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### Aging, brain plasticity, and motor learning

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### Abstract (194 words)

Motor skill learning, the process of acquiring new motor skills, is critically important across the lifespan, from early development through adulthood and into older age, as well as in pathological conditions (i.e., rehabilitation). Extensive research has demonstrated that motor skill acquisition in young adults is accompanied by significant neuroplastic changes, including alterations in brain structure (gray and white matter), function (i.e., activity and connectivity), and neurochemistry (i.e., levels of neurotransmitters). In the aging population, motor performance typically declines, characterized by slower and less accurate movements. However, despite these age-related changes, older adults maintain the capacity for skill improvement through training. In this review, we explore the extent to which the aging brain retains the ability to adapt in response to motor learning, specifically whether skill acquisition is accompanied by neural changes. Furthermore, we discuss the associations between interindividual variability in brain structure and function and the potential for future learning in older adults. Finally, we consider the use of non-invasive brain stimulation techniques aimed at optimizing motor learning in this population. Our review provides insights into the neurobiological underpinnings of motor learning in older adults and emphasizes strategies to enhance their motor skill acquisition.

### Keywords

Motor skill learning – Aging – Neuroplasticity

### Highlights

Despite poorer motor performance, older adults preserve the capacity for motor learning
Older adults demonstrate training-induced changes in brain structure and function
Motor skill learning may help to counteract age-related loss of brain structure
Training-induced neurotransmitter modulation is evident, also in older adults

5. Non-invasive brain stimulation techniques can be used for optimizing motor learning

# Abbreviations

AD	Axial Diffusivity
atDCS	anodal transcranial Direct Current Stimulation
BTT	Bimanual Tracking Task
CI	Contextual Interference
CS	Conditioning Stimulus
CSD	Constrained Spherical Deconvolution
CSE	Corticospinal Excitability
ctDCS	Cathodal transcranial Direct Current Stimulation
DKI	Diffusion Kurtosis Imaging
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EEG	Electroencephalography
FA	Fractional Anisotropy
FBA	Fixel-Based Analysis
FC	Functional Connectivity
fMRI	functional Magnetic Resonance Imaging
hMT/V5	Human middle temporal area / visual area 5
GABA	v-aminobutyric acid
IPL	Inferior Parietal Lobule
ISI	Inter Stimulus Interval
LICI	Long-interval intracortical inhibition
M1	primary motor cortex
MD	Mean Diffusivity
MEG	Magnetoencephalography
MEP	Motor-Evoked Potential
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NIBS	Non-Invasive Brain Stimulation
NODDI	Neurite Orientation Dispersion and Density Imaging
осс	Occipital brain region
PAS	Paired-Associative Stimulation
PFC	Prefrontal Cortex
PMd	dorsal Premotor Cortex
PMv	ventral Premotor Cortex
RD	Radial Diffusivity
Rs-fMRI	Resting-state functional Magnetic Resonance Imaging
rTMS	Repetitive Transcranial Magnetic Stimulation
S1	primary somatosensory cortex
SICI	Short-Interval intraCortical Inhibition
SICF	Short-Interval intraCortical Facilitation
SM1	primary sensorimotor cortex
SMA	Supplementary Motor Area
SRTT	Serial Reaction Time Task
stDCS	sham transcranial Direct Current Stimulation

tACStranscranial Alternating Current Stimulationtask-fMRItask-based fMRItDCStranscranial Direct Current StimulationTMSTranscranial Magnetic StimulationTSTest Stimulus

Journal Pre-proof

### 1 Introduction

For a long time, brain plasticity (or neuroplasticity), i.e., "the ability of the nervous system to change its activity in response to intrinsic or extrinsic stimuli by reorganizing its structure, functions, or connections" (Mateos-Aparicio et al., 2019), was assumed to reach its peak during young age and then gradually decline with advancing age. The popular saying "you can't teach an old dog new tricks" has perpetuated the idea that individuals, as they grow older, may find it challenging to learn new behaviors.

However, recent times have witnessed remarkable strides in medical imaging technologies such as functional magnetic resonance imaging (fMRI), diffusion weighted imaging (DWI), magnetic resonance spectroscopy (MRS) as well as (neuronavigated) brain stimulation techniques like transcranial magnetic stimulation (TMS) and various transcranial (direct or alternating) current stimulation techniques (tDCS, tACS). These advancements have enabled researchers to better understand brain-behavior relationships. Interestingly, this progress has also led to the emergence of mounting evidence challenging the traditional notion of limited brain plasticity at older age. Instead, an increasing amount of research supports the existence of lifelong brain plasticity, indicating that the brain preserve its capacity for change throughout the entire lifespan.

Aging is marked by a continuing decline in motor function that can start as early as the age of 30 (e.g., Serbruyns, Leunissen, et al., 2015). These declines become more pronounced at older age, leading to reduced motor functioning in older adults (Bartzokis et al., 2010; Heuninckx et al., 2004; Heuninckx et al., 2005; Heuninckx et al., 2008; Serbruyns, Gooijers, et al., 2015; Serrien et al., 2000; Voelcker-Rehage, 2008). Nevertheless, older adults have plasticity potential and have the ability to learn new motor skills, be it at similar or reduced rates of learning as compared with young adults (for reviews, see Maes et al. (2017) and Voelcker-Rehage (2008)). The extent to which motor skills can be learned in healthy older adults through practice depends on multiple aspects such as context, difficulty of as well as the familiarity level with the to-be-learned task (Voelcker-Rehage, 2008).

The newfound understanding of lifelong brain plasticity, along with the insights from behavioral research incorporating motor learning paradigms, has profound implications for our estimation of aging and the brain's capacity for learning and neuroplasticity. Considering these discoveries, the notion of age-related motor decline as an inevitable and irreversible

process is being reconsidered. Instead, a more optimistic perspective on brain plasticity and its enduring potential for behavioral change is gaining traction. Even at age 60 or beyond, the brain possesses a remarkable ability to reorganize neural circuits and adapt to new experiences, challenges, and learning tasks. As we continue to delve deeper into how the brain adapts, we uncover many ways to optimize motor function across the entire human lifespan. This insight opens exciting possibilities for interventions and therapies aimed at harnessing the brain's inherent plasticity to promote healthy aging, enhance motor and/or cognitive abilities, and facilitate recovery after injury or neurological disorders. The ultimate goal is not only to increase lifespan but also healthspan in aging adults.

To advance our understanding of training-induced neuroplasticity in the context of healthy aging, this literature review will encompass the following central topics. First, we will introduce basic principles of motor skill learning and motor memory processes. Second, we will explore the impact of age on motor skill learning and neuroplasticity, drawing insights from studies examining brain structure and function. Additionally, we will examine the role of neurochemicals (particularly  $\gamma$ -aminobutyric acid, GABA) in motor performance and learning. Third, we will discuss the optimization of motor skill acquisition and the underlying neural mechanisms in older adults using non-invasive brain stimulation (NIBS). Lastly, we will conclude this review with a synthesis including comprehensive remarks and perspectives for future directions in this fascinating and evolving field of research. Our most critical objective is to inform the scientific community about the potential for brain plasticity across the whole lifespan and to strongly encourage older citizens to actively promote the utilization of this potential for increasing healthspan and quality of life.

### 2 Basic principles of motor skill learning: motor memory processes

Here, we will discuss the basic principles of motor skill learning, which is essential for a comprehensive understanding of the remainder of this literature review. The primary aim of behavioral motor learning research is to explore how to enhance the execution of a motor skill as effectively as possible and, crucially, how to maintain these improvements over time. Motor skills fall into the broad category of procedural knowledge and are thus acquired through a procedural learning process. Unlike declarative learning, which can be established even with a single exposure to facts, procedural (motor) learning typically necessitates task practice. Memory formation in motor skill learning involves three distinct processes (Kantak

et al., 2012): (1) learning new information, (2) the conversion of the newly learned information into stable memories (memory trace storage), and (3) the ability to effectively recall that information at future times. These three processes are known as encoding, consolidation, and memory retrieval.

In the field of motor skill learning, *encoding* typically takes place during the motor practice session, also known as the acquisition phase. While there may be some overlap between encoding and consolidation, *consolidation* is the process through which the memory of the acquired motor skill becomes increasingly stable over time. Specifically, consolidation is typically considered to be an 'offline process' known to strengthen the motor memory after practice has ended or in between practice sessions. Finally, *memory retrieval* occurs when the learned motor skill is accessed or brought to mind (Kantak et al., 2012).

Motor learning is indirectly estimated by evaluating changes in motor performance over time. In other words, during the motor practice (or acquisition) session, there is typically a reported increase in performance (or decrease in error) with successive practice sessions, often termed 'online gains' in performance (Kantak et al., 2012). Following the acquisition (and consolidation) phase, the practiced motor skill can be tested under the same or altered conditions, referred to as a 'retention test.' This can occur after a short period of rest, ranging from seconds to hours, known as immediate or short-term retention testing, or after a longer period of rest, spanning hours to days and even years following motor practice, known as delayed or long-term retention.

In literature, improvements between performance observed upon completion of the acquisition phase and during a long-term retention test are often described as 'offline gains' in performance (Robertson et al., 2004). It is worth noting that performance can also show a decrease during the offline period, which could suggest insufficient consolidation, and/or the need for more practice. However, when the performance achieved at long-term retention testing remains significantly superior to the initial performance when starting the motor practice session, it is reflective of true learning and formation of a memory trace (also referred to as 'savings' of the memory trace (Krakauer et al., 2006)).

Importantly, a fundamental concept in the field of motor learning, known as the learningperformance distinction, suggests that the observed performance during the acquisition phase and/or short-term retention testing may be influenced by transient processes that run

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parallel to the more enduring effects of practice (Kantak et al., 2012; Schmidt et al., 1992). As such, the impact of practice on motor performance can be attributed to two main factors: relatively permanent effects, which are considered as learning effects, and temporary or transient effects, which include factors that enhance performance (Kantak et al., 2012; Schmidt et al., 1992). Therefore, to reliably deduce long-lasting learning effects, the inclusion of appropriate delayed or long-term retention testing becomes crucial to eliminate the transient effects. Not all studies of motor learning consider this potential confound.

Finally, motor (skill) learning progresses through different stages, though there are no definitive behavioral criteria to clearly differentiate them. Generally, during the early or fast learning stage, significant improvements are observed. In contrast, the late or slow learning stage is characterized by smaller, incremental gains. The duration of these stages varies greatly depending on the task. Learning a motor skill can last from several minutes for simple reaction time tasks to hours, days, weeks or even months and years for complex motor tasks (e.g., playing a musical instrument). Regarding brain activity, early learning is typically associated with increased and anterior brain activation, while late learning shows more posterior and reduced brain activity (Dayan et al., 2011).

### 3 Effects of motor task practice on neuroplasticity in aging

Neuroplasticity can be studied through brain structural, functional, connectivity, and neurochemical processes, offering complementary insights into the dynamic neural mechanisms underlying motor skill learning. Using anatomical and diffusion magnetic resonance imaging (MRI), investigating training-induced neuroplasticity in terms of brain structure allows us to gain valuable knowledge about the gray and white matter changes that occur in response to motor training. Complementary to research on brain structure, plasticity in brain function can be studied through fMRI, TMS, electroencephalography (EEG), and magnetoencephalography (MEG) to obtain a deeper understanding of training-induced changes in the brain's activity patterns. When the focus shifts from specific brain regions or pathways to neuronal interactions, functional and structural brain connectivity are investigated. Finally, MRS offers insights into the neurochemical mechanisms underlying motor skill acquisition. Here, we will focus specifically on the role of fluctuations in GABA levels in the context of motor learning, given the role of GABA as the primary inhibitory neurotransmitter in the human brain. Inhibitory processes are critical for motor control, and

research has shown that inhibitory control declines in older adults (for review, see Levin et al., 2014), underscoring the relevance of studying GABAergic modulation in the context of aging and motor learning. By combining insights from these different types of techniques, a comprehensive perspective emerges on how training-induced neuroplasticity manifests in the (aging) brain. Such an integrative approach enhances insights into the complexities of age-related motor skill learning and its underlying neural processes.

Both within-group and between-group comparisons have been employed to advance our understanding of motor learning and neuroplasticity. Specifically, intervention studies (withingroup designs), in which participants engage in a new motor task, offer valuable insights into neuroplasticity by tracking changes in brain structure and function over shorter or longer time scales. They also provide the opportunity to correlate individual variations in brain structure and function with progress in motor learning. Conversely, comparing different groups at a single time point (between-group designs), such as those with high versus low expertise in a specific motor task, can reveal differences in brain structure and function, possibly related to varying levels of motor practice over long time scales. By combining insights from both approaches, researchers can gain a thorough understanding of how motor practice and neuroplasticity are related.

### 3.1 Brain structure

We review the existing evidence on how inter-individual variation in brain structure (i.e., gray, and white matter macro- and microstructure) relates to motor skill acquisition and on how motor training affects brain structure in older adults. T1-weighted MRI is used to assess gray and white matter volume, as well as shape and cortical thickness of distinct brain regions. In addition, using DWI, the microstructural organization of white matter can be determined and indirectly reflects interregional communication and neural signal transmission.

### 3.1.1 Gray matter

During adolescence and young adulthood, cortical gray matter volume begins to decrease gradually. It continues to decrease in middle and older adulthood, a process known as age-related gray matter atrophy (MacDonald et al., 2021; Resnick et al., 2003). Additionally, cortical thinning has been observed in most brain regions across the lifespan (MacDonald et al., 2021; Sowell et al., 2004). Such age-related degenerative changes are inherently linked to

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normal aging and have been associated with decreased motor performance and difficulties with motor skill acquisition (Blinkouskaya et al., 2021; Fjell et al., 2010; Seidler et al., 2010). Notably, the link between age-related changes in gray matter structure on the one hand and motor performance and/or motor skill acquisition on the other hand is not limited to cortical motor regions, but has also been demonstrated for subcortical or below-cortical areas (Chalavi, Adab, et al., 2018; Kennedy et al., 2005; Seidler et al., 2010; Serbruyns, Leunissen, et al., 2015). In this section, we will concentrate on research that (1) explored the relationship between inter-individual variations in gray matter and the ability to learn new motor skills, (2) compared gray matter characteristics between high- and low-skilled older adults, and/or (3) assessed motor training-induced gray matter plasticity in the context of healthy aging.

