OA) groups engaged in learning an error-

based visuomotor adaptation task. Furthermore, we sought to offer a comprehensive understanding of the intricate neural basis of the influence of age-related changes in brain network flexibility on motor learning, particularly examining cortical excitatory/inhibitory (E/I) balance. We analyzed the PSD slope of EEG data, as E/I balance significantly contributes to brain state changes and the maintenance of optimal brain states, affecting the efficiency of information coding (Denève and Machens, 2016), transmission (Shew et al., 2011), and processing (Turrigiano and Nelson, 2004). Based on the accumulated evidence mentioned above, much is known about how the brain changes anatomically and functionally with age. Here, we expected that brain network flexibility would vary across age and that the association between brain network flexibility and motor learning ability in older adults would be entirely distinct from that in younger adults. Furthermore, we posed an additional hypothesis that this age-related difference could be partially explained by the state of E/I balance.

Materials and Methods

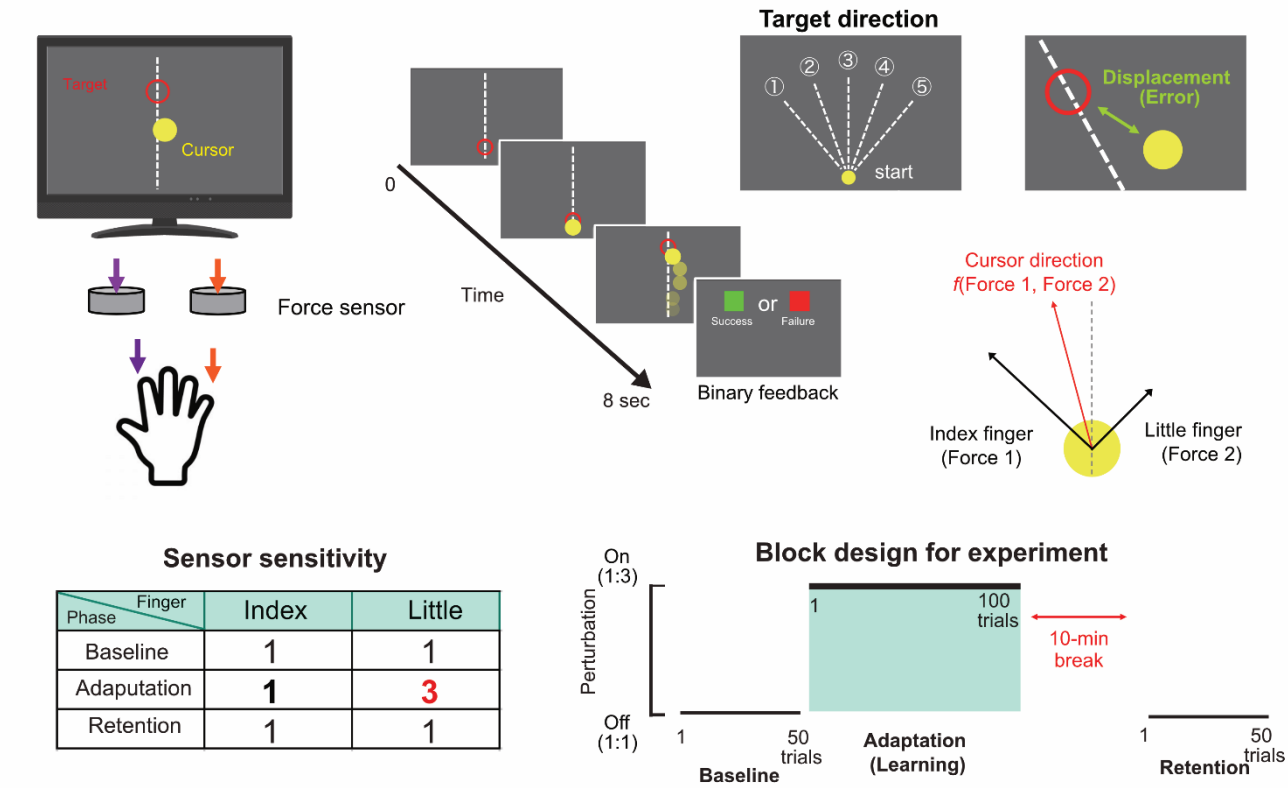
In this study, we selected an error-based visuomotor adaptation task to assess individual motor learning abilities. To estimate the number of participants required to reliably assess behavioral motor learning effects, we conducted an a priori power analysis using the G*Power program (Erdfelder et al., 2009) with the effect size set at 0.49 based on our prior data collection from seven healthy right-handed young individuals (26.4 ± 5.5 yrs, range: 22 -35 yrs, two females). Using the same experimental protocol described later (see *Experimental task and protocols*), the effect size was determined assuming changes in motor performance (i.e., the degree of the deviation of cursor position) between the early, middle, and late phases of motor learning. The statistical significance level was set at $p < 0.05$ (two-tailed) for a one-way repeated measures analysis of variance (ANOVA) with a within-subject factor (motor learning phase). This a priori power analysis estimation showed that more than 25 participants were required as the sample size. Based on this procedure, fifty-four healthy participants were recruited and divided into two groups, each consisting of 27

participants, The groups were categorized as younger-aged (YA) (27.6 ± 5.8 yrs, range: 20 - 38 yrs, 13 females) and older-aged (OA) (66.8 ± 7.4 yrs, range: 58 - 80 years old, 12 females). All participants were naïve concerning our visuomotor learning task, had a normal or corrected-to-normal vision, no history of musculoskeletal or neurological disorders, and were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971). Before data collection, all participants in the OA group underwent a Mini-Mental State Examination (MMSE) with a cutoff score of 25 points, as scores above 25 points indicate intact cognition (Folstein et al., 1975). All participants in the OA group scored above 25 points (29.1 ± 1.2 points), leading to older adults having normal cognitive functions, including orientation, memory, attention, language, and visuospatial skills. However, four out of 27 participants from each group were excluded from the final data analyses due to the failure of the motor performance or electrical noise in the EEG data that was difficult to remove. This paper therefore reports data from 23 participants in each of the groups. This experimental protocol was approved by the local ethics committee of the National Institute for Physiological Sciences in accordance with the guidelines established in the Declaration of Helsinki. Before data collection, written informed consent was obtained from all participants.

Experimental task and protocols

The electromagnetically shielded experimental room used in this study was completely darkened to minimize the availability of any visual information that was not projected on a PC monitor. Participants were seated 120 cm in front of a 24.5-inch (1920 x 1080 pixels resolution) computer display comfortably positioned on a chair with the right forearm supported by an armrest and a chin resting comfortably on a chin rest to ensure a consistent position throughout the experimental session.

Before the experimental task, participants underwent two sets of resting-state EEG recordings, involving 3-minute maintenance of the resting state while keeping their eyes open and closed, respectively, without focusing on any thoughts. During the eyes-open condition, participants were



Phase \ Finger	Index	Little
Baseline	1	1
Adaptation	**1**	**3**
Retention	1	1

Figure 1: Experimental setup and trial structure. Participants were instructed to control a yellow cursor using by pressing force transducers with their right index and little fingertips. Upon the ready cue (the red-open circle appeared), the yellow cursor was displayed on a monitor as the Go cue. After receiving the Go cue, participants began tracking the yellow target to keep the red cursor on the target throughout the trial. The cursor direction controlled by a participant was determined using a composite vector related to the force exerted in the z-direction output from the index and little fingertips. At the end of each trial, they received binary feedback on their performance, with green or red squares indicating success or failure, respectively. The two-dimensional space distance (i.e., horizontal and vertical) between the moving target and the cursor was used as an error index. We employed an error-based visuomotor adaptation task with five different target directions (10, 11, 12, 1, and 2 o'clock direction). In the first 50 trials, participants controlled the cursor with a force sensor sensitivity ratio of 1:1 for the index and little fingers during the baseline session. In the next 100 trials which corresponded to the adaptation session, the force sensor sensitivity ratio was changed from 1:1 to 1:3 for the index and little fingers. After the 100 trials were completed, participants took a 10-minute break in a resting state. Last, participants completed a 50-trial retention test in which the force sensor sensitivity ratio was returned to the baseline session value. Throughout data collection, multi-channel EEG data were recorded continuously from all participants.

instructed to see the fixation cross placed at the center of the monitor. Following this, participants performed three times of maximal voluntary contraction (MVC) in the right index and little fingers, respectively. The maximum force was defined as an MVC value and used to determine cursor control during the task.