### 3.1.1.1 Inter-individual variation in gray matter and its relation to motor skill learning

Training-related gains in motor skill performance vary substantially from one individual to another. Therefore, inter-individual variations in brain structure, which can be large in an aging population, are often studied in association with (initial) motor learning. In the study by Raz et al. (2000), the volumes of the cerebellar hemispheres, putamen and caudate, dorsolateral prefrontal cortex (DLPFC), and hippocampus were measured in 68 participants aged between 22 and 80 years. Training included four blocks (mean duration of ~7 minutes per block) of a pursuit rotor task, which involves an individual trying to follow a small disc ("target") with their dominant (right) hand on a rotating turntable. The training was spread over three consecutive days (blocks 1 and 2 were performed on the first day). On a behavioral level, both older and younger adults showed significant improvement on the task (= total time on target), although the older adults progressed at a slower rate, ultimately demonstrating age-related differences in the later learning stages. The authors found a mediating effect of gray matter volumes of the cerebellar hemispheres and the putamen on the relationship between age and initial acquisition of this unimanual pursuit rotor task (i.e., during the first day of practice). In other words, when regional brain volumes of cerebellar hemispheres and putamen were considered, individual age differences no longer correlated with motor performance during initial learning stages. However, as performance progressed towards asymptotic levels during later stages of acquisition, greater volumes of the cerebellar hemispheres were associated with better pursuit rotor performance, while the volumes of the

putamen no longer showed a significant association with performance. Note that the authors did not explore gray matter volume in primary and secondary motor areas. Later work by Kennedy et al. (2005) aimed to study whether inter-individual differences in brain structure, specifically the volume of the lateral prefrontal cortex, hippocampus, cerebellar hemispheres, and caudate nucleus, are associated with age and sex differences when acquiring perceptual-motor skills. The participants, aged 22-80 years, performed a mirror-drawing task on three separate days. The results showed that larger lateral prefrontal cortex volume was correlated with better performance on the mirror-drawing task when only the oldest participants (60 years or older, n = 26) were considered, especially in later phases of acquisition. Overall, the studies show associations between individual differences in gray matter structure and perceptual-motor skill acquisition and that such associations between brain volume and performance during different stages of skill acquisition may differ as a function of age.

Previous work has addressed the association between baseline regional gray matter brain volumes and learning simple, unimanual motor tasks in older adults. In contrast, the study of such relationships in more complex skills, requiring extended practice, has been explored less profoundly. Using voxel-based morphometry, Basak et al. (2011) assessed whether regional gray matter volume was related to learning a "real-time strategy" videogame in aging individuals (n = 20, mean age: 70.1 years). Videogaming can be regarded as a complex skill involving motor as well as perceptual and cognitive processes (for a review of neuroanatomical predictors of complex skill acquisition during video game training in young and older adults, see Kovbasiuk et al. (2022)). The training protocol included acquisition over five or six weeks with at least 20 hours of practice. Improvements in the time required to successfully play a complex video game were correlated with baseline gray matter volumes in five specific regions: (1) left medial prefrontal cortex, (2) bilateral cerebellum, suggesting that this brain region may be relevant for acquisition of simple as well as more complex skills (Raz et al., 2000), (3) somatosensory cortex, (4) right ventral anterior cingulate cortex and left DLPFC. Overall, this suggests that learning success of a complex skill is associated with volumetric measures in areas responsible for specific sensorimotor as well as more generic functions such as attention deployment, working memory, and conflict processing.

Thanks to recent advancements in analysis techniques, cutting-edge methods are now available to identify even subtle age-related subregional differences in neuroanatomy

between age groups. Shape analyses address age-related associations between subregional shape of the medial subcortical gray matter structures (i.e., caudate, putamen, thalamus, hippocampus, pallidum, and nucleus accumbens) which can be associated with traininginduced performance improvements (Chalavi, Adab, et al., 2018). In this particular study, a cohort of young (n = 25, mean age: 21.08 years) and older participants (n = 23, mean age: 68.65 years) were instructed to practice a complex bimanual tracking task (BTT) across five days (distributed over two weeks), wherein they had to track the movement of a white target dot by rotating two dials simultaneously, either at same (isofrequency, easy task) or different (non-isofrequency, difficult task) rotational speeds. At a neural level, age-related differences were found for global volume, i.e., smaller global volume in subcortical gray matter structures for older versus younger adults. In addition, besides a few age-related regional expansions, the shape analysis revealed widespread compressions in all subcortical structures of interest in older relative to younger adults, reflecting age-related degeneration of subcortical gray matter. Interestingly, findings revealed associations between training-induced performance improvements and both the overall volume and specific shape of subcortical structures, within and across both age groups. Overall, these associations were more pronounced for performance improvements during the more difficult (non-isofrequency) task conditions compared to the easier (iso-frequency) task conditions. Furthermore, interaction analyses involving the more difficult task variant revealed a stronger correlation in older relative to younger adults between performance improvements and shape of the left thalamus, bilateral putamen, and bilateral nucleus accumbens. Concerning improvements on the easier task, stronger associations were found in older relative to younger adults with the shape of the right thalamus, right caudate, right putamen, and bilateral nucleus accumbens (Chalavi, Adab, et al., 2018). As such, it appears that pre-existing (baseline) neuroanatomical characteristics of subcortical gray matter structures, known to be involved in motor learning, are differentially related with skill acquisition capacity in younger and older individuals.

All together, studies point out that inter-individual differences in gray matter cortical (i.e., volumetric variations) as well as in subcortical (i.e., variations in volume as well as shape) brain structure show associations with learning motor skills in older adults. Overall larger gray matter volume is associated with better skill acquisition. Even though causality cannot be

inferred, these results are consistent with the important role assigned to cortical and subcortical brain regions in motor learning.

### 3.1.1.2 Gray matter volume in high- versus low-skilled older individuals

Relationships between motor learning and brain structure are sometimes investigated by comparing individuals who have spent a long time developing a specific motor skill to individuals who have not built that specific expertise. One domain that involves extensive motor learning over many years is playing a musical instrument. Numerous studies have shown that (young) adult musicians who regularly play for extended periods show larger gray matter volumes in specific cortical and subcortical brain areas (motor cortex, auditory cortex, cerebellum, and basal ganglia) as compared to non-musicians (Gaser et al., 2003; Vaquero et al., 2016). Given that musical training is a form of motor learning that is often pursued up to an older age, musicians represent a particularly intriguing population for examining the impact of prolonged motor activity on the brain. Yamashita et al. (2021) examined this by comparing skilled older musicians (n = 36, mean age: 70.8 years; > 22 years of experience, all actively playing) with non-musicians (n = 34, mean age: 71.4 years). Findings revealed that older musicians had higher gray matter volume in the cerebellum (bilateral crus I) relative to nonmusicians. Additionally, a negative association between age and gray matter volume was found in the non-musicians' cerebellar areas, whereas no such association was observed in the musicians. The authors suggested that non-musicians are more vulnerable to age-related atrophy, while lifelong musical experience may help maintain cerebellar volume in older age. However, it should be noted that the correlation values were not directly compared between the two groups, and hence these findings do not allow for firm conclusions regarding differences between non-musicians and musicians.

Rus-Oswald et al. (2022) examined the gray matter structure in older musicians (n = 16, mean age: 76.6 years), young musicians (n = 16, mean age: 21.3 years), and older non-musicians (n = 15, mean age: 74.9 years). A surface-based method was applied at a whole-brain level to provide a set of gray matter macrostructural metrics: thickness (distance between white matter and pial surface), volume, surface area (total area of the cortex), and gyrification (brain's folding pattern). Overall, these gray matter metrics were higher in young compared to older adults, with largest differences between young and older musicians being observed in the superior temporal gyrus, precuneus, lateral and medial orbitofrontal cortex, fusiform

gyrus, postcentral cortex, and superior frontal regions. No differences were found between older musicians and older non-musicians. However, when assessed as a function of age, older non-musicians showed reduced gray matter thickness with advanced age, while older musicians showed a maintained or even increased gray matter thickness with higher age. These effects were apparent in the superior frontal and anterior cingulate areas, pre- and post-central gyri, inferior frontal gyrus, and caudal and rostral middle frontal areas. The "last in, first out" principle of brain aging suggests that brain areas maturing later are the first to show atrophy, making frontal areas particularly vulnerable. Additionally, gray matter volume and surface area decreased with age in young musicians (due to maturation and/or neuroplastic impact) but remained stable or increased with age in older musicians. These findings were observed in para- and postcentral areas, superior parietal lobe, precuneus, and posterior cingulate area, which are generally prone to age-related atrophy. The findings of Rus-Oswald et al. (2022) indicate favorable plasticity in the frontal areas of older musicians, possibly suggesting a protective effect from long-term musical training.

Along the same lines, Chaddock-Heyman et al. (2021) investigated the relationship between gray matter volume and musical expertise in older adults (n = 73, mean age: 65.9 years). The participants were amateur musicians with varying levels of expertise. Despite MR assessments being done on average 6.5 years prior to collecting self-reported musical expertise data through a survey, the findings revealed that musical training (including the degree of musicianship and musical training) demonstrated a positive correlation with gray matter volume in the inferior frontal cortex and bilateral parahippocampus. These brain regions are recognized for their role in executive functioning and memory formation, respectively. The authors suggested that musical training might help mitigate age-related reductions in gray matter in older individuals.

Aside of playing a musical instrument, dancing is also a motor skill of interest here. Niemann et al. (2016) compared gray matter volume in older women with regular dance experience (n = 28, mean age: 73.10 years; 5-34 years of dance experience, actively dancing at time of testing) to active women but without dance experience (n = 29, mean age: 72.73 years). Using voxel-based morphometry, the authors observed that the groups did not differ with regards to gray matter volume. They suggested that the similarity in fitness levels of both groups might be a key factor, indicating that fitness level may be a prerequisite for observing effects on gray

matter volume in older adults. These findings contrast with the interventional studies conducted by Rehfeld et al. (2018) and Muller et al. (2017), see below, which directly compared dance interventions with fitness interventions and observed gray matter volumetric increases following the dance intervention only. However, in the study of Niemann et al. (2016), participants had been practicing dance for many years, potentially leading to high levels of automaticity and a regression of the initially expanded gray matter volume. Such effects might be explained by the expansion-normalization model. Although applied to young adults, this model proposes that practice leads to an initial growth in gray matter, possibly indicating an increase in neural resources. Subsequently, a selection process is initiated that causes the gray matter to return, either fully or partially, to its original baseline (Wenger, Brozzoli, et al., 2017; Wenger, Kuhn, et al., 2017).

In sum, although the evidence is limited, long-term engagement in motor skill practice has been linked to better maintenance of gray matter volume in older age. However, this effect appears to be highly dependent on the specific type of task being practiced, the recruited cognitive resources, and the overall level of physical activity.

### 3.1.1.3 Training-induced gray matter plasticity

A different approach to studying associations between gray matter structure and motor learning is to employ standardized training regimes (and ideally control interventions) and examine motor learning-induced changes in gray matter measures over time. In a pioneering study, Draganski et al., (2004) demonstrated that consistent juggling practice over three months resulted in transient gray matter volume increases in the bilateral motion sensitive visual processing region (hMT/V5) and in the left posterior intraparietal sulcus. Moreover, a significant association was reported between gray matter changes and juggling performance. Although their study involved young adults only, the findings highlight the brain's capacity for structural gray matter adaptation through repetitive practice.

Similarly, Boyke et al. (2008) studied the effects of juggling training on gray matter volumetric changes in healthy older adults. They compared older adults (n = 25, mean age: 60 years) who practiced juggling with three balls for three months with older adults (n = 25, mean age: 60 years) who did not undergo juggling training (see also Malik et al., 2022). Longitudinal gray matter increases were observed in right hMT/V5, right hippocampus, and bilateral nucleus accumbens only in the training group from pre- to post-intervention but receded after an

additional period of no practice (3 months). Note that no significant association was found between gray matter alterations and juggling performance.

Recently, Worschech et al. (2023) examined the effects of 12 months of piano lessons versus music listening on fine motor skills and gray matter volume in motor-related brain regions, namely bilateral primary motor cortex (M1), putamen, and thalamus (n = 136, mean age: 69.7 years). Both the piano playing and music listening groups engaged in weekly 60-minute sessions plus 30 minutes of daily homework assignments. Throughout the study, participants underwent a battery of motor control tests, along with MRI sessions at baseline, six months (i.e., halfway intervention), and 12 months later (i.e., intervention completion). After 12 months, the piano playing group showed greater improvement in fine motor skills (i.e., the Purdue Pegboard test) than the music listening group, indicating transferable behavioral effects. Surprisingly, brain imaging revealed shrinkage in bilateral M1 and putamen for both groups after 12 months. Specifically, in the music listening group, volume of bilateral M1, left putamen, and left thalamus was reduced during the first six months, whereas in the piano playing group, bilateral putamen was reduced in the first six months, and shrinkage of bilateral M1 occurred only during the second six-month intervention. The authors related these findings to the 'exploration-selection-refinement model' (Lindenberger et al., 2019). This model states that during the initial stages of learning, neuronal microcircuits that might be important for the task at hand are extensively explored and consequently undergo structural changes. This exploratory phase is succeeded by periods of experience-driven selection and refinement, where reinforced microcircuits are enhanced, and newly formed structures linked to non-selected circuits are gradually eliminated. For the findings of Worschech et al. (2023), this suggests that M1 may have become less crucial as piano playing became more automated, which is possibly reflected in reduced M1 volumes after this period. They also found a positive association between M1 shrinkage and Purdue Pegboard performance in the group of older adults playing the piano.

Using a whole-brain approach, Muller et al. (2017) explored gray matter volumetric changes following 18 months of practicing new dance choreographies involving complex coordination of limbs and high memory demands compared to conventional fitness activities with low coordination and memory demands (i.e., strength-endurance with repetitive exercises). Both intervention programs were performed in a group context with music and were comparable

regarding intensity, duration, and frequency. Twenty-two healthy older adults (mean age: 68 years) were divided into the two groups. The interventions were divided into two phases, with the participants training twice per week in 90-minute sessions for six months during the first phase, and—for practical reasons—a reduced training frequency of once per week for 12 months during the second phase. The authors found that gray matter volume was increased in the dancers (1) in the left M1 after six months, with these volume increases remaining stable until the end of the 18-month training interval, and (2) in the right parahippocampal region after 18 months, whereas no volume changes could be observed in the fitness group. The observed gray matter volume increase in M1 may be associated with the demanding and dynamic movement patterns they performed, requiring simultaneous coordination of various body parts in different directions. The volume increase in the parahippocampal gyrus, an integral part of the limbic system, may be explained by its vital role in working and episodic memory retrieval (Pantel et al., 2003).