On each trial, the target moved straight ahead at a constant speed acceleration in one of five

directions (10, 11, 12, 1, and 2 o'clock) in a randomized order within each session. Participants were instructed to track a moving target on the screen by controlling the cursor as accurately as possible. Our experimental system allowed participants to freely control cursor speed and direction by pressing two force-torque transducers (USL06-H5, Tec Gihan, Co. Ltd., Japan) using their right index and little fingertips. Force signals were amplified via an amplifier device (GDA-06B, Tec Gihan, Co. Ltd., Japan) and then stored on a computer via a NI-DAQ device (USB-6002, National Instruments, United States) at a sampling frequency of 1 kHz with analog-to-digital conversion. The index finger controls leftward cursor movement, while the little finger is responsible for rightward cursor movement. Therefore, the cursor direction was determined by the vector component calculated from the force applied by the index and little fingers. Cursor velocity was also controllable by pressing hard or weakly the force-torque transducer.

Visual cues, cursor control, cursor and target positions on the screen, and trigger signals sent to the EEG amplifier were managed by a dedicated software package (Graphical Design Lab, Japan), implemented in National Instruments LabVIEW software (version 2019, National Instruments, United States).

For the experimental protocol, participants were asked to learn the force mapping in their right index and little fingers through an error-based visuomotor adaptation task. Our experimental protocol, task structure, and apparatus are illustrated in Figure 1. Participants completed a total of 200 trials after performing sufficient familiarization trials (approximately 25 trials) within the allotted time. The experiment consisted of three conditions: baseline (unperturbed), adaptation (perturbed), and retention. At the beginning of each trial, the target circle appeared after a 5-second preparation period, signaling the "Go Cue". Participants were asked to accurately track the target by controlling the cursor. At the end of each trial, they received binary feedback on their performance, with green or red squares indicating success or failure, respectively. In the baseline condition consisting of 50 trials, participants tracked the moving cursor with a force sensor sensitivity ratio of 1:1 between the index and little fingers. During the adaptation phase, participants completed 100 trials with the force

sensor sensitivity ratio of 1:3 between the index and little fingers, requiring them to adapt to the de-novo force mapping. After taking a 10-minute break in a resting state, a 50 trial-retention test was conducted with the sensor sensitivity returned to the baseline value. Note that the luminance of the colors used for the cursor, target, and binary feedback was uniformly set to avoid any biases related to visual perception.

Data recording

Behavioral data. Time series of the two-dimensional target and cursor positions (x- and y-axes) on the screen were contentiously acquired at a sampling rate of 100 Hz using the dedicated software package as described above.

Electroencephalography. To recode neural activity during data collection, we utilized a multi-channel EEG amplifier system (actiCHamp, Brain Products GmbH, Germany). EEG signals were continuously recorded from 63 electrodes positioned on the scalp following the international 10/10 system, using active electrodes embedded in a wearable elastic cap (actiCAP, Brain Products GmbH, Germany). A ground reference electrode for data acquisition was placed at AFz. During the data recording, all electrodes were referenced to the right earlobe while the left earlobe was also recorded as an electrode for re-referencing. Electrooculography (EOG) signals are widely used to detect activities of eye movements and are available to remove eye movement-related noises from the EEG signals. In addition to EEG, EOG was recorded using electrodes placed above and below the left eye for monitoring vertical eye movements and below the left and right eyes for monitoring horizontal eye movements. EEG and EOG signals were amplified and digitized with 24-bit resolution at a sampling rate of 1 kHz. These signals were continuously stored on a personal computer via BrainVision recorder software (Brain Products GmbH, Germany). Skin/electrode impedance was consistently maintained below 10 kΩ throughout the data collection.

Data analysis

Behavioral data were analyzed using custom-written code on MATLAB 2019b (MathWorks, Natick, United States). EEG data were also analyzed using functions from EEGLAB toolbox (Delorme and Makeig, 2004) implemented on MATLAB in combination with custom-written code. Statistical analyses for behavioral and EEG results were implemented using R environment (R Development Core Team, version 4.2.2, www.r-project.org/) unless otherwise noted.

Behavioral data. In this study, a 2-dimensional space distance (i.e., screen height and width) between the moving target (red circle) and cursor (yellow circle) was utilized as an error index. Throughout the error-based visuomotor adaptation task, participants had to reduce this error. To index the error, the Euclidean distance (d) from the moving cursor to the moving target was calculated at each timepoint (t) between the "Go" cue (t_0) and end of the target tracking (t_{end}) at each trial. We then calculated the cumulative error for each trial as follows:

$$d(t) = \sqrt{(x_{2t} - x_{1t})^2 + (y_{2t} - y_{1t})^2},$$

where x_{1t} and y_{1t} are the cursor center coordinates and x_{2t} and y_{2t} are the target center coordinates. Subsequently, the cumulative error (CE) for motor performance within each trial was calculated in the following formula:

$$\text{Cumulative error (CE)} = \int_{t_0}^{t_{\mathrm{end}}} d(t)dx\ .$$

To examine the effects of motor learning effects, we computed the average error over five consecutive trials, defining this as one epoch.

With regard to quantifying motor learning, the learning curve of error across the trials in the perturbation phase was fitted within each participant by using an exponential function (Bönstrup et al., 2020) as follows:

$$L(t) = k_1 - k_2 \cdot \left(1 - e^{-k_3 t}\right),$$

where L is the CE and k_{1-3} denote initial performance (function intercept), maximum performance (function plateau), and learning rate (function slope), respectively. t represents trial number.

To further determine how brain network flexibility relates to the ability to maintain and recall a learned motor performance, we calculated the degree of retention by averaging the first five trials immediately after the 10-minute break (see Figure 1). This is because retention is a hallmark of the effectiveness of motor learning. A high retention value indicates that the motor performance has been solidly learned and can be recalled, effectively.

EEG data. For preprocessing and artifact removal, consecutive EEG signals were re-referenced offline to the averaged signals of bilateral earlobes and segmented into 14-second epochs from 5 s before to 9 s after the "Go" cue. These segmented EEG data underwent band-pass filtering between 1-50 Hz while eliminating 60 Hz power line noise. Independent component analysis (ICA) was then applied to the filtered EEG signals associated with eye movements, blinks, and muscle contractions. The ICA-derived noise components were automatically identified using the ADJUST algorithm (Mognon et al., 2011). As a final preprocessing step, we applied the current source density transformation via the current source density (CSD) toolbox (version 1.1) utilizing the spherical spline algorithm (Perrin et al., 1989; Kayser and Tenke, 2006). This step minimizes the impact of volume conduction on EEG data. Subsequently, artifact-corrected EEG data were used for brain oscillation analysis.

To quantify functional brain networks and their flexibility, we utilized a neural oscillation with a phase-based approach (Lachaux et al., 1999; Varela et al., 2001; van Diessen et al., 2015). This approach aligns with the dynamical systems observed in the brain (Lachaux et al., 1999), where phase synchrony of neural activity significantly contributes to information processing within the brain (Rodriguez et al., 1999; Varela et al., 2001; van de Vijver and Cohen, 2019). First, to decompose

the single-trial EEG signals into time-frequency representations of the instantaneous phase, we applied complex Morlet's wavelet that can be defined as the product of a complex sine wave and Gaussian window (Tallon-Baudry et al., 1996; Cohen, 2019). The CSD-transformed EEG signals were convoluted by a Morlet's wavelet function $w(\tau, f)$:

$$w(\tau, f) = e^{2i\pi f\tau} e^{\frac{-\tau^2}{2\sigma^2}},$$

where i is the imaginary unit. τ and f denote time points and the center frequency, respectively. σ is the width of the Gaussian, which is defined as

$$\sigma = \frac{n}{2\pi f}.$$

The parameter n is defined as the "number of cycles (n_{co})". In the present study, we set $n_{co} = 3$ and f increased from 1 to 50Hz in 1-Hz steps (Lachaux et al., 2000). We then calculated the instantaneous phase synchrony index (PSI) at each frequency for all electrode pairs using the following formula;

$$\mathrm{PSI}(\tau, f) = \frac{1}{T}\left|\sum_{\tau=1}^{T} e^{i\theta(\tau)}\right|,$$

$$\theta_{mn}(\tau) = |\varphi_m(\tau) - \varphi_n(\tau)|,$$

where T denotes the total number of time points corresponding to three cycles of the center frequency, employing 90% overlapping windows, as per previous literature (Uehara et al., 2023). The utilization of 90% overlapping windows enables the generation of time-dense phase synchrony information, facilitating the observation of highly time-resolved brain network dynamics during the task. We posit that this window width setting enhances the analysis of brain network flexibility. $\varphi_m(\tau)$ and $\varphi_n(\tau)$ represent the instantaneous phase of the m_{th} and n_{th} electrodes at time point τ. The PSI represents phase synchronization between EEG signals from two different electrodes at each time point within each time window. This index ranges between 0 and 1, where a value of 0 indicates complete randomness, while a value of 1 denotes perfect synchrony (i.e., complete phase alignment) in EEG signals from the two electrodes and provides valuable information about functional connectivity within the whole brain (Lachaux et al., 2000; Varela et al., 2001).

As the final step, the whole-brain network flexibility was determined using the Louvain-like algorithm (Blondel et al., 2008; Mucha et al., 2010), which is a mathematical method for revealing the inherent community structure within complex networks. This approach is rooted in network analysis, employing graph theory and has recently been applied to analyze neuroimaging data, including fMRI and EEG, which is unveiling functional relationships between brain network flexibility and cognition as well as action (Bassett et al., 2011, 2013; Betzel et al., 2017; Paban et al., 2019; Uehara et al., 2023). Initially, the generalized Louvain algorithm was employed for multilayer community detection. In the present study, a multilayer community was defined wherein each network node (i.e., EEG electrode) in one time window is connected to itself in neighboring (preceding or following) time windows (i.e., layers). This step can be calculated using the following formula (Mucha et al., 2010; Bassett et al., 2013):

$$Q_{\text{multilayer}} = \frac{1}{2\mu} \sum_{nmlr} \left[(A_{nml} - \gamma_l P_{nml})\, \delta_{lr} + \delta_{nm} \cdot \omega_{mlr} \right] \delta(g_{nl}, g_{mr}),$$

where Q represents the multilayer modularity index, l denotes the number of layers in the multilayer network, and μ signifies the total edge weights encompassing both intra- and inter-layer connections. A_{nml} represents the time-by-time $N \times N$ PSI-derived functional connectivity matrices (where N denotes the number of EEG electrodes) between nodes n and m (i.e., PSI value). P_{nml} signifies the weight of the edge between nodes n and m under the null model, while γ_l denotes the structural resolution parameter that defines the weight of the intralayer connections. g_{nl} represents the community assignment of node n in layer l while g_{mr} is the community assignment of node m in layer r. ω_{mlr} denotes the connection strength between nodes across two layers. In this study, the parameters ω and γ were set to 1, constituting their default values as per previous literature (Bassett et al., 2013). $\delta(g_{nl}, g_{mr})$ corresponds to the Kronecker delta, taking a value of 1 if $g_{nl} = g_{mr}$ and a value of 0 if $g_{nl} \neq g_{mr}$.

Subsequently, we determined brain network flexibility by counting how often a node altered its module assignment throughout time, adjusting for the total potential changes. Brain network flexibility was averaged in the theta (4-8 Hz), alpha (9-13 Hz), and beta (14-30 Hz) frequency bands across all EEG electrodes to capture the global flexibility of the whole cortical regions on each single trial. This flexibility index ranges from 0 to 1, where 0 indicates no change in communities, while 1 indicates a change in community across every layer. Before averaging across trials, the flexibility of the whole brain network was averaged within each trial across predefined frequency bands during the 5-second preparation period immediately preceding the onset of action. This is because we presumed that our brain must dynamically and flexibly reconfigure brain networks before movement onset to the given perturbation throughout learning. A previous human behavioral study demonstrated that the preparation of motor action during a motor learning paradigm plays a critical role in the ability to learn in an adaptation task (Haith et al., 2015). Preparatory neural activity patterns have the potential to retain motor memory (Sun et al., 2022). Focusing more directly on brain network flexibility, preparatory brain network flexibility for musical playing is necessary for feedback control, rather than feedforward control, in skilled motor performance by expert musicians (Uehara et al., 2023). Together, these previous studies motivated us to investigate how the flexibility of neural preparatory activity affects motor learning ability across different ages. Moreover, we quantified temporal changes in brain network flexibility throughout the trials during adaptation to identify how inter-trial brain network flexibility changes within the adaptation period and how these changes relate to motor learning ability with age. We perform this analysis to test the assumption that reduced flexibility may stabilize brain networks optimized by learning, minimize noise, and enhance focus on relevant neural signals. This hypothesis is supported by previous human EEG study, which suggests that the suppression of trial-by-trial neural variability is closely associated with perceptual abilities (Arazi et al., 2017). To test this, we calculated the differences in brain network flexibility values between the averages of the first and last fifty trials according to the predefined frequency bands at the individual level.

Regarding the assessment of cortical E/I balance, we employed a non-inversive method to quantify E/I balance using the slope of the power-law exponent of the electrophysiological power spectrum that has been recently used in the field of human neuroscience research. Recent studies have proposed the slope of the power spectral density (PSD) in log-log form as a proxy for cortical excitability, particularly for evaluating E/I balance (Gao et al., 2017; Kosciessa et al., 2021; Wiest et al., 2023; Kałamała et al., 2024). Generally, the PSD slope shows an inverse relationship between frequency and power. Computational modeling studies suggest that the PSD slope can capture the summation of stochastic excitatory and inhibitory currents (Destexhe et al., 2001; Gao et al., 2017; Sheehan et al., 2018). Moreover, empirical validation has demonstrated that E/I balance can be inferred by parameterizing the PSD slope and steeper PSD slopes, reflecting increases in lower-frequency power and decreases in higher-frequency power, correspond to the predominance of inhibitory over excitatory activity (Gao et al., 2017; Trakoshis et al., 2020; Chini et al., 2022). This is because high-frequency activity is most likely to be often associated with excitatory activity, while low-frequency activity is more related to inhibitory activity. In line with brain network analysis, our focus was on age-related changes in E/I balance during the preparatory period and how this change influences brain network flexibility. For this purpose, we performed a single trial PSD analysis from 1Hz to 48 Hz for each electrode and averaged across electrodes. The frequency band between 8 - 12 Hz was excluded from the analysis since a narrowband alpha peak would lead to a bias for the slope fitting for PSD (Kosciessa et al., 2020).