These findings were partly confirmed by the same research group in a separate study involving a shorter intervention period of six months (Rehfeld et al., 2018). In this study, 38 older adults were appointed to a dance (n = 20, mean age: 68.16 years) or a fitness group (n = 18, mean age: 68.72 years). During the latter three months of the intervention, the dance group faced increased coordinative demands and time pressure through more intricate dance movements and a higher tempo. In contrast, participants in the fitness group performed repetitive exercises including three types of training: endurance, strength-endurance, and flexibility. Both interventions were conducted twice a week, each session lasting 90 minutes. Consistent with their previous results (Muller et al., 2017), dance training, as compared to fitness training, led to an increase in gray matter volume in the left M1. Moreover, this study revealed gray matter volume increases also in the left supplementary motor area (SMA), and in the anterior and medial cingulate cortex, the left medial frontal gyrus, and the left insula, as well as the left superior temporal gyrus and left postcentral gyrus. Conversely, participants in the fitness group showed greater volume increases in occipital and cerebellar regions compared to the dance group. Whereas the observed effects in the occipital regions were rather unexpected, the volume changes in the cerebellum may be attributable to the repetitive character of the fitness training, as the cerebellum is an important brain area for planning and execution of movements. Still, similar effects of cerebellar gray matter volume increase could have been

expected for the dance group, given that dancing, possibly more than fitness training, requires motor planning and movement execution. It thus remains to be elucidated whether this group difference is robust enough to be replicated in future studies, and if so, which factors contribute to differential cerebellar involvement. According to the 'exploration-selectionrefinement model' (Lindenberger & Lövdén, 2019), the dance group may have refined their cerebellar neural circuits faster as compared to the fitness group due the specific challenges of dancing, leading to prompt macrostructural changes that were no longer detectable at testing after three months. More fine-grained imaging schedules could test this hypothesis. In addition, the complex integration of music and movement in dance may qualitatively differ from the simpler movements in fitness training.

The longitudinal studies conducted by Muller et al. (2017) and Rehfeld et al. (2018), which implemented interventions targeting coordination and memory in healthy older adults, demonstrated gray matter volume increases in motor areas, with indications of involvement from regions associated with higher cognition as well as the parahippocampal structure. While the precise mechanisms underlying these volume changes require further investigation, dance interventions may hold potential for mitigating or delaying age-related decrease in gray matter in certain brain regions. More specifically, the strength of dance interventions is that they combine fitness training with complex motor coordination, multisensory integration, as well as the training of movement sequences that solicit executive functioning (e.g., updating, switching, inhibition). Hence, they combine physical benefits with requirements for higher cognitive functions.

In summary, research on training-induced gray matter changes in older adults has primarily focused on specific training interventions, namely juggling, piano courses, and dance choreographies. While the reported effects seem promising, more studies employing a wider range of training interventions are needed to establish generalizable effects of movement interventions on the preservation or alteration of gray matter during aging. Furthermore, the studies prompt questions about the relevance of the temporal dynamics in gray matter volume changes. Specifically, longitudinal designs allow for observing specific patterns of gray matter shrinkage and expansion within each intervention group over time. To better understand these temporal dynamics, future research should include multiple MRI acquisition time points over the course of training to provide fine-grained information regarding the

evolution of neuroplastic changes and their relationship to motor performance improvements. By investigating these dynamics, we can gain valuable insights into the underlying mechanisms of transient or enduring gray matter plasticity induced by motor training and its functional implications during the aging process.

Overall, several lines of evidence indicate a clear link between gray matter volume and motor skill learning in aging individuals. Like younger adults, older individuals can undergo gray matter volumetric changes through motor practice interventions. These changes appear taskspecific, occurring in motor- and sensory-processing cortical and subcortical areas and in (pre)frontal and hippocampal structures for new task learning and memorization. Notably, these studies typically employ long training interventions (> 3 months) focused on specific motor skills such as juggling, piano playing, and dancing, reflecting real-life settings. However, these studies often lack a direct assessment of the association between volumetric changes and the acquisition of a motor skill, leaving the functional relevance of gray matter plasticity unclear. Despite this, baseline inter-individual differences in gray matter volume are frequently linked to better motor skill learning, particularly in older adults. This suggests that preserving gray matter, through long-term motor practice (or other interventions), may counteract age-related atrophy and support learning of new skills. Additionally, volumetric differences in gray matter between older adults with extensive experience in specific motor tasks (such as musical or dance expertise) and novices are reported, but they are highly taskdependent and the evidence is very limited. For example, gray matter volume changes are more often reported in the context of playing a musical instrument (involving primarily fine motor skills) relative to dancing (involving primarily gross motor skills).

### 3.1.2 White matter

Age-related atrophy affects not only gray matter but also extends to the brain white matter. In addition to a decrease in white matter volume (Jernigan et al., 2001; Liu et al., 2016), its microstructural organization and efficient connectivity within and between brain regions tends to decline with increasing age (Yeatman et al., 2014). Such white matter characteristics have traditionally been examined with diffusion tensor imaging (DTI) providing metrics such as fractional anisotropy (FA), and diffusivity measures such as mean (MD), axial (AD), and radial (RD) diffusivity which demonstrate high sensitivity to the effects of aging (Bender et al.,

2016). FA, which offers insights into the microstructural organization of white matter, demonstrates a notable decline (i.e., reduced microstructural organization) from the age of 30 when averaged at the whole-brain level, and this decline accelerates further after reaching the age of 50. On the other hand, diffusion metrics like MD, AD, and RD, which capture diffusion levels across all directions, parallel and perpendicular to the fiber tracts, respectively, show an inverse trend (i.e., a decline in white matter microstructural organization). These metrics show reductions when averaged at the whole-brain level until the 40s and subsequently demonstrate an increase (Beck et al., 2021). Note also that brain white matter shows age effects along an anterior-to-posterior gradient which implies that prefrontal structures deteriorate earlier than parietal or occipital structures (e.g., Head et al., 2004; Pfefferbaum et al., 2003; Sullivan et al., 2006; Yoon et al., 2008).

In addition to detecting changes related to aging, DTI metrics are sensitive to detect changes related to motor learning (see further). However, it is important to note that these metrics cannot distinguish between intra- and extracellular components and are affected by overall fiber architecture, such as crossing white matter fibers. More advanced diffusion MRI models have improved the specificity of these findings. Models such as Diffusion Kurtosis Imaging (DKI) (Jensen et al., 2005; Lu et al., 2006), Neurite Orientation Dispersion and Density Imaging (NODDI) (Zhang et al., 2012), and Fixel-Based Analysis (FBA) (Dhollander et al., 2021; Raffelt et al., 2017) offer valuable additions to traditional DTI. In relation to aging, FBA, for example, has shown age-related changes in white matter *micro*structure (indicated by lower fiber density), white matter *macro*structure (indicated by a reduced cross-section in fiber bundles) and alterations in the outcome measure combining fiber cross-section and density that reflects both the micro- and macrostructural underlying neurobiology (Zivari Adab et al., 2020).

White matter structure is known to play a key role in the control of unimanual (e.g., by inhibiting the ipsilateral cortex through the corpus callosum) as well as bimanual or wholebody coordination tasks (for reviews, see Gooijers et al., 2014; Seidler et al., 2010). Therefore, we will specifically focus on studies that (1) explored the relationship between inter-individual variations in macro- and microstructural white matter and the ability to learn new motor skills, (2) compared white matter between high- and low-skilled older adults, and/or (3) assessed motor training-induced white matter plasticity in the context of healthy aging.

3.1.2.1 Inter-individual variation in white matter and its relation to motor skill learning Only few studies addressed motor learning-related white matter structure-behavior interactions in older adults (Adab et al., 2018; Bennett et al., 2011; Schulz et al., 2014; Vien et al., 2016). These studies have shown that behavioral learning-related outcome measures using serial reaction time tasks (SRTT) (Bennett et al., 2011), motor sequence learning tasks (Schulz et al., 2014; Vien et al., 2016), (complex) reaching tasks (Kraeutner et al., 2024; VanGilder et al., 2022), and bimanual coordination task (Adab et al., 2018) were associated with white matter microstructural properties in aging individuals. These studies provide insights into inter-individual differences in white matter at older age and their potential role in the ability to acquire motor skills.

Bennett et al. (2011) used a one-day training paradigm employing an alternating SRTT to study implicit motor sequence learning in young (n = 14, mean age: 18.9 years) and older adults (n= 14, mean age: 67.6 years). Learning outcome was assessed by reaction time and accuracy measures, each averaged within three blocks (resulting in three "stages of learning"). All participants improved on task performance over time, with an age-related difference (i.e., less learning in older adults) occurring in the later stages of learning. At a neural level, three a priori defined bilateral white matter tracts of interest were reconstructed based on previous literature, namely the caudate-DLPFC, the hippocampus-DLPFC, and the putamen-SMA. An age-related difference in white matter microstructure was found in the left and right caudate-DLPFC tract, as indicated by lower FA values (i.e., a decline in microstructural organization) for older versus young adults. For the remaining tracts, no age-related differences in FA were found. A positive relationship between reaction time and FA of the right hippocampus-DLPFC and the left caudate-DLPFC tract was reported in the second learning stage when both age groups were pooled together. Moreover, in late learning (block 3), a positive association was found between accuracy scores and FA values in the left caudate-DLPFC tract. Note that a separate regression analysis of block three data revealed that learning was not significantly predicted by the interaction effect between age group and FA values; in other words, age did not moderate the relationship between white matter microstructure and motor sequence learning performance.

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In the study by Schulz et al. (2014), young (*n* = 11, mean age: 23.6 years) and older adults (*n* = 11, mean age: 73.1 years) learned a visually guided nine element motor sequence task using four digits of their non-dominant (left) hand over a period of five days, with daily practice sessions of 20 minutes each. DTI-based probabilistic tractography was used to reconstruct intra- and interhemispheric cortico-cortical pathways between primary and secondary motor areas at nine months following training. For most reconstructed pathways, an age-related difference in white matter microstructure was observed, i.e., lower FA values in older versus younger participants. Furthermore, although FA values were assessed nine months post-training, correlation analyses performed among the older adult cohort revealed positive links between motor performance enhancements post-training and FA values in specific tracts: (1) contralateral M1-ipsilateral dorsal premotor cortex (PMd), (2) ipsilateral SMA-contralateral M1, (3) contralateral M1-contralateral SMA, and (4) ipsilateral SMA-ipsilateral PMd. Conversely, in the young participants, no significant associations were observed between motor learning and FA values. Note that the tracts linked to learning in older adults displayed significantly higher correlation coefficients compared to those observed in younger adults.

VanGilder et al. (2022), investigated the association between pre-training white matter microstructural organization of tracts connecting parietal and frontal areas, using DTI, and upper limb motor training in older adults (*n* = 19, mean age: 68.4 years). Participants engaged in weekly sessions in which they practiced 50 trials of a reaching movement (like feeding actions) with their non-dominant hand for a duration of three weeks. One week later, a retention test was conducted. Participants also performed a visuospatial memory task (Rey-Osterrich Complex Figure Test) twice, 30 minutes apart to assess delayed recall. With regards to the motor task, participants improved over time (i.e., decreased trial time), and were able to maintain their motor performance after a week without additional training. Motor skill retention which was combined with the delayed recall score into one composite score, revealed positive associations with baseline (pre-training) FA of the bilateral anterior thalamic radiation, bilateral corticospinal tract, and right superior longitudinal fasciculus. In addition, a negative association with FA was found in the left anterior thalamic radiation, left superior longitudinal fasciculus, and left corticospinal tract. In the latter cluster also a positive association with RD values was observed.

Also applying the DTI model, Kraeutner et al. (2024) investigated inter-individual variability in FA values of the frontoparietal white matter tract in relation to learning a complex reaching task. Both young adults (*n* = 13; mean age: 20.3 years) and older adults (*n* = 22; mean age: 65.8 years) practiced a game-like reaching task over four weeks, with two to three sessions of 30 minutes each per week. At baseline, older adults had lower FA values in frontoparietal tracts compared to young adults. However, significant associations between FA values and skill acquisition rates were found in both age groups. Specifically, lower FA values were linked to a greater rate of improvement on the task. This may be due to differential biophysical processes not fully captured by FA as the main outcome measure, as FA is a summary measure, which is not specific to the type of biological processes.

In contrast to the above-mentioned studies, making use of pre-selected tracts of interest and/or applying the DTI model (unlike other diffusion models, being affected by crossing fibers), Vien et al. (2016) investigated the relationship between white matter structure and behavior using a whole-brain approach and applied constrained spherical deconvolution (CSD), which more effectively handles crossing fibers as compared to traditional DTI. The authors aimed to investigate associations between white matter and motor sequence learning in young (n = 28, mean age: 24.5 years) and older adults (n = 29, mean age: 62.8 years). Participants underwent training on an explicit SRTT and were retested within the same day. Diffusion-weighted images were acquired after the retest. The study focusing on early learning revealed (1) improvements in performance in both age groups, (2) widespread age-related differences in FA, and (3) a positive relationship between learning rate and FA in the corticospinal tract (at the level of the internal capsule) as well as the genu of the corpus callosum (negative associations were found with RD and MD). Please note that these associations between white matter metrics and initial motor learning were similar for both age groups. Importantly, since diffusion data were obtained after training, these could theoretically have been affected by the learning process. In young adults, it has been demonstrated that even short-term learning (over the span of a few hours) can induce changes in white matter metrics (Hofstetter et al., 2013).

With respect to motor *coordination* learning, Adab et al. (2018) investigated the relationship between white matter microstructural organization of transcallosal motor-related pathways and BTT performance (for more detail on the task, see 3.1.1.1) during different stages of

learning. Young (*n* = 22, mean age: 21.05 years) and older adults (*n* = 22, mean age: 68.41 years) engaged in seven training sessions in total, with the first (pre-test) and last session (post-test) conducted in the MR scanner. Early learning was characterized as the skill improvement obtained during the initial MRI session, while later learning referred to the performance gain between the initial and final MRI session). To reconstruct white matter pathways between bilateral M1s (IM1–rM1), left PMd and contralateral M1 (IPMd–rM1) and right PMd and contralateral M1 (rPMd–IM1), diffusion-weighted imaging data was acquired pre-training, and probabilistic CSD-based tractography was used to obtain tract-specific FA values. The authors found that older adults initially performed poorer than their younger counterparts, but showed greater improvements, especially during the early learning stage. On a neural level, they observed lower FA values in older relative to young adults in all tracts of interest. Furthermore, larger performance gains in the early learning phase were associated with higher baseline FA values between bilateral M1s, whereas performance gains in the late learning phase were associated with higher baseline FA values in the pathway connecting rPMd and IM1. These effects were evident irrespective of age.

Overall, the above-mentioned studies provide initial indications for associations between measures of motor learning and brain white matter characteristics. In all but one study, white matter microstructural characteristics, obtained at baseline (pre-training), were associated with performance gains on the practiced task irrespective of age. This means that although older adults generally demonstrated lower FA values than their younger counterparts, it generally seems beneficial to learning to have higher FA and/or lower RD and MD values in task-relevant white matter tracts pre-training. Note that some studies also report a negative association between FA and performance improvements. In addition, most of the research has focused on predefined white matter pathways of interest rather than employing a data-driven approach. This choice is understandable, given that data-driven methods require large sample sizes, which are often impractical for time-intensive learning studies. Consequently, there is a need for further research with larger samples, and for research to ascertain a causal link between these brain-behavior measures. This raises the question whether interventional/training approaches that target alterations of white matter may enhance learning capacity.