Statistics

Motor learning profiles. To test age-related differences in the motor learning profiles between the YA and OA groups, we used an independent-sample t-test for the learning slope and retention, respectively.

Brain network flexibility. To test age-related differences in brain network flexibility across the

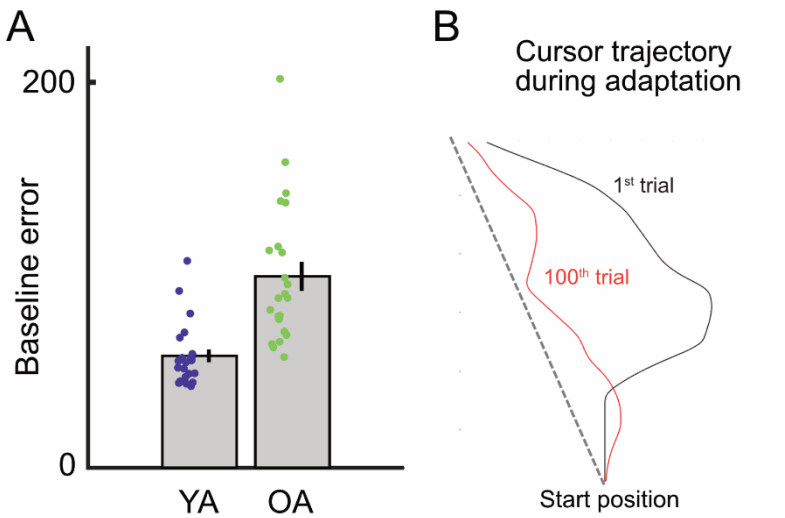
frequency bands, we used a two-way repeated measures ANOVA for mixed design on each resting EEG data and preparatory EEG data respectively, with the GROUP (YA and OA) as the between subject-factor and FREQUENCY (theta, alpha, and beta) as the within subject-factor. In this study, we are interested in how changes in brain network flexibility are associated with the progression of motor learning. To test this, a three-way repeated measures ANOVA for mixed design with the GROUP (YA and OA) as the between subject-factor and FREQUENCY (theta, alpha, and beta) and PHASE (first and last 50 trials) as the within subject-factors was conducted. With regard to the age-related changes in the PSD slope, which is a proxy for E/I balance, an independent t-test was conducted. In addition, we explored how brain network flexibility is modulated by functioning E/I balance within neural circuits. For this purpose, we computed Pearson's skipped correlations using the Robust Correlation Toolbox (Pernet et al., 2013) implemented in MATLAB. To minimize the effect of possible outliers on the correlation analyses, we adopted a bootstrap approach. Using a bootstrapped confidence interval (CI) with 1,000 permutations effectively controls for false positives. Correlations were considered significant if the 95% CI range did not include zero. Note that a Greenhouse-Geisser correction for a series of ANOVA was used when the assumption of sphericity was violated. Post-hoc explorations using Holland-Copenhaver correction for multiple comparisons were performed if a significant effect was detected from the ANOVA (Holland and Di Ponzio Copenhaver, 1988).

Neuro-behavioral relationship. The primary goal of this study was to determine the neural associations of the preparatory brain network flexibility or inter-trial changes in brain network flexibility across the frequency bands and the ability of motor learning including learning rate and retention. To achieve this, we employed a least absolute shrinkage and selection operator (LASSO) regression model, which incorporates penalized regression (Tibshirani, 1996). LASSO regression enables the selection of explainable variables using a weighted combination of L1 norm regularization. The LASSO regression used in the present study was performed using the *glmnet*

package implemented in R software package (Friedman et al., 2010). The trial-averaged brain network flexibility at theta, alpha, and beta frequencies at the individual level was treated as independent variables. The individuals' learning rate and retention were treated as dependent variables, respectively. To ensure the goodness-of-fit of the model, a coefficient of determination value (R^2) was used. We repeated the regression 100 times and identified the median of R^2 across these repetitions because the results of LASSO regression are indeed sensitive to the choice of the hyperparameter, especially λ. These repetitions can help to provide a more robust estimate of model performance. Based on this median R^2, we then reported relevant brain network flexibility most associated with the motor learning profiles.

Results

Behavioral results. Overall motor learning profiles are shown in Figure 2. A representative cursor trajectory during motor learning is depicted in Supplementary Figure 1B. Figure 2A shows the



Supplementary Figure 1: Baseline motor performance (A) and a typical cursor trajectory during adaptation (B). **A**. Group-averaged error at the baseline across the fifty trials. The degree of error in the YA group was smaller than that in the OA group, indicating that the YA group demonstrated more precise cursor tracking compared to the OA group. Each dot represents data from an individual, and each error bar indicates the standard error of the mean across participants. **B**. A typical cursor trajectory during adaptation from a representative participant in the YA group. The deviation of the cursor was decreased consistently across the 100 trials.

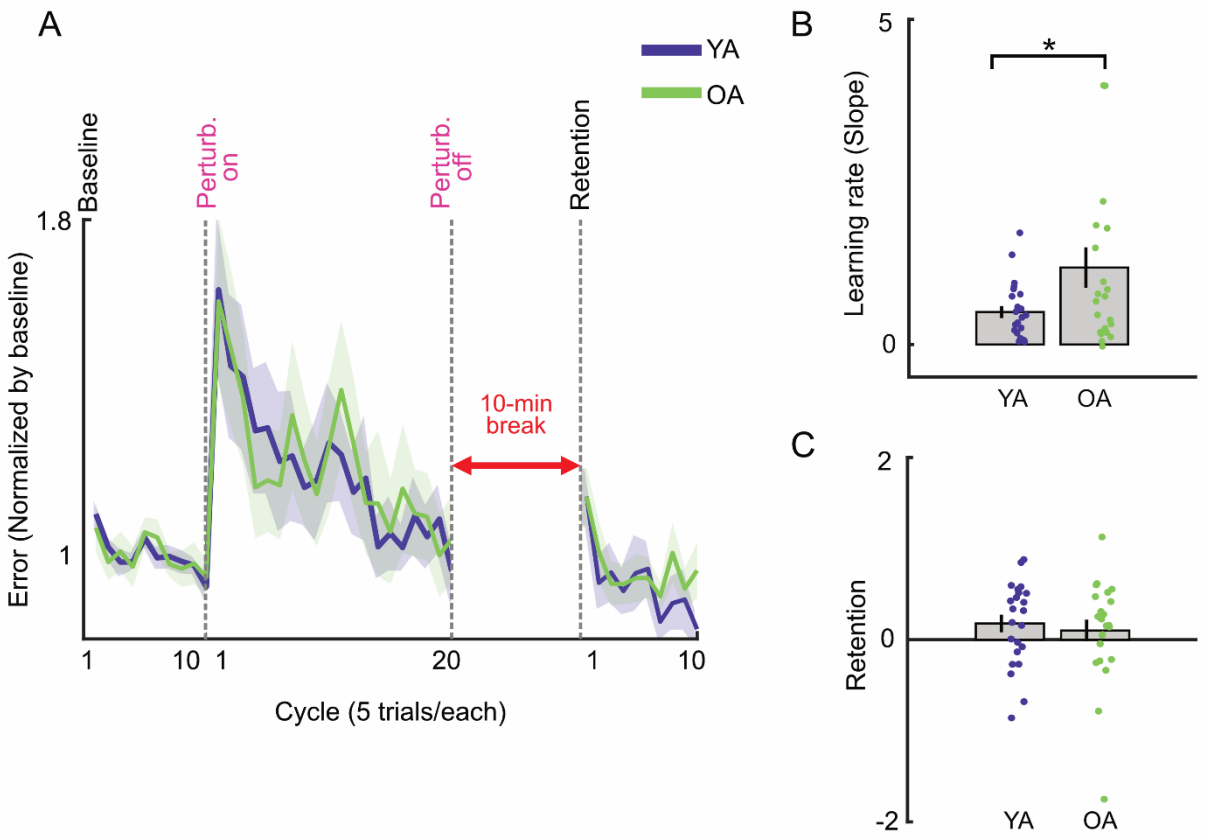


Figure 2: Behavioral results. **A.** Group-averaged performance error normalized by the baseline value throughout the data collection. Solid lines and shaded areas showed mean and SEM for five trials of epoch across participants (n=23 of each). **B.** Learning rate was determined by the slope value (k^3) of the exponential function. Group-averaged learning rates significantly differed between the groups. A lower value indicates continued performance improvement until the end of the session. **C.** Group-averaged retention was used as a hallmark of the effectiveness of motor learning. We calculated the degree of retention by averaging the first five trials after the 10-minute break. A higher value indicates that the motor performance has been solidly learned and can be recalled effectively. Each dot represents an individual, and each error bar indicates the standard error of the mean across participants. Statistical significance is denoted by $*$ $p < 0.05$.

degree of behavioral performance across motor learning observed from the YA and OA groups. Motor learning was evaluated by the degree of baseline-normalized performance error. This is then transformed into parameters representing each profile. As predicted, the degree of error was attenuated along with the number of trials, and this was visible from the first few trials after the start of the adaptation period even though baseline accuracy (i.e., first 50 trials without the perturbation) differed between the groups (Supplementary Figure 1A). This indicates that motor learning occurred

throughout the adaptation period in both groups. Subsequently, we found that the learning rate, parameterized by the slope (β value) of an exponential fit per individual, significantly differed between the groups (Figure 2B) according to an independent t-test (t = 2.574, p = 0.013). The YA group exhibited a lower slope value compared to the OA group, indicating that the YA group was able to sustainably attenuate performance error throughout the adaptation period. No significant difference in retention was detected between the groups (t = -0.504, p = 0.616) (Figure 2C). These results suggest that age had minimal impact on the effectiveness of motor learning and the ability to recall motor memory.

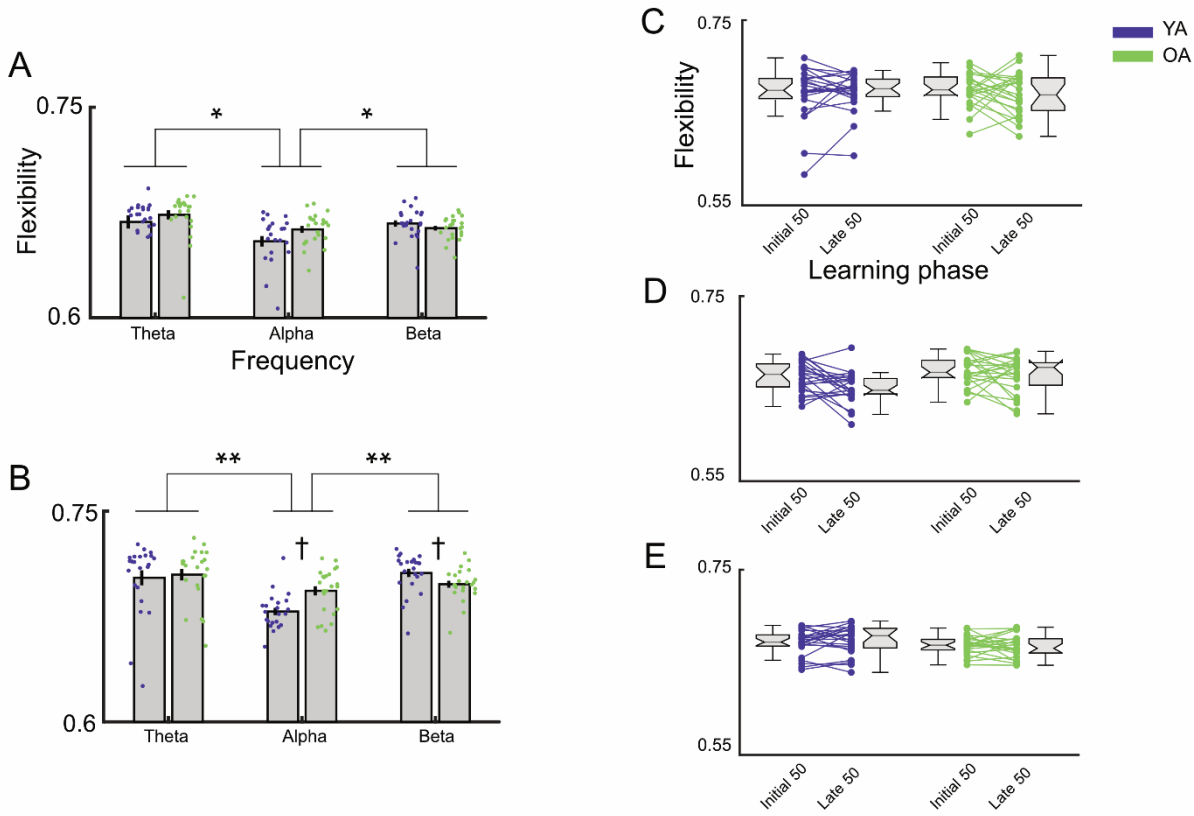


Figure 3: Age-related changes in brain network flexibility. **A.** Group-averaged brain network flexibility during an eyes-open resting state in response to the predefined frequency bands. Brain network flexibility significantly differed between the frequency bands, but not by age. A higher value indicates greater flexibility among the networks. **B.** Group-averaged brain network flexibility during the preparatory period in the motor learning task. Brain network flexibility significantly differed between the frequency bands and the age groups. Significant group comparisons are denoted by a dagger symbol. **C-E.** Changes in group-averaged brain network flexibility from the initial to the late fifty trials were compared for each frequency band (C: Theta, D: Alpha, and E: Beta). Each dot represents an individual, and each error bar indicates the standard error of the mean across participants. Statistical significance is denoted by $*$ $p < 0.05$, or $**$ $p < 0.001$, respectively.

Brain network flexibility. We first sought to verify how brain network flexibility at the resting state differs between both groups (Figure 3A). A two-way ANOVA found a significant main effect of frequency bands ($F_{1.9,87.2}$ = 11.52, p < 0.001), but no significant age effect ($F_{1,44}$ = 1.01, p = 0.31). The interaction was close to the significance level, although it was not significantly different ($F_{1.9,87.2}$ = 2.86, p = 0.062). A post-hoc test revealed that the alpha band had significantly lower brain network flexibility compared to other frequency bands (p < 0.05, Holland-Copenhaver corrected). Brain network flexibility in the alpha band tended to differ between the groups (p = 0.061). Next, we tested age-related differences in brain network flexibility during the preparation period (Figure 3B). A two-way ANOVA found a significant main effect of frequency bands ($F_{1.91,84.1}$ = 28.03, p < 0.001), but no main effect of age ($F_{1,44}$ = 0.521, p = 0.47). A significant interaction between frequency bands and age was detected ($F_{1.91,84.1}$ = 9.51, p < 0.001). Specifically, in all groups, the alpha band had significantly lower brain network flexibility compared to other frequency bands as in the resting state (p < 0.001 adjusted for multiple comparisons). Furthermore, the OA group exhibited significantly higher brain network flexibility in the alpha band compared to the YA group (p < 0.001, Holland-Copenhaver corrected) and the beta band showed the opposite relationship to the alpha band (p < 0.043, Holland-Copenhaver corrected).