### 3.1.2.2 White matter microstructure in high-versus low-skilled older individuals

Like gray matter, musical expertise in older adults has been related to white matter characteristics. Andrews et al. (2021) applied DTI in healthy expert musicians (n = 8) with a mean age of 44.1 years (range: 20-67 years), who were playing a musical instrument on average for 38 years. Although this study had a very small sample size and no control group of non-musicians, the findings revealed significant positive associations between FA of the superior longitudinal fasciculus and uncinate fasciculus and musical proficiency and age.

### 3.1.2.3 Training-induced white matter plasticity

Important findings in this area or research were first reported by Scholz et al. (2009). Although focused on a young adult population, the result revealed that consistent practice of juggling over several weeks led to alterations in white matter microstructure within specific brain regions involved in visuomotor processing. These discoveries have paved the way for investigating similar white matter plasticity in older adults, even though research in this population remains sparse.

Both Burzynska et al. (2017) and Rehfeld et al. (2018) examined white matter callosal plasticity following a six-month longitudinal dance intervention including complex dance sequences versus an equivalent time-engaging program that only included simple physical exercises with low coordination and memory demands. In the study by Burzynska et al. (2017), white matter neuroplasticity, i.e., changes in FA, RD, AD, and MD, was investigated in 174 healthy older adults (mean age: 65.4 years), who were divided into four different lifestyle intervention groups, namely (1) dance, (2) walking, (3) walking + nutrition, and (4) active control (toning and stretching). Each intervention consisted of one-hour sessions three times a week across six months. Out of 20 white matter tracts of interest, only the fornix (connecting various nodes of the limbic circuitry) a white matter tract involved in the encoding, consolidation, and recall of declarative and episodic memory, was differently modulated between intervention groups over time. Whereas FA was found to increase in the dance group, a decrease was found in the walking and active control group. The authors observed that this interaction effect was paralleled by changes in RD and MD measures. They argued that the role of the fornix extends beyond memory and they suggested a relation between fornix integrity and working memory,

motor performance, and problem solving in the context of healthy aging (Burzynska et al., 2017; Zahr et al., 2009).

In another study that examined training-induced white matter plasticity, older adults (age range: 63-80 years) participating in a six-month dance program (n = 20) were compared with age-matched controls following a conventional fitness program (n = 18; discussed in section 3.1.1.3) (Rehfeld et al., 2018). Here, white matter plasticity was assessed by comparing volumetric changes as a function of time and type of intervention. The authors found larger volumetric increases in the body and splenium of the corpus callosum as well as in bilateral frontal and right parietal white matter in the older adults involved in dance as compared to the fitness program group. Participants in the conventional fitness program, however, demonstrated larger volumetric increases in the dance program.

Overall, intervention studies looking into training-induced white matter alterations in the context of healthy aging have been limited to specific dance training regimes over long time spans. In these works, six months of dance intervention led to indications of white matter plasticity, or the preservation of white matter during aging, as reflected by (1) changes in microstructure (increase in FA, decrease in MD and RD) in white matter related to memory formation (Burzynska et al., 2017), and (2) larger volumetric increases in interhemispheric tracts, as well as in bilateral frontal and right parietal white matter (Rehfeld et al., 2018). Even though these types of dance interventions seem to be promising in combining cognitive, physical, and social factors, more studies are needed whereby a larger range of training types are employed in order to establish generalizable effects of movement interventions on the alteration or preservation of white matter during aging. Another valuable avenue for further research is to explore the temporal dynamics of training-induced white matter plasticity in healthy aging. Current studies have shown changes over six months, but short-term effects (i.e., following shorter training periods which have been conducted in young adults) and longterm retention of training-induced alterations should be considered as well. This extended analysis would provide a broad understanding of the evolution of changes in white matter and their sustained benefits in older adults.

3.2 Brain function

In addition to exploring the relationship between motor learning and brain structure (as detailed in section 3.1), researchers have investigated the dynamic *functional* changes that arise in the brain during or following practice, often at shorter time intervals. Various methodological tools have been used to probe functional neuroplasticity within the domain of motor learning. Specifically, studies have employed fMRI for its high spatial resolution in mapping brain activity, and TMS to reveal insights into (alterations in) corticomotor excitability. Alternative imaging techniques such as EEG and MEG have also been applied. These modalities offer invaluable insights into the complex processes of learning, especially at short timescales. However, considering the comprehensive nature of the current review, studies involving EEG and MEG have not been included. Three major lines of analysis have been applied to deepen our knowledge of motor learning in the context of brain function alterations. First, fMRI studies can reveal which brain areas show significantly higher or lower activity as compared to control or non-learning conditions as well as changes in brain activity across practice. Importantly, such fluctuations in brain activation must be compared to reasonable control conditions, such as a motor performance task without learning, or rest. Second, fMRI can be applied to obtain functional connectivity (FC) metrics which reveal brain areas that are activated or deactivated together over time, forming functional networks whose role can shift with practice. Third, TMS is a powerful technique to investigate motor learning and its associated effects on neurophysiological outcomes of brain functioning, such as corticospinal excitability (CSE), inhibitory and facilitatory circuits, connectivity between two brain regions and their modulation during motor learning. It offers valuable and more localized insights into the neural mechanisms underlying motor skill acquisition. In what follows, we will review evidence derived from these different approaches.

### 3.2.1 Functional activity as assessed by fMRI

Studies making use of fMRI have consistently found heightened brain activity in older as compared to young adults during performance of motor and other behavioral tasks. This has been interpreted as age-related over-activation or hyperactivation (Calautti et al., 2001; Goble et al., 2010; Heuninckx et al., 2005; Heuninckx et al., 2008; Mattay et al., 2002; Seidler et al., 2010; Van Impe et al., 2013; Van Impe et al., 2011; Ward, 2006; Ward et al., 2003). Nevertheless, under- or hypo-activation has also been documented (Coxon et al., 2016; Monteiro et al., 2017), as well as no age-related differences (Chettouf et al., 2022).

Two primary hypotheses have been proposed in the literature to explain this age-related overactivation: de-differentiation and compensation. Briefly, the "de-differentiation hypothesis" suggests that aging is associated with a decline in functional specificity of brain activation in response to task demands, resulting in non-selective recruitment of additional brain regions, possibly because of decreased inhibitory processes (such as reduction of GABA). This phenomenon manifests itself in additional brain activity (compared to young adults) but this is not associated with benefits in skill performance (Grady et al., 1994; Li et al., 1999; Logan et al., 2002; Park et al., 2004; Riecker et al., 2006; Sala-Llonch et al., 2015). Conversely, the "compensation hypothesis" postulates that the additional brain recruitment seen in older adults reflects a compensatory mechanism that helps to counteract age-related performance deficits that are attributed to structural and functional brain alterations. If such increased activation is positively related to motor skill performance, it is often interpreted as reflecting compensatory recruitment of neural resources (Cabeza, 2001; Goble et al., 2010; Grady, 2012; Heuninckx et al., 2008; Mattay et al., 2002; Naccarato et al., 2006; Reuter-Lorenz et al., 2008; Reuter-Lorenz et al., 2005; Schneider-Garces et al., 2010; Ward et al., 2003; Wu et al., 2005). Nevertheless, the presumed positive association may be more complex than it seems at first sight, because older adults who are confronted with error-prone performance may also recruit additional brain regions to overcome these performance deficits at the short term while improvements only occur at later phases of training. As such, it can be envisioned that such increased brain activity is compensatory but not accompanied with higher motor performance instantaneously. An alternative hypothesis suggests that the over-recruitment of cortical regions serves to counteract the under-recruitment of subcortical regions, but supportive evidence is still lacking (Monteiro et al., 2017). In addition, correlations between interindividual differences in brain activation and interindividual differences in motor performance cannot be interpreted mechanistically, i.e. to reflect compensatory processes per se.

While many studies have focused on age differences in brain activation during motor performance, few have addressed the modulatory effects of motor training on brain activity. In young adults, research on motor sequence learning mainly has demonstrated that during the initial learning phase, brain activation levels vary depending on the region: some areas show increased activity, likely due to the recruitment of additional cortical regions needed to

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learn the new task, while others showed decreased activity, suggesting more efficient neural processing as learning progresses. As individuals move from the initial to the later stages of learning, a shift from anterior to posterior brain areas is often observed. This shift is thought to indicate a reduction in reliance on attentional resources and executive functions over time (Dayan et al., 2011). Addressing such modulatory effects in older adults is interesting because it could provide valuable insights into the brain's capacity for neuroplasticity across the lifespan.

Daselaar et al. (2003) demonstrated pronounced effects of learning an SRTT in both young (*n* = 26, mean age: 32.4 years) and older (*n* = 34, mean age: 66.4 years) adults, with older adults showing greater improvement (i.e., reduced response times) after just six minutes of practice (i.e., fast learning stage). During a subsequent six-minute practice session, young adults did not further improve in response time, whereas older participants showed greater improvements compared to the first session (which were only one minute apart). Despite these behavioral differences, no differences in brain activity were observed between the two training sessions or between young and older adults. The findings suggested that there is no detectable correlation between the extent of learning and degree of brain activity, as examined by means of fMRI.

Rieckmann et al. (2010) found that better learning, as reflected by improvements in motor performance over time, across the acquisition of an SRTT in a single session of approximately ten minutes (i.e., fast learning stage), was related to functional activation increases in striatal and medial temporal lobe activity over time. This occurred from the first half to the second half of the session in a group of older adults (*n* = 13, mean age: 68.08 years). In a group of young adults (*n* = 14, mean age: 24.71 years), more learning across time was likewise related to increased recruitment of the striatum but, in contrast to the older adults, *decreased* recruitment of the medial temporal lobe over time. It should be noted that consolidation processes were not explored because a retention test was not performed. As no age-related learning decrements on the sequence learning task were observed in this study and increased recruitment of the medial temporal lobe was positively associated to behavioral changes only in the group of older adults, the authors speculated that medial temporal lobe activity observed in the older group may have reflected compensatory brain recruitment while learning the sequence task. Although the striatum and medial temporal lobe were the main

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regions of interest of the study, age-dependent performance-related changes in brain activity were not restricted to the medial temporal lobe. In that regard, older as compared to younger adults were found to show greater performance-related increases in frontal areas, namely the lateral and medial prefrontal cortex (PFC), and superior frontal and orbitofrontal cortex. Furthermore, young as compared to older adults showed greater performance-related increases in brain activity in the striatum, thalamus, parietal, insular and occipital cortex as well as the cerebellum.

Durand-Ruel et al. (2023) also investigated brain correlates of fast motor learning. Using their nondominant left hand, older adults (*n* = 43, mean age: 69,5 years) learned to modulate grip force in a sequential task with their nondominant left hand over two training sessions (lasting 12 minutes each) within the same day while fMRI data was acquired simultaneously. Note that consolidation processes were not investigated as no retention test was obtained. At the behavioral level, older adults improved their performance, i.e., an increase in accuracy and a decreased time to complete trials were observed during the training sessions. Activity in bilateral premotor cortices, right M1, and left superior parietal lobule increased gradually in both practice sessions, whereas activity in the right ventromedial PFC, bilateral anterior and middle cingulate areas, and bilateral thalami were reduced in both practice sessions. The authors also found that increased activation in regions associated with the sensorimotor network, namely bilateral primary somatomotor and premotor cortices, was related to increases in accuracy. Also, shorter execution time (i.e., better behavioral performance) was associated with increased recruitment of bilateral superior parietal regions.

In contrast to previous studies by Daselaar et al. (2003), Durand-Ruel et al. (2023) and Rieckmann et al. (2010) who all focused solely on investigating acquisition process correlates *during* task performance, Berghuis et al. (2019) examined brain activity changes over time in young (*n* = 15, mean age: 25.5 years) and older adults (*n* = 15, mean age: 63.1 years) from pre-acquisition to post-acquisition and retention (tested 24 hours later) of a visuomotor tracking task. The training session for this task lasted approximately 13 minutes, reflecting the early learning phase. Despite older adults generally performing worse on the task compared to young adults, both groups showed similar improvements in task performance over time. Brain activity reductions from pre-acquisition to post-acquisition to post-acquisition to post-acquisition to post-acquisition to post-acquisition to post-acquisition to part adults generally performing worse on the task compared to young adults, both groups showed similar improvements in task performance over time. Brain

and occipital brain areas across both age groups, suggesting more efficient visuospatial processing post-training. Notably, activity levels in these regions returned to pre-acquisition levels from post-test to retention across both age groups. Contrasting brain activation, training-induced changes in brain *deactivation* were dependent on age, with young adults showing greater deactivation (decrease in brain activity) from post-acquisition compared to retention in certain brain regions (parietal, occipital, temporal), while older adults did not show significant modulation of brain activity in these areas. Note that the effects in the temporal area were no longer significant when whole-brain gray matter volume was added as a covariate to the model. In contrast, older adults showed trends towards reduced deactivation (increase in brain activity) in the left inferior frontal gyrus from post-acquisition to retention, which was not observed in young adults. The lack of modulation in default mode network (DMN)-associated regions (precuneus, angular gyrus, temporal gyrus) in older adults aligns with previous findings indicating age-related changes in DMN function, characterized by decreased resting-state FC (Ferreira et al., 2013) and reduced deactivation of DMN during task execution (Grady et al., 2006; Lustig et al., 2003; Sambataro et al., 2010). Observing comparable learning rates between both age groups, but different brain activation patterns, particularly from post-test to retention, were suggested to reflect compensatory strategies in the group of older adults even though significant correlations with performance were not reported.

Similarly, but using a visuomotor force-tracking task, Godde et al. (2018) investigated effects of aging on neural activations during the initial stage of motor learning. Young (*n* = 12, mean age: 29.67 years) and middle-aged adults (*n* = 12, mean age: 57.75 years) performed a force-tracking task with their right thumb and index finger for a total duration of 7.25 minutes. Behaviorally, the middle-aged group showed a trend towards poorer task performance relative to the younger group but demonstrated comparable learning gains. Overall, during task performance, the middle-aged group showed stronger brain activations than the younger group, particularly in the motor network including both cortical and subcortical structures. Moreover, independent of age, brain activations reduced after practice in frontal, parietal, temporal, and cingulate areas. Although no direct comparison between young and middle-aged participants was performed, separate analyses for each group revealed that older adults demonstrated larger reductions in brain activations than the young adults. Moreover, while

younger adults showed additional increases in brain activation after practice, middle-aged adults did not demonstrate a similar effect. The authors suggested that with practice, brain activation patterns of middle-aged participants became more like those of younger adults before practice.