Another important point was how the degree of brain network flexibility was changed over time throughout adaptation. Three-way ANOVA revealed significant a main effect of FREQUENCY ($F_{1.77,77.37}$ = 10.62, p < 0.001) but no significant main effects of PHASE ($F_{1,44}$ = 3.75, p = 0.065) or AGE ($F_{1,44}$ = 0.327, p = 0.572) and no significant interactions involving PHASE (p > 0.25 for all), as shown in Figure 3C, D, and E. However, the p-value for the interaction between PHASE and FREQUENCY approached statistical significance ($F_{1.9,83.52}$ = 2.77, p = 0.070). Brain network flexibility in the alpha band tended to decline with the progression of learning, particularly in the YA group, as shown in Figure 3D. We investigated how many network modules were mediated by the flexible nodes because there was a concern that the network could be considered highly flexible even if each node was only moving back and forth between a limited number of modules. Therefore,

it was essential to ensure that we were not merely capturing pseudo-brain network flexibility. To ensure this point, the number of modules (Figure 4A) and network complexity (Figure 4B), as indicated by Lempel-Ziv complexity, are reported, respectively. A three-way ANOVA for the number of modules detected significant main effects of STATE ($F_{1, 44}$ = 133.30, p < 0.001) and FREQUENCY ($F_{1.90, 83.7}$ = 17.32, p < 0.001), but not the main factor of AGE ($F_{1, 44}$ = 0.160, p = 0.691) or any of their interactions (p > 0.05 for all). Follow-up post hoc tests revealed that the number of modules in the task preparatory state was significantly higher than those in the resting state (p < 0.05 for all). Among the frequency bands, the beta frequency band had the highest number of modules. A three-way ANOVA for the values of Lempel-Ziv complexity detected no significant difference between the groups ($F_{1, 44}$ = 0.127, p = 0.723) or no significant interactions related to the main factor of age (p > 0.05 for all). Interestingly, there were significant main factors of STATE ($F_{1, 44}$ = 167.14, p <0.001) and FREQUENCY ($F_{1.93, 85.0}$ = 921.97, p <0.001) and their significant interaction ($F_{1.78, 78.1}$ = 24.85, p <0.001). Post hoc tests revealed that the value became significantly smaller in response to an increase in the frequency band in both task preparation and resting state (p < 0.001). Given that no age-related differences in the properties of brain networks, we can eliminate the possibility that intrinsic network architectures impacted our results regarding brain network flexibility.

To further describe how the age-related difference in E/I balance, as estimated by the slope of EEG-based PSD, was involved in our obtained results, we first conducted an independent t-test for the PSD slope during the preparatory period. We found a significantly steeper slope in the OA group than that in the YA group (t = -5.00, p < 0.001: Figure 5A). This indicates that aging shifts the E/I balance lower during the preparatory period for the motor learning task.

We were interested in testing whether E/I balance is correlated with the degree of brain network flexibility. This analysis provides a more direct link between brain network flexibility and fundamental principle of neural dynamics. Figure 5B and C shows our bootstrapped correlation analyses using the Pearson correlation coefficient. Brain network flexibility in the alpha frequency band obtained from the YA group was positively correlated with the degree of the PSD slope (95%

CI [0.045 to 0.722], r = 0.686). Similarly, a significant negative correlation was found between the beta frequency band and the PSD slope in the YA group (95% CI [-0.732 to -0.223], r = 0.70), as shown in Figure 5B. In contrast to the YA group, no significant correlations were detected in the OA group as shown in Figure 5C. In the last few years, our research field begun by discussing relationships between the E/I balance and brain network properties, showing that the dynamics of brain networks are influenced by the E/I balance (Okun and Lampl, 2008; Sukenik et al., 2021). This balance is considered one of the core elements for maintaining effective neuronal communication. Our observations suggest that the E/I balance, and brain network dynamics are interrelated in young individuals, but this relationship appears to weaken with age.

Taken together, the present study assessed age-related differences in brain network flexibility and related neural features. Our data analyses highlight that brain network flexibility significantly differs with age.

Neuro-behavioral relationship. Lastly, we aimed to clarify the role of brain network flexibility in motor learning. To address this, LASSO regression models incorporating brain network flexibility and the inter-trial changes in brain network flexibility (i.e., changes occurring throughout learning) across three different frequency bands for each group. Table 1 summarizes the relationships between brain network flexibility and the learning properties, while Table 2 shows the relationships between the inter-trial changes in brain network flexibility and the learning properties based on the LASSO regression analyses. In this context, learning rate refers to the speed at which a person acquires or improves a motor skill through repeated trials, while retention refers to the ability to maintain a learned motor skill after a break (i.e., consolidation and effectiveness).

To put it simply, motor learning ability in the YA group was influenced by both preparatory and inter-trial changes in brain network flexibility, whereas this was not the case for the OA group, as even though the model was selected through LASSO regression, the R^2 value was very low. Thus, we present novel evidence indicating that age-related differences exist in the relationship between

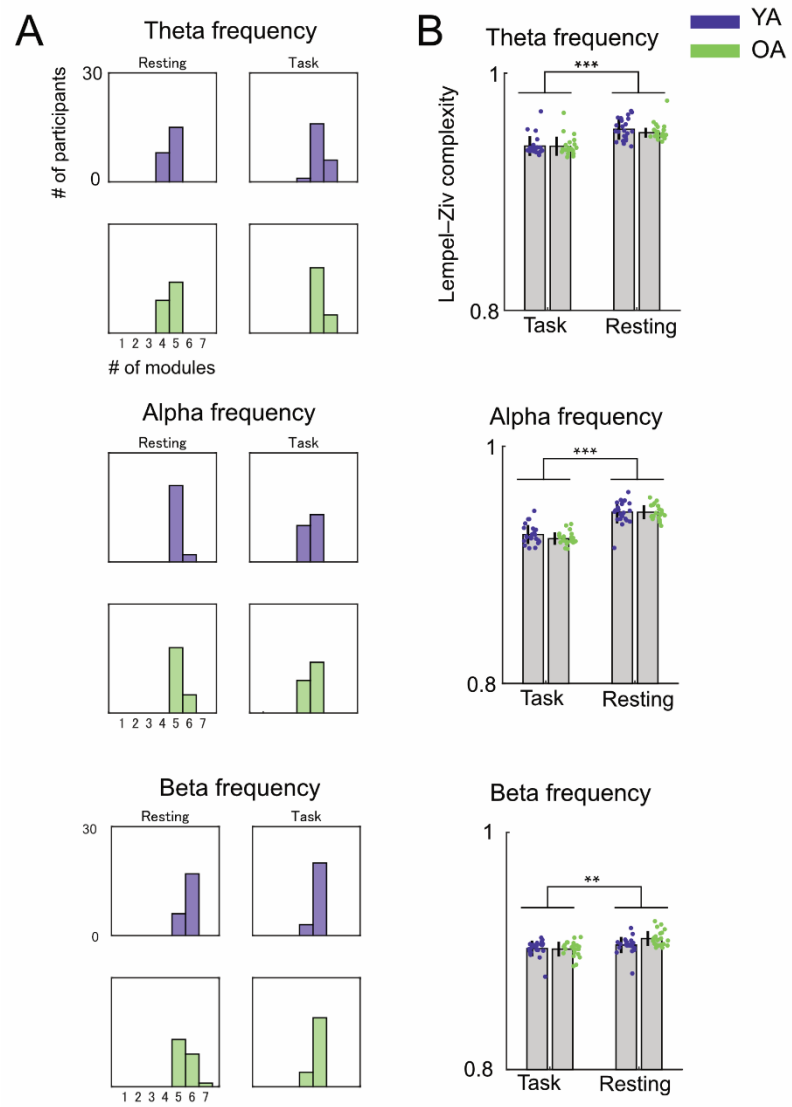


Figure 4: Characteristics of brain network structures. **A.** Number of modules in the extracted brain networks for predefined frequency bands under the resting state and the preparatory period during the motor learning. **B.** Comparisons of brain network complexity. A higher value indicates that the extracted brain networks are complex and contain many unique patterns and is less repetitive. Although significant state-dependent differences (rest vs learning task) were found, no significant differences were observed between the groups. Each dot represents an individual, and each error bar indicates the standard error of the mean across participants. Statistical significance is denoted by ** $p < 0.001$ or *** $p < 0.001$, respectively.

motor learning and brain network flexibility. Notably, preparatory brain network flexibility in the alpha frequency band was associated with retention (Table 1). Additionally, Inter-trial changes in brain network flexibility were associated with the learning rate and retention in the beta and alpha frequency bands, respectively (Table 2).

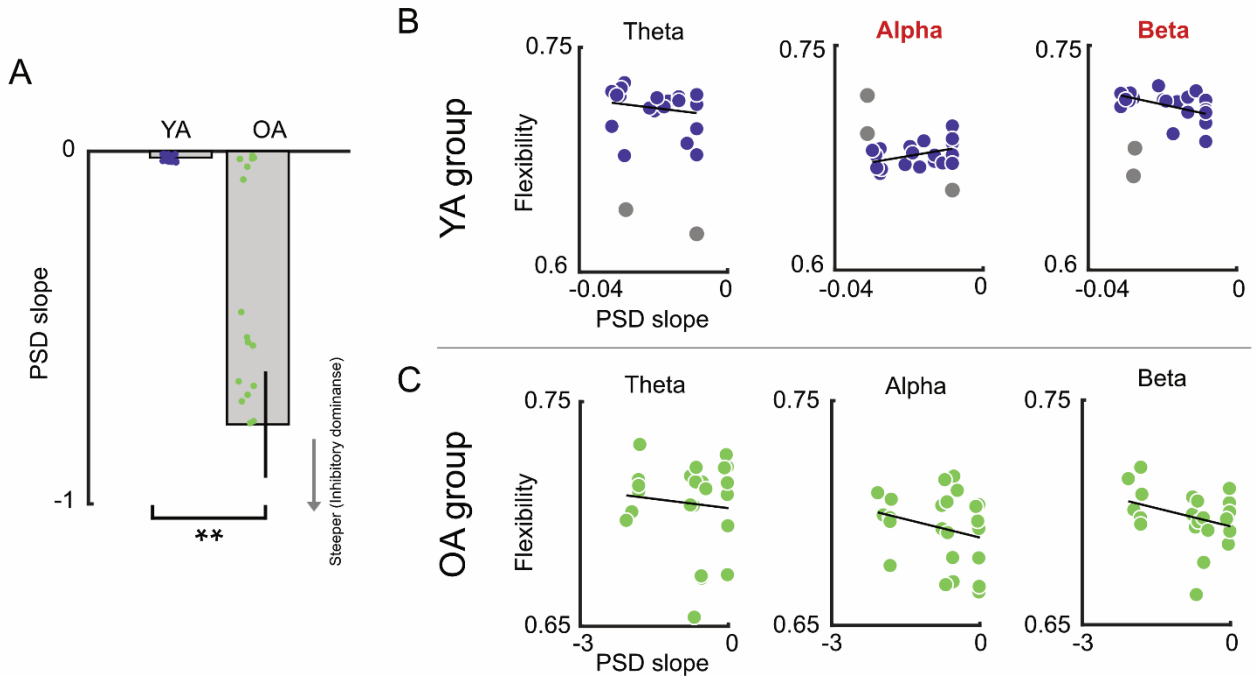


Figure 5: PSD-based E/I balance and its relationship to brain network flexibility. **A.** Age-related difference in the PSD slope that estimates E/I balance. A lower value (i.e., a steeper PSD slope) suggests inhibitory dominance. **B** (YA group) and **C** (OA group) depict statistical correlations between brain network flexibility and E/I balance (i.e., PSD slope). Red-bold font indicates significant correlations based on a bootstrap method. A significant correlation was considered if the 95% CI did not include zero. An outlier is displayed as a gray dot. Each dot represents an individual, and each error bar indicates the standard error of the mean across participants. Statistical significance is denoted by ** $p < 0.001$.

Table 1: Summary of the LASSO regression between brain network flexibility and learning properties

Group	Frequency	Learning rate	Retention
YA	Theta	0	0
	Alpha	0	0.456
	Beta	0	0
	R^2	**—**	**0.347**
OA	Theta	0	0
	Alpha	0	0
	Beta	-0.44	0
	R^2	**0.066**	**—**

Table 2: Summary of the LASSO regression between inter-trial changes in brain network flexibility and motor learning properties

Group	Frequency	Learning rate	Retention
YA	Theta	0	0
	Alpha	0	1.11×10^{-16}
	Beta	0.152	0
	R^2	**0.127**	**0.134**
OA	Theta	0	0.080
	Alpha	0	0
	Beta	0	0
	R^2	—	**0.067**

Discussion

Brain network flexibility focuses on how smoothly different brain areas can form and dissolve connections, enabling efficient and adaptive information processing in response to various external environments and cognitive demands (Bassett et al., 2013; Mattar et al., 2016; Bassett and Mattar, 2017). Recently, this concept has become central to addressing neuroscientific hypotheses within network neuroscience. Based on this conceptual rationale, we sought to determine whether age-related differences in brain network flexibility exist and how these differences are related to human motor learning abilities by leveraging the visuomotor learning task and multichannel EEG recordings. Revealing this relationship is particularly important for understanding how different populations (e.g., younger vs. older individuals) acquire, retain, and refine motor skills.

As expected, age-related differences in motor learning properties (Figure 2), brain network flexibility (Figure 3), and their relationships (Table 1 and 2) were found. In younger adults, retention for motor learning was associated with brain network flexibility during the task preparatory period at the alpha frequency band. However, this association was not observed in older adults (Table 1). Another perspective is how brain network flexibility changes throughout learning (i.e., inter-trial changes) are associated with motor learning properties. We found that inter-trial changes in brain network flexibility were also associated with the learning rate and retention in younger adults, but this was not the case in older adults. Together, these findings suggest that brain network flexibility plays a role in acquiring and maintaining new motor skills in younger adults, but this relationship becomes less effective with aging. Here we discuss our findings with an emphasis on the role of brain network flexibility in motor learning across different ages.

For the behavioral results, both groups were able to adapt to the perturbation in response to changes in the sensitivity of force mapping. Interestingly, although older adults had less precise cursor control compared to younger adults at the baseline (Supplementary Figure 1), they exhibited motor learning effects similar to those of younger adults as they adapted well to novel force mapping (Figure 2). This observation is consistent with previous studies (Seidler, 2006; Yotsumoto

et al., 2014; Nemanich and Earhart, 2015; Bakkum et al., 2021; Durand-Ruel et al., 2023), suggesting that aging does not impair the ability to learn. Nevertheless, we observed a significant difference in the learning rate between younger and older adults with the learning effect in older adults reaching completion and plateauing prematurely. On the other hand, there was no age-related difference in retention. This result is repetitively reported by earlier human studies (Cirillo et al., 2011; Berghuis et al., 2019; Bootsma et al., 2021). According to previous literature (Krakauer and Mazzoni, 2011; Krakauer et al., 2019; Leech et al., 2022), we defined learning rate as the acquisition of new information related to sensorimotor action, whereas retention refers to the ability to maintain and recall learned information or skills over time. In this study, dissociation between learning rate and retention was observed across different ages. This finding emphasizes that age-related differences are more pronounced in the acquisition phase rather than the retention of motor learning. While age may affect motor skill acquisition, the ability to retain and consolidate learned skills appears to be preserved across the lifespan. One interpretation is that the flexible formation of new neural connections may still be possible in older adults, as they initially exhibited a greater learning rate. However, their motor learning quickly plateaued and long-term learning progress was likely hindered. It is suspected that older adults may have deficits in working memory or declarative memory that affect motor learning. It has been suggested that working memory as well as declarative memory function is not restricted to cognitive demands, as learning motor skills can also require these memory functions (Krakauer and Mazzoni, 2011; Maxwell et al., 2017; Krakauer et al., 2019). Specifically, working memory was engaged during the adaptation process for learning an arbitrary visuomotor association, contributing to temporal information storage, the flexible updating of visuomotor mapping, and coordination with reinforcement learning (i.e., reward history) (Anguera et al., 2010; Rajsic et al., 2020; Yoo and Collins, 2022; Hassanzadeh et al., 2024). Based on accumulating evidence, further neurological interpretations of these behavioral results will be elaborated, along with our findings from analyzed EEG data.