Monteiro et al. (2017) investigated motor training-induced plasticity in brain activity beyond a single training session, i.e., reflecting the early as well as later learning phase. The study involved both young (n = 25, mean age: 21.5 years) and older adults (n = 18, mean age: 68.6 years). Participants underwent fMRI scans during task performance before and after five practice sessions spread over two weeks. The task required complex bimanual coordination, i.e., the BTT (for details on the task, see section 3.1.1.1), performed either with or without augmented visual feedback, with each scan session lasting 60 minutes. A retention test was conducted six months after the post-test. Older adults performed worse than young adults, but demonstrated larger learning gains, likely resulting from the overall lower initial performance level. At the retention stage, older adults seemed to maintain their skills at a level comparable to younger adults, though they showed larger error rates compared to the young adults. fMRI revealed that older adults demonstrated widespread cortical hyperactivation (consistent with previous research) but also subcortical hypoactivation as compared to younger adults. Both young and older adults showed training-induced changes in brain activity, characterized by an overall decrease in activation, indicating more efficient neural processing over time. Furthermore, a stronger positive association was found between prefrontal activation during the initial learning phase and later performance gains over the training period in older compared to younger adults. In contrast, young relative to older adults showed such associations with more posterior and cerebellar regions. These findings indicate that performance gains from pre- to post-test and the accompanying reduction in brain activity are maintained in older age. However, practice did not eliminate the typical brain hyperactivation observed in older adults.

In a study by Aznárez-Sanado (2022), brain activation during early motor sequence learning (~14-15 minutes) was examined in middle-aged individuals (n = 25, mean age: 56.3 years) without a young adults control group. To study the fast *and* slow learning phase, a subsample (n = 11, mean age: 54.6 years) was also assessed after three months of daily practice (~14-15 minutes per practice session). Participants practiced two eight-element sequences with four

digits, including a novel and a control sequence. Task-based fMRI was acquired during the first session for all participants, and after three months of daily practice for the subsample. During early learning, participants showed rapid improvements, accompanied with activity in sensorimotor, premotor, preSMA/SMA, parietal, DLFPC, striatal, and cerebellar areas. During late learning (after three months), individuals performed the task accurately with reduced neural activation. Early learning showed higher activation in the precuneus, preSMA, left SFG and right precentral gyrus compared to late learning, which showed no regions of increased activation. Age was not significantly associated with brain activity. The reduced neural resources needed during late learning in the current sample were largely comparable to what is generally reported in younger adults (which were not included as a control group here).

In addition to the afore-mentioned studies, research has also focused on the impact of practice schedules on motor learning and brain activity in young and older adults. This refers to either blocked practice (repetitive practice of each variant separately before moving to the next) or random practice (interleaved practice of all variants). Typically, young adults practicing under a blocked practice scheme outperform those in a random practice scheme during initial learning. However, during retention assessments, the pattern reverses, with random practice leading to better performance (Shea et al., 1979). This suggests that introducing challenge via random practice contexts enhances long-term skill retention, which is referred to as the contextual interference effect (CI) (Shea et al., 1979). The CI effect has been consistently observed in various tasks among young adults (for a review, see Magill et al., 1990). A few studies have also explored the CI effect in aging populations, equally demonstrating that older adults showed better retention with random practice (Beik et al., 2022; Lin et al., 2012a, 2012b; Lin et al., 2016), but the behavioral benefits seem to be mediated by the level of task complexity (for a review see Wulf et al., 2002).

Studies on the CI effect in young adults have revealed distinct neural patterns depending on the type of practice employed (for reviews, see Lage et al. (2015) and Wright et al. (2016)). Lin et al. (2012a) investigated age-related effects on brain activity patterns associated with blocked and random practice during an SRTT of several minutes trained on two consecutive days in young (n = 16, mean age: 26.4 years) and older adults (n = 16, mean age: 66.2 years). Behaviorally, the CI effect was present in both age groups. Additionally, the study revealed that young adults demonstrated higher DLPFC activity during random compared to blocked

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practice, an effect absent in older adults. Furthermore, in young adults, DLPFC activity during acquisition was associated with larger CI benefits during retention (performed three days later, at day five). In contrast, older adults showed higher activity in sensorimotor regions (such as M1, SMA, and rostral PFC) during random versus blocked practice, which was linked to the behavioral advantages of CI in this age group (Lin et al., 2012a). These findings suggest that different brain regions mediate CI benefits in young and older adults, emphasizing how aging modulates neuroplasticity. For related findings using TMS, see section 3.4.1).

In another study examining a three-day practice schedule of the BTT (see 3.1.1.1 for task description), Chalavi et al. (2018) and Pauwels et al. (2018) confirmed the CI effects in both young (n = 32, mean age: 21.8 years) and older adults (n = 28, mean age: 66.5 years). During the skill acquisition phase, blocked practice led to activation in sensorimotor areas, while random practice resulted in more activation in visual processing areas. Even during delayed retention without augmented visual feedback, both age groups showed higher recruitment of visual processing regions after random practice, suggesting greater attention to task-specific visual features. This study's findings differ from previous CI research (Lin et al., 2012a, 2012b; Lin et al., 2016), which reported predominant frontoparietal activity during random practice on an SRTT. Separate analyses for young and older adults, revealed interaction effects between time and CI (Pauwels et al., 2018). In young adults, motor-related brain regions as well as non-motor frontal and parietal areas, showed reduced activity from day one to day three during blocked practice, but no change during random practice. In older adults, blocked practice showed reduced activity in sensorimotor and cerebellar regions over time, while random practice resulted in increased activity in these areas and the superior temporal gyrus. Interestingly, practice also modulated activity in DMN regions in older adults. Traditionally, neuroimaging studies on brain function have focused on activations within task-relevant regions. However, interest is growing in investigating deactivations within the DMN, a tasknegative network (Buckner et al., 2008). Activity in the DMN increases during periods of taskunrelated thoughts, or mind wandering (Allen et al., 2013; Buckner et al., 2008; Smallwood et al., 2015). These thoughts occur during rest or while being engaged in a task, but their frequency decreases as task demands rise (Antrobus et al., 1970; McKiernan et al., 2006; McKiernan et al., 2003). Evidence suggests the DMN is particularly susceptible to age-related changes, such as (1) a decline in resting-state functional connectivity within the DMN (Ferreira
et al., 2013) and (2) reduced deactivation in DMN regions during tasks (Grady et al., 2006; Lustig et al., 2003; Sambataro et al., 2010). In blocked practice, DMN regions showed increased activity with practice, while random practice resulted in decreased activity. During delayed retention, random practice led to lower posterior cingulate cortex activity (part of the DMN) in older adults, correlating with better retention performance. Thus, in older adults, the contextual demands of Cl influenced activity in both DMN and task-relevant brain regions. Blocked practice, a less demanding task, led to reduced sensorimotor engagement and increased DMN involvement, suggesting increased automaticity. Random practice, a more challenging context, elicited age-related neuroplastic changes with increased task-relevant brain region engagement and decreased DMN activity, especially in the posterior cingulate cortex during retention. The finding that enhancing task engagement through a random practice schedule may promote greater differentiation in activity levels between task-relevated and DMN regions, thereby yielding positive behavioral effects, holds considerable promise for practical applications.

The reported studies show that the behavioral CI effect is similar in both young and older adults, indicating that random practice is more favorable than blocked practice for learning a set of new motor skills, independent of age. However, the neural findings are more mixed and appear to depend on the specific task. For tasks where visual feedback is less crucial, random practice, compared to blocked practice, is associated with frontoparietal activation. In contrast, for more complex tasks requiring visual feedback, random practice leads to predominant activation in visual processing areas. A common finding is that random practice is accompanied by more extensive brain activity, which is related to better performance. Importantly, aging significantly influences these effects, with older adults recruiting different brain regions and/or showing increasing activation in the same brain regions.

In summary, while functional activation studies focused on *motor performance* rather consistently report cortical over-activation in older relative to young adults, studies on *motor learning* present a more heterogeneous picture. Overall, older adults demonstrate training-induced brain activity modulation in several task-related brain regions to a comparable degree as young adults. The modulation is primarily characterized by reduced brain activation, indicative of increased neural efficiency (Aznarez-Sanado et al., 2022; Berghuis et al., 2019; Monteiro et al., 2019). Despite this, the persistent cortical hyperactivation still leaves the older

as compared to young adults with elevated brain activations by the end of practice, suggesting that over-activation in older adults is not easily overcome. Contrarily, some studies report no modulation (Daselaar et al., 2003), or differential modulation between young and older adults (Rieckmann et al., 2010). It is important to note that most of the studies only investigated the very initial learning phase while Monteiro et al. (2017) covered also later learning stages. Moreover, there is a clear variation in the level of complexity of the tasks used for studying learning. Additionally, brain activation levels in prefrontal and parietal areas during initial learning are overall correlated with later performance gains, particularly in older adults. The increased prefrontal brain activity observed in older adults during task performance and learning suggests increased cognitive control of action relative to young adults. Nonetheless, given the mixed findings, potentially because of different training durations and contexts, the exact role of training-related brain modulations in aging remains to be fully understood.

## 3.2.2 Functional connectivity as assessed by fMRI

Aside from looking at activity in separate brain regions, interactions within and between brain regions are critical for behavioral functions and can be assessed through functional connectivity (FC) analyses, i.e., correlations of brain activity in anatomically close or distant regions over time. Such analyses can either be conducted on brain activity at rest (rs-fMRI), i.e., resting-state FC, or on brain activity during task execution (task-fMRI), i.e., task-related FC. Functional networks are typically arranged in subnetworks, where nodes within the same network are strongly interconnected and nodes between networks show lower connectivity (Durand-Ruel et al., 2023). Such intra-network connectivity is interpreted to reflect functional specialization of that subnetwork. In contrast, connections between subnetworks reflect inter-network connectivity and may promote functional integration (at least under certain circumstances). There are many approaches towards the study of FC. Some researchers take a whole-brain network approach. Others are more concerned about connectivity between preselected regions or between a target region and the rest of the brain. Here, we will start from whole-brain approaches and then zoom into smaller scale FC approaches.

Previous research has already shed light on the altered functional network characteristics of the aging brain. Specifically, a defining feature of aging is the decline in the segregation of functional brain networks, characterized by a marked increase in FC between brain networks during both resting-state and task performance (Antonenko et al., 2014; Archer et al., 2016;

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Betzel et al., 2014; Cao et al., 2014; Chan et al., 2014; Damoiseaux, 2017; Ferreira et al., 2016; Geerligs et al., 2014; Geerligs et al., 2015; Grady et al., 2016; King et al., 2018; Monteiro et al., 2022; Monteiro et al., 2019; Monteiro et al., 2020; Ng et al., 2016; Siman-Tov et al., 2016; Spreng et al., 2016).

In young adults, rs-fMRI studies examining motor training-related changes in FC revealed that resting-state FC may be modulated within and/or between practice sessions (Albert et al., 2009; Daselaar et al., 2010; Ma et al., 2011; Tung et al., 2013; Vahdat et al., 2011; Woolley et al., 2015). Furthermore, Vahdat et al. (2011) found that greater reductions in FC between M1 and cerebellar regions after a short practice session (median duration: 16 minutes), were associated with more motor learning. This suggests that functional network reorganization in young adults plays a role in training-induced behavioral changes. Only few studies have investigated training-related modulations in FC in the aging brain (Aznarez-Sanado et al., 2022; Balazova et al., 2021; Maes et al., 2020; Monteiro et al., 2019; Solesio-Jofre et al., 2018).

Balazova et al. (2021) conducted a six-month motor learning intervention study comparing older adults in a dance program (n = 36, mean age: 69.2 years) with a control group following their usual routine (n = 32, mean age: 69.0 years). The dance group underwent rs-fMRI scans prior to and upon completion of the intervention, while the control group had two rs-fMRI scans at the same intervals but without any intervention. The dance program included 60minute lessons, three times per week. Using Independent Component Analysis, the researchers identified 10 functional networks and found an interaction effect between group and time for the default mode network (i.e., intra-network FC). Specifically, FC increased in the precuneus in the dance group and decreased in the control group. Regarding internetwork FC, baseline differences were found between groups, with higher FC in the control relative to the dance intervention group for the following connections: cerebellum-visual network, cerebellum-language network, and language-sensorimotor network. Significant group x time interactions were also observed. The dance group, compared to the control group, showed increased FC between (1) the salience and right frontoparietal network, (2) the visual and language network, (3) the visual network and DMN, (4) the cerebellar and visual network, and (5) the cerebellum and language networks. The authors also found that traininginduced changes in the right frontoparietal and salience networks correlated with improvements in attention and executive function. However, some of these connections

already demonstrated group differences at baseline. The greater number of findings related to inter-network FC compared to intra-network FC may be linked to network dedifferentiation seen in aging populations.

Monteiro et al. (2019) investigated motor training-induced changes in FC within cortical and subcortical (basal ganglia and cerebellum) regions during rest and bimanual (BTT) performance. They studied young (n = 25, mean age: 21.5 years) and older (n = 18, mean age: 68.6 years) adults practicing the BTT (see section 3.1.1.1 for details on the task) over five sessions across two weeks, with fMRI scans administered at the start and after two weeks of practice. Despite similar improvement rates in task performance across both age groups, the study did not identify significant changes in resting-state or task-based FC associated with the two-week practice in either of the age groups, nor any interaction effects related to aging. Furthermore, corroborating earlier findings of reduced segregation among different networks with advanced age (King et al., 2018), older adults showed higher between-network FC among cortical structures during both rest and task execution (pre- and post-tests combined) compared to their younger counterparts (Monteiro et al., 2019). Notably, greater betweennetwork connectivity at the cortical level was associated with poorer task performance, suggesting that such increased inter-network FC (i.e., reduced inter-network segregation) may not be beneficial in older adults (see also King, Saucier, et al., 2017). With regard to intranetwork FC, the results were mixed. While resting-state FC was generally lower in older than younger adults, it showed both network-specific increases and decreases during task performance.