To the best of our knowledge, there have been relatively few studies on age-related changes

in brain network flexibility, particularly those focusing on neural oscillations and their dynamics. Despite the presence of neurovascular coupling, a human fMRI study sought to investigate the impact of age-related brain network flexibility on motor skill (Monteiro et al., 2019). This study demonstrated that overall BOLD-based brain network flexibility was reduced in older adults. However, some key brain regions, especially in subcortical areas, showed increases in brain network flexibility with advancing age. This indicates that BOLD-based brain network flexibility is likely affected by age in a heterogeneous manner. One of the reasons is that there is a limited temporal resolution for BOLD-based recording of neural activity. To overcome this limitation, we used multichannel EEG recordings that can be measured in a millisecond order and found age-related differences in brain network flexibility, as hypothesized. In the present study, older adults exhibited greater flexibility than younger adults in the alpha frequency band during both the resting state and the preparatory period of the visuomotor learning task. In contrast, the beta frequency band showed the opposite pattern (figure 3A and B). Why was brain network flexibility in older adults greater than in younger adults across most frequency bands in this study? A plausible explanation, which is referred to as the dedifferentiation theory, exists. This theory suggests that brain areas become functionally dedifferentiated with aging, affecting large-scale functional networks (Dennis and Cabeza, 2011; Geerligs et al., 2014, 2015). Moreover, neural representations become less distinctive in older adults (Carp et al., 2011), and a widespread decrease in the specificity of functional networks in older adults has been confirmed (Geerligs et al., 2014). Combined with the previous studies, our results indicate that a decrease in the specificity of functional networks may lead to a more diffuse, and less focused network configuration, which could account for the greater brain network flexibility observed in older adults. Nonetheless, if the above interpretation is on point, it should be reflected in results for both the number of modules and network complexity, as shown in Figure 4. However, our dataset showed that no age-related differences were found in the number of modules (Figure 4A) or network complexity (Figure 4B). This point is still under investigation and our further study will provide a clearer understanding.

Another important question is why age-related differences in brain network flexibility emerge in the alpha and beta frequency bands. This observation aligns with accumulating evidence that shows a slowing and reduction of alpha rhythms with advancing age (Chiang et al., 2011; Knyazeva et al., 2018; Scally et al., 2018; Park et al., 2024). Beta rhythms are similarly affected by aging (Laera et al., 2021). These changes are known to stem from various biological factors, such as neurotransmitter alterations and increases in neural noise (Babiloni et al., 2006; Voytek and Knight, 2015; Colombo et al., 2019; Hill et al., 2022; Montemurro et al., 2024). Thus, both alpha and beta frequency bands are susceptible to age-related changes and this effect may be involved in age-related changes in brain network flexibility.

The primary goal of this study was to determine the neurophysiological relationships between brain network flexibility and motor learning characteristics, as well as to assess how age influences these relationships. Our LASSO regression analyses found that younger adults exhibited positive associations between brain network flexibility during the preparatory period or inter-trial changes in brain network flexibility and retention, particularly in the alpha frequency band. This suggests that the consolidation of motor learning may rely on increases in brain network flexibility (Table 1). Note that inter-trial changes were calculated by subtracting the first fifty trials from the last fifty trials. Therefore, a higher value indicates minimal change in brain network flexibility throughout the adaptation period. Consequently, maintaining brain network flexibility during the adaptation period supports high retention (Table 2). Together, younger adults who exhibit higher brain network flexibility during the preparatory period and maintain this flexibility are better able to retain and recall learned information. These findings are supported by previous evidence describing that motor skills acquired through intensive long-term learning, cross-day learning with sequential motor learning, and reinforcement learning observed in younger adults can be explained by brain network flexibility (Bassett et al., 2011; Gerraty et al., 2018; Uehara et al., 2023). On the other hand, interpreting the learning rate is likely to be somewhat complicated. In younger adults, inter-trial changes in brain network flexibility in the beta frequency band were positively associated with the learning rate,

meaning that smaller changes in brain network flexibility during the adaptation resulted in faster learning but led to an earlier plateau. This implies that network flexibility does not always contribute efficiently to the acquisition of motor skills. We therefore infer that brain network flexibility in the alpha and beta frequency bands has functionally dissociable and separable contributions to the acquisition of motor skills. To tackle newly emerging questions from the present study, we will design a new study utilizing non-invasive brain stimulation to uncover causal relationships.

Surprisingly, these associations were not observed in older adults from our cohort, indicating that age-related differences, as expected, exist. To our surprise, older adults seem to rely little, if at all, on brain network flexibility for the acquisition of motor skills. This finding is, however, consistent with previous evidence from an MRI study (Yotsumoto et al., 2014). Yotsumoto et al., (Yotsumoto et al., 2014) showed that visual perceptual learning in older adults involves the reorganization of white matter beneath the visual cortex, unlike in younger adults. This suggests that older adults do not primarily rely on changes in brain activity for learning. In the present study, while older adults successfully acquired motor skills, this was not associated with changes in brain network flexibility. We assume that other neural mechanisms, which are yet to be revealed, may account for the acquisition of motor skills in older adults. Related to this, one potential clue from our empirical data as shown in Figure 5 may help us better understand these age-related differences. First, the PSD-based E/I balance seen during the preparatory period differed significantly between the two age groups. Older adults exhibited greater inhibitory influence relative to excitatory influence compared to younger adults. Second, in younger adults, brain network flexibility in the alpha and beta frequency bands was significantly correlated with the degree of E/I balance. Previous studies have suggested that E/I balance is closely linked to the functioning of brain networks and changes in this balance can alter the formation of neural oscillations (Atallah and Scanziani, 2009; Vogels and Abbott, 2009; Stagg et al., 2014). Based on our findings and accumulating evidence, we argue plausibly that E/I imbalance may lead to defects in the organization of brain networks and their flexible dynamics, which may prevent these mechanisms from being effectively utilized for motor learning as age advances.

In conclusion, we present here, for the first time, that age-related differences in brain network flexibility and their relationships to motor learning properties, particularly in learning rate and retention during the visuomotor learning task. This was achieved by multi-channel scalp EEG recordings and a network science approach in humans. Our study reveals dissociated roles of brain network flexibility in motor learning across different age groups. Understanding flexible brain dynamics can lead to help development of novel tools for enhancing motor learning and overcoming the ceiling effect of aging. While further studies are necessary to provide solid evidence supporting our findings, these results provide a clue to designing new research that explores the associations between neural dynamics, cognition, and action.

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Conflict interests

The authors declare no conflicts of interest associated with this paper.

Data and code availability

The data and code that support the findings in this study are available from the corresponding author upon reasonable request.

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