Solesio-Jofre et al. (2018) studied modulations in resting-state FC following dedicated motor practice in the context of aging by exploring both inter- and intrahemispheric connectivity changes within a broader motor network. Specifically, young (n = 23, mean age: 21.19 years) and older (n = 21, mean age: 68.85 years) adults underwent a two-week extensive training intervention, which consisted of five training sessions focused on learning the BTT (see section 3.1.1.1 for details on the task). At the beginning (on the 1<sup>st</sup> day) and end of training period (after two weeks of training), rs-fMRI scans were conducted before and after short task performance (36 minutes in total) to evaluate short-term changes in FC, i.e., following a short session inside the scanner. Modulation in FC within and between motor-related areas was explored using a priori selected regions based on results obtained by Monteiro et al. (2017),

i.e., bilateral SMA, PMd, ventral premotor area (PMv), M1, and primary somatosensory area (S1). At the behavioral level, older adults performed the task generally worse compared to young adults but exhibited larger gains in performance. At the neural level, resting-state FC was differently modulated in young and older adults. Specifically, both inter- and intrahemispheric FC during resting-state increased in young adults but decreased in older adults as a result of short task performance during the early (on the first day) and late training phase (after two weeks of training). Regarding long-term practice effects (comparing FC prior to the first practice session with FC upon completion of the last practice session), an increase in intrahemispheric connectivity within the right hemisphere was observed across both age groups while interhemispheric connections were not altered at group level. Interestingly, at the inter-individual level, long-term training-induced increases in interhemispheric FC (although not significant in itself at group level) were related to behavioral improvements in motor performance in both age groups. The latter finding indicates that the motor network at rest might contribute to adapting the motor system, facilitating motor skill learning, irrespective of age.

Aznárez-Sanado et al. (2022), examined changes in FC during and between the early (single session) and late stages (after three months of daily practice) of motor sequence learning in middle-aged adults (for details on task and participants, please see section 3.2.1). Regions of interest for FC analyses were determined based on overlapping functional activations during early and late learning stages, as well as differences between the two stages. FC between the left precuneus seed area (five-millimeter sphere) and every other voxel in the brain was measured. Connectivity between left precuneus and bilateral middle cingulate cortex, right cerebellum, left angular gyrus, left IPL, and left middle occipital gyrus reduced from the early to late stage of learning. No significant increases in FC were observed from early to late learning were critical for developing new visuospatial motor representations and became less important during late learning. Additionally, FC was modulated by age, with lower FC observed between the left putamen and parietal cortex, posterior cingulate, and middle orbital frontal gyrus as age increased, especially during the late learning stage when movements became more automatized.

Maes et al. (2020) studied the effect of task complexity on FC seeded from PMd and how this effect is modulated by age and task practice. Young (n = 16, mean age: 21.4 years) and older (n = 14, mean age: 66.8 years) adults practiced the BTT (see section 3.1.1.1 for details on the task) over three days of training. A challenging practice scheme was used in which task variants of different complexity levels were randomly presented (CI effect, see above). Additionally, two distinct conditions for visual feedback were introduced, i.e., after-trial and continuous feedback, reflecting internally or externally generated movements, respectively. Task-based fMRI scans were obtained during the first (early phase of learning) and last (late phase of learning) day of training. Behaviorally, older relative to young adults performed poorer on the BTT, but equally improved with practice across task variations. Bilateral PMd areas were chosen as seeds for the FC analysis, as this was considered a critical region for dealing with task complexity and motor learning in both age groups. For internally generated movements, PMd-seeded FC was not differently modulated in older versus young adults from early to late phases of learning. In both groups, FC between right PMd and bilateral frontal areas increased following training. However, for externally generated movements, FC between the left PMd and bilateral cerebellum, as well as the left lateral occipital region, young adults demonstrated a significantly greater increase from the early to late phase of learning, compared with older adults. The authors argued that PMd-cerebellar as well as PMd-occipital connectivity is particularly important for the integration of intended versus actual motor output based on the provided feedback. These findings appear to suggest that the ability to modulate functional coupling between PMd and task-specific brain areas in relation to motor practice is diminished at older age.

To study the role of CI in motor learning in older adults, Lin et al. (2012b), administered an SRTT (random or blocked practice schedule) to 16 older (mean age: 66.2 years) and 16 younger (mean age: 26.4 years) participants over the course of two days. Three days later, participants performed a delayed retention test during which fMRI data was acquired (i.e., task-fMRI). Results demonstrated a beneficial effect of random practice on task performance at the retention test in young and older adults. At the neural level, random practice resulted in higher FC at retention in older relative to younger adults between the following brain regions: (1) right and left DLPFC, (2) right PMd and inferior parietal lobe, and (3) right DLPFC and left inferior frontal gyrus. The reversed contrast, i.e., higher FC in younger relative to older

participants, revealed a significant effect between the right DLPFC and SMA. Additionally, in young adults, a positive correlation was found between the learning benefits of random practice and increased FC between the right DLPFC and SMA, as well as between right DLPFC and inferior frontal lobe. This is line with the idea that practicing under conditions of CI may strengthen connectivity between prefrontal and premotor areas with other brain regions, leading to improved performance on the SRTT. In contrast, in older adults the benefits of random practice were positively associated with FC between right PMd and inferior parietal lobe, the right DLPFC and rostral frontal lobule, and between bilateral DLPFCs. The authors posited that for older adults, random practice particularly strengthened sensorimotor integration, as reflected by the key role of the right PMd. Moreover, (pre)frontal connectivity appeared to be somewhat more prominent in older adults at retention, suggesting increased cognitive control.

Notably, Lin et al. (2016) also employed a network analysis on the same fMRI retention data (Lin et al. (2012a)) acquired during SRTT training to uncover the underlying Cl graph theoretical networks. Graph theoretical network analysis refers to mapping how distinct brain regions are connected and exchange information with each other. Lin and colleagues' analysis revealed that brain networks were characterized by stronger connections between brain regions following random practice compared to blocked practice. Both young and older adults performed better on retention (three days after training), i.e., shorter reaction times, after practicing a random rather than blocked practice order. Intriguingly, these findings demonstrated that in young adults, the CI networks showed a small-world topology during retention, which refers to the idea that the brain is organized in a way that allows for both local specialization and efficient global communication, i.e., an optimal balance between functional integration and segregation (Watts et al., 1998). This beneficial network architecture was not observed in older adults (Lin et al., 2016). These findings appear to suggest that the neural networks supporting CI benefits in motor sequence learning can differ with age, and they highlight that age can affect the utilization of neural substrates in memory consolidation and retrieval processes.

Overall, it appears that training-induced modulation of FC can occur in both young and older adults at short and longer time scales but there are also studies not showing such effects or smaller effects in older adults. The direction of this modulation is less consistent across age

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groups and may depend on task characteristics, training context, the duration of training, the brain areas targeted, and whether resting-state or task-related FC is studied. Note also that individual differences (or changes) in FC patterns are sometimes associated with task performance (Monteiro et al., 2019; Solesio-Jofre et al., 2018). Solesio-Jofre et al. (2018) reported increases in inter-hemispheric FC as a function of practice to be positively associated with task performance across both age groups (Solesio-Jofre et al., 2018). Monteiro et al. (2019) found that greater inter-network FC (averaged over pre-and post-intervention measurements) was negatively associated with task performance.

Despite variation in findings across the studies, network organization clearly is different between young and older adults, which appears more apparent for inter-network connectivity than intra-network connectivity. A well-replicated finding is that inter-network FC is generally increased in older adults (i.e., reduced network segregation). This appears less than optimal because increased inter-network FC tends to be associated with reduced motor performance (King, Saucier, et al., 2017; Monteiro et al., 2019). The question then emerges whether network segregation can be altered (inter-network FC reduced) with task practice in older adults. Findings thus far are inconsistent, showing increases, decreases, or no changes in internetwork FC after training in aging individuals. This may reveal an apparent underlying conflict in current connectivity research. On one hand, one might argue that training-induced decreases in inter-network FC (that is typically higher in older than young adults) may reflect an improvement in segregation. On the other hand, training-induced increases in internetwork FC may be a proxy of improved collaboration between task-related networks and mark enhanced information integration for skilled performance. This effect may also differ between training-induced changes in resting-state versus task-related inter-network FC.

The findings may also shed light upon brain network efficiency, i.e., the capability to deactivate non-task related networks while activating task-related networks during behavioral performance. There is some evidence in older adults that brain activity in regions typically associated with the DMN (like medial PFC, posterior cingulate cortex, angular gyrus, hippocampus, and lateral temporal cortex) are differently modulated according to CI practice schedules with DMN brain activity being more reduced during the more challenging random practice arrangement. Moreover, training-induced increased deactivation of posterior cingulate cortex was correlated with increased retention performance following random

practice in older adults (Pauwels et al., 2018). In other words, the training-induced ability to suppress this core region of the DMN could be beneficial for skill retrieval. This suggests that older adults can modulate brain networks through learning such that inter-network segregation is enhanced (i.e., inter-network FC decreased) under specific conditions.

## 3.3 Brain neurochemicals: the role of y-aminobutyric acid (GABA) in motor learning

y-aminobutyric acid (GABA) is an inhibitory neurotransmitter and crucial for optimal brain function such as the neural processes accompanying learning and memory (Le Roux et al., 2008; Trepel et al., 2000). Levels of neurochemical substrates (including GABA) can be determined in the brain by means of MRS, which is a non-invasive MR-imaging technique used to measure the concentration of specific metabolites in the brain. In general, MRS studies conducted in *young adults* have demonstrated that the acquisition of a novel motor skill (concerning short- or long-term motor learning) is accompanied by a decline in GABA levels (e.g., Floyer-Lea et al., 2006; Kolasinski et al., 2019; Sampaio-Baptista et al., 2015). These practice-related reductions in GABA levels are believed to promote synaptic plasticity because the reduced inhibition paves the way for increased inter-neuronal communication (Stagg, 2014; Stagg et al., 2011). However, note that others have revealed no changes during motor task learning (e.g., Bell et al., 2023; Eisenstein, 2024; Rasooli et al., 2024). In addition, baseline GABA levels in the sensorimotor cortex are associated with both initial and late motor learning capacity in young adults (Kolasinski et al., 2019; Li, Chalavi, et al., 2024). However, Bell et al. (2023) observed no correlation between baseline GABA levels and motor skill acquisition.

Despite notable research efforts on this topic in young adults, albeit with contradictory findings, our understanding of the role of pre-training GABA levels in predicting future learning and learning-related GABAergic modulation in the healthy aging population remains limited. This gap is surprising, as older adults often show motor learning and memory impairments and demonstrate diminished GABA concentrations in various brain areas (Cassady et al., 2019; Chalavi, Pauwels, et al., 2018; Cuypers et al., 2020; Gao et al., 2013; Hermans et al., 2018; Maes et al., 2021; Porges et al., 2021).

Chalavi, Pauwels, et al. (2018) investigated how motor learning affects GABA levels in the sensorimotor (SM1) and occipital (OCC) region during bimanual task learning (BTT, see section

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3.1.1.1 for details on the task) in both young (n = 32, mean age: 21.8 years) and older adults (*n* = 28, mean age: 66.5 years). Training was performed either following a blocked or a random practice schedule (refer to 3.2.1 on CI). The study revealed distinct alterations in OCC GABA levels but not in SM1 between the pre-training and post-training timepoints based on the type of practice structure employed. In the random practice group, GABA concentrations in OCC decreased, while with blocked practice they increased. These changes were evident across age groups, but older adults demonstrated a statistically stronger effect. While a decrease in GABA (random practice) is considered critical for plasticity in the cortex, the authors proposed that higher GABA levels (blocked practice) might enhance the accuracy of neural responses by inhibiting irrelevant neurons and fine-tuning task-specific neuron activity. Additionally, repeated exposure to a stimulus tends to diminish neural responses, suggesting a more efficient representation and processing of that stimulus. The authors speculated that occipital GABA levels may have rapidly adjusted during the early stages of learning in the blocked practice group. Since the task involved repetitive practice over nearly an hour with the same frequency ratio, this scenario aligns with a repetition suppression effect (Chalavi, Adab, et al., 2018). This likely led to increased GABA levels in the occipital region, reduced activity in irrelevant neurons, heightened activity in task-relevant neurons, and ultimately improved neural processing and performance. In sum, these findings appear to suggest that practice schedules may affect GABA levels in the brain differently while aging may mediate this effect. However, future research is needed to confirm these observations.

Another study, exclusively focusing on older adults (> 60 years), examined changes in GABA levels in SM1 and resting-state functional connectivity (FC) associated with initial learning of a motor sequence task (12 practice blocks, ~16 minutes in total) followed by anodal tDCS (King, Rumpf, Verbaanderd, et al., 2020). One group received tDCS following the practice sessions (n = 17, mean age: 66.6 years), whereas the other group received sham stimulation (n = 19, mean age: 67.6 years). Behaviorally, clear learning effects were noticed in both groups from the beginning towards the end of the session. At the group level, neither GABA levels nor FC between M1 and task-relevant networks were modulated by motor learning or subsequent anodal tDCS. However, individual variations in learning-related GABA level changes were associated with the extent of learning, baseline GABA levels, and age. A stronger reduction in GABA due to motor practice was linked to both a larger extent of learning and higher baseline

GABA levels, as well as to younger age. Therefore, younger individuals showed a more pronounced reduction in GABA and experienced greater learning gains. Since baseline GABA concentrations decrease with increasing age (Gao et al., 2013; Hermans et al., 2018; Maes et al., 2021), the ability of GABA to show modulation may also be decreased with aging. The group level findings differ from previous studies in young adults (Floyer-Lea et al., 2006; Sampaio-Baptista et al., 2015) but align with those of Chalavi, Pauwels, et al. (2018), where practice on the BTT also failed to modulate SM1 GABA levels in young as well as older adults. Nevertheless, individual GABA levels can be modulated as a result of task practice in older adults, and it may partly depend on sufficient baseline GABA levels. Additionally, the authors investigated the relationship between (changes in) GABA levels, (changes in) FC and motor learning. They found that baseline GABA levels in SM1 were positively associated with training-induced inter-network FC changes. Overall, the study indicated that reductions in sensorimotor GABA levels related to motor learning, along with increased FC, were primarily observed in those older adults who had higher baseline GABA levels and demonstrated more learning (King, Rumpf, Verbaanderd, et al., 2020).

In sum, some studies report no group-level modulation of GABA in sensorimotor areas in response to motor learning in either younger or older adults, which, at least for the younger group, contradicts previous findings. Specifically, in younger adults, the majority of studies have reported a motor training-induced reduction of GABA (Li, Rodriguez-Nieto, et al., 2024). Nonetheless, the observed associations between the individual level of GABA modulation and skill acquisition suggest intriguing relationships that warrant further investigation. Clearly, more research encompassing a diverse array of motor learning tasks as well as a wider range of brain regions of interest to quantify local GABA levels is warranted. Moreover, this work can be complemented by a focus on excitatory neurotransmitters to obtain insights into the balance of inhibition and excitation in the brain and its changes during learning. Such endeavors are vital to gain a deeper understanding about whether and how age impacts the modulatory effects of local neurochemical levels in relation to learning.

## 3.4 Neurophysiological mechanisms and their modulation

TMS protocols are instrumental in investigating the effects of aging on motor learning and the associated neurophysiological changes. Using TMS, corticospinal excitability (CSE) can be

assessed by applying single magnetic stimuli to M1 and measuring the resulting motor-evoked potentials (MEPs) in a target muscle. In addition, inhibitory and/or facilitatory circuits within M1 can be investigated using paired-pulse TMS. Here, the first stimulus, known as the conditioning stimulus (CS) potentially modulates the MEPs resulting from the second stimulus, called the test stimulus (TS), which is applied a few milliseconds after the CS. Depending on whether the paired pulses result in smaller or larger MEPs as compared to single pulses, this modulation can be characterized as inhibitory (e.g., Short-Interval Intracortical Inhibition (SICI), Long-Interval Intracortical Inhibition (LICI), etc.) or facilitatory (e.g., Short-Interval intraCortical Facilitation (SICF)), respectively (Hallett, 2007).

# 3.4.1 Corticospinal excitability

Studies applying TMS have provided important evidence into the plasticity of M1. For example, cortical finger representations can increase in size after years of practicing sensorimotor skills (Pascual-Leone et al., 1993), or they can decrease as a result of peripheral injury such as amputation (Flor et al., 1995). Motor training has repeatedly shown effects on CSE which are comparable in young and older adults. However, distinct effects have been observed for different motor tasks. For example, training on a visuomotor task led to an increase in CSE after training, whereas training on a ballistic motor task (i.e., brief muscle contractions at maximum velocities and accelerations) did not significantly influence CSE for either age group (meta-analysis of 11 studies with a total of younger adults: *n* = 132, mean age: 22.4 years; older adults: n = 128, mean age: 68.1 years; see Berghuis et al. (2017)). Note that the studies included in this meta-analysis had a mean practice duration of 13 minutes, constituting the very early (initial) learning phase. Moreover, this meta-analysis revealed that motor skill learning was not directly associated with CSE changes in both age groups. Additionally, training of a metronome-paced finger tapping sequence with the dominant hand (five blocks of practice (one minute each), with 30 seconds rest between blocks) did not influence CSE at rest of the non-dominant hemisphere, neither in young (n = 15, mean age: 26.2 years) nor in older (n = 11, mean age: 63.7 years) adults (Nuzum et al., 2021). Of note, not only the trained motor task itself, but also the specific training schedule (i.e., CI effect) may determine the effects of motor training on neurophysiological measures. In a study by Lin et al. (2012a), young (n = 16, mean age: 26.4 years) and older (n = 16, mean age: 66.2 years) adults practiced a visually cued four-element SRTT with their left hand following blocked

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practice or randomized practice for two successive days, followed by a retention test five days later (Lin et al., 2012a) (see 3.2.1 for more detail about the CI effect). CSE at rest was shown to be increased after random practice, whereas blocked practice led to a less pronounced or undetectable CSE increase after training in older and young adults, respectively. The increased CSE after random practice was significantly more pronounced in the group of older relative to younger adults. Moreover, since this increase in CSE was positively correlated with sequencespecific learning (i.e., improvement in key-pressing speed) in both young and older adults, it was suggested to be vital for motor learning-related cortical neuroplasticity (Lin et al., 2012a).

## 3.4.2 Inhibitory TMS measures

Regarding paired-pulse TMS, thus far only inhibition and specifically SICI, measuring GABAAreceptor mediated inhibition in M1 (Ziemann et al., 2001), has been investigated in the context of motor learning and aging. Although similar baseline SICI values have been reported for young and older adults, inhibition (i.e., SICI) was decreased by approximately 20% in older but not young adults after training on a visuomotor task for an average duration of 13 minutes (for review see Berghuis et al., 2017). In contrast, ballistic motor training with a similar duration did not lead to detectable changes in inhibition (for review see Berghuis et al., 2017). Note that prior to the intervention, there were no differences in ballistic motor performance between age groups, whereas visuomotor performance was significantly poorer in older adults compared to younger adults. With regards to motor learning, the extent of skill acquisition was significantly lower in older relative to young adults following ballistic task practice. However, on the visuomotor tasks, age did not influence motor skill acquisition (Berghuis et al., 2017). In an experimental paper published later, practicing a complex sequence of finger tapping with the dominant hand for approximately five minutes was reported to increase inhibition in the untrained hemisphere of young (n = 15, mean age: 26.2 years), but not older (*n* = 11, mean age: 63.7 years) adults. Note that there were no effects of age on task performance or learning, with both groups showing improvements post-training in the trained hand (Nuzum et al., 2021). Furthermore, the meta-analysis by Berghuis et al. (2017) revealed that a greater increase in inhibition after training on a visuomotor task was associated with higher levels of motor skill acquisition in young adults, whereas there were no significant correlations for older adults or for motor training on a ballistic task.

By combining the outcomes of CSE and inhibition measurements, it appears that motor training schemes that are rather complex in that they involve multisensory integration (e.g., visuomotor task) or integration of streams of movements over time (e.g., sequential finger tapping task) appear more likely to influence neurophysiological brain measures obtained at rest as compared to simpler motor task training without such integration components (e.g., ballistic motor task) for both young and older adults. Furthermore, the aforementioned TMS results suggest an overall increase in CSE and decrease in inhibition in young and older adults in visuomotor task training, which might be connected. Whereas most authors found this increased CSE/decreased inhibition post training to be more pronounced in older adults (Berghuis et al., 2017; Lin et al., 2012a), others report a larger change in young adults (Nuzum et al., 2021). It should be considered that measuring CSE and inhibition at rest might not be specific enough to detect changes related to learning. Rather, measuring TMS outcomes during execution of the learned task or muscle contraction, or during movement preparation might lead to more profound insights into motor learning in older adults (Berghuis et al., 2017).

# 3.5 Optimizing motor skill learning in older adults through Non-Invasive Brain Stimulation techniques (NIBS)

Here, we explore various non-Invasive Brain Stimulation (NIBS) techniques aimed at optimizing motor learning in older adults through modulation of learning-related mechanisms. Numerous human studies have demonstrated that NIBS can enhance motor skill learning (see reviews by Ammann et al., 2016; Bolognini et al., 2009). Other studies have not observed such effects in young adults (Vancleef et al., 2016), or found no consistent differences in the effects of various NIBS techniques on motor learning (Lopez-Alonso et al., 2018). We delve into four NIBS techniques that are commonly used: (1) transcranial Direct Current Stimulation (tDCS), (2) transcranial Alternating Current Stimulation (tACS), and (3) Paired-Associative Stimulation (PAS), and repetitive TMS (rTMS). tDCS involves the application of a low constant electrical current to the scalp through electrodes. We will discuss its potential to enhance motor learning in older adults and examine the multitude of factors that can influence its effectiveness. In contrast, tACS targets brain oscillations (i.e., the rhythmic or repetitive patterns of neural activity observed in the central nervous system) and their

frequencies. Our discussion will revolve around how tACS impacts motor learning in aging individuals and the diverse effects observed with different stimulation frequencies. PAS combines peripheral nerve stimulation and TMS to modulate neuroplasticity during learning. We will investigate how PAS protocols may influence motor learning and whether these have potential for improving motor skills in older adults. Finally, rTMS involves delivering repeated magnetic pulses to specific brain areas to induce lasting inhibition or facilitation during or beyond the stimulation period (i.e., online vs. offline effects). The effects are highly dependent on the specific pulse paradigm and have the potential to facilitate motor performance and learning.

## 3.5.1 Transcranial direct current stimulation (tDCS)

Improved synaptic efficacy seems to play a key role in motor skill learning. Long-term potentiation is proposed as a physiological mechanism driving improvements in motor skill acquisition induced by tDCS in young adults. However, the positive *retention* effects of anodal tDCS appear to depend on the interplay between task features and the specific parameters of the tDCS application (for review, see Guimaraes et al., 2023). To date, evidence on the effectiveness of tDCS to support motor learning in healthy aging is equivocal. Zimerman et al. (2013) reported that in a sham-controlled crossover tDCS study, a finger-sequence tapping task training combined with anodal tDCS (atDCS) over left M1 composed of five three-minute blocks, significantly enhanced right-hand sequence tapping performance in healthy older (n = 10, mean age: 68.5 years) but not in younger adults (n = 10, mean age: 25.2 years). Furthermore, the authors reported that these beneficial effects lasted for at least 24 hours after the end of the intervention. Notably, the older the participant, the greater the performance improvement observed with atDCS. Although the sample size was limited (n =10), these findings appear to suggest that atDCS-enhanced training may have a more substantial impact on older participants. Dumel et al. (2018a) revealed that a five-day (20 minutes/day) at DCS (n = 18) intervention as compared to sham tDCS (stDCS; n = 19) over left M1 during practicing an SRTT with the right hand significantly improved motor learning in healthy older adults (mean age: 61.0 years; no control group of young adults). Aftereffects lasted up to three months. The same research group also showed a generalization effect to an untrained Purdue Pegboard test in aging individuals (n = 32, mean age: 62.0 years) after a similar five-day (20 minutes/day) atDCS (n = 16) vs stDCS (n = 16) intervention combined with

SRTT training, assessed one day after the end of the intervention. Furthermore, this transfer effect was significantly correlated with a reduction of GABA<sub>B</sub>-receptor mediated intracortical inhibition from pre- to post-training (i.e., the higher the disinhibition, the better the performance on the Purdue Pegboard task) as measured using a TMS-derived long-interval intracortical inhibition (LICI) paradigm (Dumel et al., 2018b).

Rumpf et al. (2017) studied the effect of a single session (15 minutes) atDCS over left M1 (n = 12, mean age: 65.1 years; no control group of young adults) following explicit motor sequence learning (five-element finger tapping with the right hand) in older adults and found that retest performance at 8 and 22 hours after training was significantly improved as compared to cathodal tDCS (ctDCS; n = 11, mean age: 65.3 years) over M1, atDCS over the premotor cortex (n = 12, mean age: 64.3 years), or sham tDCS (n = 12, mean age: 66.7 years). Notably, the results revealed better consolidation of motor memories when atDCS was applied immediately post-training, contrasting with no effects observed when applied one or two hours at the end of the practice session.

Although these studies revealed beneficial effects of tDCS on motor performance and learning in older adults, other studies report more ambiguous, undetectable, or even adverse effects. King et al. (2020) showed that one session of atDCS (15 minutes; n = 20, mean age: 67.8 years) over the non-dominant (right) M1 *after* motor training hindered consolidation of a left-hand motor sequence learning task (four-element finger tapping), as compared to stDCS (n = 20, mean age: 67.3 years) in healthy older adults. However, no control group of young adults was included. This disruption of consolidation on the behavioral level was paralleled by sustained engagement of brain areas which are important for initial learning as revealed by task-related fMRI, while these regions generally showed a decrease in activation after successful initial learning (King, Rumpf, Heise, et al., 2020). In contrast, atDCS (n = 18, mean age: 65.8 years) over the dominant (left) M1 after motor training had no effect on the right-hand motor sequence learning task when compared to stDCS (applied during motor training) in a sample of older adults (n = 17, mean age: 65.8 years) when the hand respectively contralateral to the stimulated M1 was trained (King, Rumpf, Heise, et al., 2020).

In line, Raw et al. (2016) did not find improvements in learning a sequential aiming task using a handheld stylus after a single session (30 minutes) of dominant (left) M1 atDCS or non-dominant (right) M1 ctDCS in a sample of healthy older adults (n = 17, mean age: 69.8 years).

In a group of older (n = 16, mean age: 75.0 years) and younger adults (n = 16, mean age: 23.0 years), Mooney et al. (2019) reported no effect of 20 minutes of atDCS (as compared to sham) applied over the non-dominant M1 during training of a sequential visual isometric wrist extension task with the non-dominant hand on skill acquisition or retention. While for both age groups no significant learning effects were observed, the results showed increased corticomotor excitability and decreased intracortical inhibition as measured with TMS. Whereas most studies have focused on M1, Greeley et al. (2022) investigated the effects of two 20-minute sessions of atDCS over the right and left PFC, SMA, and left M1 in a group of young (n = 64, mean age: 20.5 years) and older adults (n = 63, mean age: 70.7 years). They demonstrated in the older adults sample that atDCS over the right PFC and SMA hindered motor learning during three-day practice of a motor sequence task with the right hand (i.e., slower gains in reaction times during atDCS compared with sham). Similarly, atDCS over the left PFC hindered motor learning, but this effect was notable as slower gains in chunking performance. Authors attributed their findings, i.e., atDCS-induced hampering of learning, to the potential disruption of the right PFC involvement in early sequence learning and the left PFC in chunking, which is the ability to group individual elements for better memorization. Furthermore, the authors indicated that older and younger adults were impaired to the same extent. In conclusion, there was no beneficial effect of any type of atDCS in the older adults with regards to sequence learning.

Ghasemian-Shirvan et al. (2023) investigated the effect of different atDCS (1, 2, 3 mA or sham) intensities applied over left M1 on motor learning in healthy older adults (*n* = 25, mean age: 72.1 years; no control group of young adults). A sham-controlled cross-over design was used (i.e., all participants participated in single sessions receiving one intensity per session, spread over a period of four weeks). An SRTT was performed with the right hand on two consecutive days with tDCS accompanying SRTT performance on the first day and recall performance on the second day of the same sequence. The authors found that all atDCS conditions (1, 2, 3 mA and sham) resulted in decreased reaction times on day 1 (training with atDCS) and day 2 (recall), indicative of implicit motor learning and memory consolidation. Overall, it can be concluded that effects of atDCS on motor learning did not significantly differ between the various stimulation intensities and sham.

In summary, the above-mentioned tDCS studies yielded mixed results, demonstrating positive, undetectable, or even negative effects on motor learning. Note that this ambiguity in results is rather general to tDCS research and is not restricted to aging research in particular. In this respect, it should be noted that the precise mechanisms behind the effects of tDCS are still not fully understood and likely depend on a combination of several factors, such as stimulation location, intensity, duration, timing (during or post-training), electrode montage, electrode size/shape, number of sessions, scalp properties, and individual brain anatomy (Thair et al., 2017). Even though tDCS in older adults may enhance motor learning under specific conditions, the inconsistent findings so far raise questions about the precise conditions necessary to achieve beneficial effects. Moreover, future studies should include younger control groups in the study design to enable age-specific conclusions.

# 3.5.2 Transcranial alternating current stimulation

While tDCS is expected to modulate the brain's excitability, transcranial alternating current stimulation (tACS) is believed to interact directly with the natural brain oscillations that can be observed according to different frequency bands with the alpha ( $\alpha$ ), beta ( $\beta$ ) and theta ( $\theta$ ) bands being most frequently targeted (for review see Bestmann et al., 2017). In young adults, research on the effects of tACS on motor learning has yielded overall positive results (e.g., Hu et al., 2022; Krause et al., 2016; Ma et al., 2021; Miyaguchi et al., 2020; Sale et al., 2022; Sugata et al., 2018), while some report no or negative effects (Giustiniani et al., 2019; Roshchupkina et al., 2020; Wilkins et al., 2024). These effects appear to be influenced by various factors, including stimulation parameters such as frequency, location, timing, the learning stage that is modulated (Byczynski et al., 2023), and the specific task characteristics being learned. In the context of aging, Rumpf et al. (2019) investigated how 10 Hz ( $\alpha$ -tACS, n = 16, mean age: 68.5 years) and 20 Hz ( $\beta$ -tACS, n = 17, mean age: 66.8 years) tACS protocols over left M1 affected motor learning consolidation in healthy older adults when applied after practicing (~20 minutes) an explicit motor sequence learning task with the right hand (Rumpf et al., 2019). No control group of young adults was included. The authors found that, relative to sham, consolidation was impaired after  $\alpha$ -tACS, but not after  $\beta$ -tACS. However, these results need to be interpreted with caution as no significant difference was found between the two tACS conditions when compared directly. Although the mechanisms for explaining these results

remain unclear, it has been proposed that  $\alpha$ -tACS is important in the modulation of inhibitory processes (Mathewson et al., 2011), hindering consolidation.

In another study, the effect of  $\alpha$ -tACS applied over left M1 between two sessions of performing an SRTT with the right hand (duration 12-15 minutes) was investigated in a group of older adults (n = 15, mean age: 61.7 years) (Fresnoza et al., 2020). tACS applied at the  $\alpha$  peak frequency ( $\alpha$ tACS) and at the  $\alpha$  peak frequency plus 2Hz ( $\alpha$ 2-tACS) improved general motor skill and sequence-specific skill consolidation. As compared to their older counterparts, younger participants (n = 20, mean age: 23.8 years) only showed a slight improvement in general motor skills and even demonstrated impaired sequence-specific consolidation after  $\alpha$ tACS. Additionally, consolidation was impaired after  $\alpha$ 2-tACS for both general motor and sequence-specific skills in the young adults. Overall, these results suggest that  $\alpha$  rhythm tACS applied after task performance could be beneficial for the consolidation of some motor skills in older individuals, while being disadvantageous in young adults.

Also, the effect of bifocal  $\theta$  (4-8 Hz) range tACS over the right frontoparietal network during motor sequence learning with the right hand (training duration: 20 minutes) on two separate days was investigated in older adults (*n* = 21, mean age: 69.6 years, no control group of young adults) (Draaisma et al., 2022). This intervention resulted in improved performance (i.e., higher speed and accuracy) when sequence learning had a high relative to a low working memory load. The authors suggested that the effectiveness of bifocal  $\theta$ -tACS applied simultaneously to frontal and parietal regions depends on the cognitive demands of the specific motor task being performed.

Taken together and based on the limited evidence available so far, it appears that tACS could potentially be an effective tool to support motor learning in healthy aging. However, of the reported studies, most did not include a control group of young adults, and the one study with a young control group even showed negative (i.e., hindering learning) effects of tACS in the young control group. Hence, further research is required on the mechanisms behind agerelated differences and impact of tACS on motor learning. It appears that the tACS stimulation protocols may entrain the natural brain rhythms, paving the way for enhanced neural processing during motor learning and consolidation. Future studies should also take younger control groups into account in the study design to allow for conclusions specific to age groups.

3.5.3 Paired-associative stimulation (PAS)

In the PAS paradigm, a TMS stimulus delivered to M1 is preceded by a percutaneous electrical stimulus to a peripheral nerve a few milliseconds earlier, to positively influence the level of neuroplasticity, either measured in motor skill performance/acquisition or in neurophysiological TMS outcomes. So far only two studies have investigated the effect of PAS on motor learning in the context of aging (Opie et al., 2019; Opie, Pourmajidian, et al., 2020). Both studies primed the ulnar nerve and M1 with 200 paired-associative stimulations 20 minutes before motor training on a sequential visuomotor force-matching task in three test sessions, approximately one week apart. In the first study, two different PAS protocols were compared with a control intervention in young (n = 14, mean age: 20.4 years) and older (n = 14, mean age: 13, mean age: 69.0 years) adults (Opie et al., 2019). Each motor training session, consisting of 12 practice blocks with eight self-paced five-target sequence repetitions, was preceded by PAS. The interstimulus interval (ISI; between peripheral and central stimuli) was equivalent to the latency of the N20 response after peripheral stimulation plus five milliseconds to induce long-term potentiation. Although it was hypothesized that the PASLong term potentiation (LTP) protocol would enhance model-based motor learning, it unexpectedly led to a decrease in motor skill acquisition during the training period in both young and older adults. In addition, post-training performance was negatively affected in older adults but was not significantly affected in younger adults following both PAS<sub>LTP</sub> and PAS<sub>Long term depression (LTD)</sub>. The latter protocol (PAS<sub>LTD</sub>) used an inter stimulus interval set to the latency of the N20 response to ulnar nerve stimulation minus 10 milliseconds, aiming to reduce M1 excitability through long-term depression. Lastly, neither PAS protocol affected performance in the 24-hour retention test (Opie et al., 2019).

In a second study, older adults (n = 30, mean age: 68.2 years) were assigned to one of two PAS conditions: (1) a PAS<sub>LTD</sub> protocol with a fixed ISI of 10 milliseconds, or (2) a control intervention with an inter stimulus interval of 100 milliseconds. All participants were trained on the same sequential visual isometric task for three consecutive days, completing 12 practice blocks with 8 self-paced sequence repetitions each. PAS was performed prior to the practice sessions with the aim to improve skill acquisition and retention (Opie, Pourmajidian, et al., 2020). Here, no significant modifications in motor skill acquisition were observed, i.e., motor skill acquisition did not differ between the two PAS conditions. However, the retention test seven days after the last practice session showed higher retention rates for the PAS<sub>LTD</sub> group as compared to

the control group. The authors also found a predictive value of higher PAS-induced MEP facilitation in the third practice session for better long-term skill retention in older adults (Opie, Pourmajidian, et al., 2020).

In conclusion, the use of PAS as a method to optimize motor learning in aging adults needs further investigation. To date, results indicate that PAS protocols must be chosen with great care and should be specifically tested for the target population since otherwise none (Opie, Pourmajidian, et al., 2020) or even negative (Opie et al., 2019) effects on motor skill acquisition can occur. However, positive long-term effects on motor skill retention in older adults have been reported (Opie, Pourmajidian, et al., 2020), suggesting a beneficial effect of priming motor skill learning with PAS over multiple sessions but further confirmation is required.

## 3.5.4 Repetitive transcranial magnetic stimulation (rTMS)

To enhance motor performance and learning, rTMS can be applied to the motor cortex using a repetitive paired-pulse paradigm (rppTMS; Khedr et al., 2004; Sommer et al., 2001; Thickbroom et al., 2006). This method delivers two pulses to the cortex at short intervals and repetitively, engaging and modulating the excitability of intracortical circuits more robustly than a single pair of pulses. This rppTMS method increases the MEP amplitude (known as SICF) by repetitively applying paired pulses with a short interval between the two pulses (i.e., a few milliseconds) and longer intervals between pairs of pulses (i.e., a few seconds). These are designed to facilitate brain activity (with effects lasting up to 50 minutes) and influence motor behavior in young adults (Benwell et al., 2006; Teo et al., 2012). Through this stimulus pattern and depending on the interval between the paired stimuli, rppTMS targets specific indirect (I)waves, which are known as waves of neural activity that are generated in the motor cortex in response to TMS, after the first direct wave (Di Lazzaro et al., 2001). Multiple I-waves follow the direct wave at different intervals. Aging is associated with changes in brain activity related to late I-waves occur, and these alterations, as assessed by SICF (Opie et al., 2018), have been related to poorer motor control in older adults (Opie, Hand, et al., 2020).

Hand et al. (2023) investigated whether rppTMS applied with different inter-stimulus intervals between the paired pulses could affect these brain circuits in older adults and enhance their motor skill learning. The study involved young (n = 22, mean age: 24.2 years) and older adults (n = 15, mean age: 67.9 years) practicing a target-based isometric pinch task with the right

hand. The effect of two types of rppTMS interventions on motor learning was tested on different days. Two types of rppTMS (and a control intervention) were applied over left M1 (inducing a PA-directed current in M1) at 0.2 Hertz with a 10% jitter, and with inter-stimulus intervals of 1.4 or 4.5 milliseconds between paired pulses, aiming to facilitate early and late Iwaves, respectively. To assess neurophysiological changes due to rppTMS and motor learning, SICF was assessed several times throughout the protocol with both a 1.4 and 4.5 millisecond interstimulus-interval between the CS and preceding TS. These intervals were chosen to match the timing of the I-waves that were influenced by the rppTMS protocol, and for both AP-(targeting later I-waves) and PA-induced (targeting earlier I-waves) currents in the brain. Furthermore, CSE was assessed by comparing the MEP sizes of the test stimulus alone. During each visit, participants were tested on baseline SICF, CSE, and motor performance before the intervention, then again after the rppTMS session, and following early (two blocks of 12 trials) and late (eight blocks of 12 trials) learning phases. The results showed that, in both age groups, rppTMS increased CSE of M1, with the strongest effects observed when using PA-induced currents to measure CSE and when the late I-waves (4.5 millisecond inter-stimulus interval) were targeted during rppTMS. Both age groups experienced improved visuomotor skill learning following the early I-wave facilitatory rppTMS (1.4 milliseconds inter-stimulus interval, but not 4.5 milliseconds) protocol. Finally, in older adults only, both rppTMS and motor learning induced increased CSE in M1 for AP-induced currents during testing. These findings suggest that rppTMS may be beneficial to motor skill learning in young as well as older adults.

# 4 Conclusions and future directions

The present review aims to deepen the understanding of motor training-induced neuroplasticity in the context of healthy aging (see Figure 1 for conceptual overview). Previous research indicated that aging generally affects motor performance, resulting in slower movements and/or reduced accuracy. Nevertheless, most studies show that older adults can improve their motor performance similarly to younger adults. We provide further insight into this retained ability to learn motor skills by showing that improvements in performance are accompanied by both structural and functional alterations in the brain. Additionally, we emphasize that inter-individual variations in brain structure and function are linked to the

degree of motor skill learning in the aging population, indicating that larger gray and white matter volume, as well as better white matter microstructural quality in dedicated brain areas and pathways, respectively, are beneficial to learning new motor skills. Finally, we review noninvasive brain stimulation techniques for optimizing motor learning in older adults, noting their potential benefits while emphasizing the need for careful protocol selection and interpretation.

## 4.1 Motor learning and brain structure

Regarding gray matter in the brain specifically, we can conclude that older adults maintain the ability to alter its volume in response to skill learning. Given that aging is accompanied with a decrease in gray matter and that having larger gray matter volumes seems beneficial for learning, motor skill training could potentially counteract such age-related declines. Some evidence suggests that training-induced increases in gray matter are related to improved motor performance. However, to determine the functional relevance of these volume changes in detail, it is critical to assess these relationships more thoroughly, i.e., in well-controlled longitudinal designs with large sample sizes. Moreover, it is important to note that such effects might be very task specific. This raises questions about generalizability and about whether other approaches exist that promote more generic gray matter effects (such as physical exercise or approaches targeting more generic cognitive (executive) functions that potentially underlie successful motor performance). Moreover, the temporal dynamics of gray matter alterations, i.e., when in the learning process such gray matter changes occur, remain relatively unexplored. Understanding how these changes evolve over time is essential to tailoring interventions. Therefore, we recommend that future studies include multiple assessment points throughout the learning intervention to track gray matter volume changes comprehensively (e.g., Wenger, Kuhn, et al., 2017).

The role of white matter in motor learning in the aging context remains relatively unknown as this is very rarely investigated. From the two studies that have been reported to date, including a six-month dance intervention, we may tentatively conclude that dance trainingspecific increases in volume and microstructural properties can be induced in aging individuals. To further substantiate these findings, expanding such research to different training durations, training protocols, and contexts is required. As for gray matter, applying white matter imaging multiple times throughout training would allow to investigate the

temporal dynamics of change. Note that advanced white matter imaging analyses such as NODDI, FBA, and DKI are needed to understand in detail what kind of neurobiological changes are occurring in the brain's anatomical connections. Moreover, the research performed to date has not sufficiently explored the relationship between training-induced improvements on the motor task at hand and training-induced changes in white matter. Since FA is generally lower in older relative to younger individuals, and training is accompanied with increases in FA and white matter volume in the aging population, one could argue that the traininginduced alterations are beneficial. However, these findings seem to be highly task-specific, and research directly linking training-induced white matter plasticity with increased task performance is currently virtually non-existent in the aging population.

## 4.2 Motor learning and brain function

Studies in young adults typically demonstrate a region-specific increase or decrease in brain activity during learning, with an overall reduction in activity when learning progresses, indicating increased neural efficiency. However, findings in older adults are more varied, with reports of increased, decreased, or unchanged brain activity during and after motor skill learning. Despite this inconsistency, increased activation in certain brain regions, particularly the (pre)frontal and parietal areas, during early learning appears to be associated with better skill acquisition in older adults. While evidence on functional changes during late learning in the aging population is scarce, it could provide valuable insights into how improved skill automaticity leads to greater neural efficiency in the aging population.

With respect to functional connectivity (*FC*), older adults show higher inter-network FC than young adults (i.e., less segregation). Since several studies revealed that this reduction in network segregation is associated with poorer performance, this age-related change in FC may not necessarily be positive. In combination with findings concerning the DMN, less internetwork network segregation in older adults may be indicative of reduced deactivation of non-task related networks. Overall, these indications may be reflective of brain dedifferentiation processes in aging adults. However, there are some indications that learning may promote brain deactivation in older adults (Pauwels et al., 2018). With regard to intra-network FC, limited evidence points towards an increase after practice, which occurs irrespective of age. Overall, it seems that older adults may be able to modulate FC to benefit on a behavioral level, but the results are mixed and depend on factors like training duration, task characteristics,

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targeted brain areas, and whether FC is assessed at rest or during task performance. Apparently, the age-induced reduction in segregation is not easily overcome by training.

When examining *neurophysiological changes* in M1 using TMS after brief motor practice (early learning), complex tasks are more likely to induce changes in CSE compared to simple tasks. Combining this with evidence from inhibitory TMS measurements, a training-induced increase in CSE might be linked to decreased neural inhibition. Although speculative, this change in neurophysiology might be driven by a change in connectivity from simple to more complex motor tasks (within-motor or across systems). However, single- and paired-pulse TMS is a local measurement of neurophysiological outcome measures that does not allow for conclusions about connectivity. Better-suited approaches would be dual-site TMS (Van Malderen et al., 2023) or fMRI. In addition, it is suggested that applying TMS not only at rest, but also during or directly prior to task performance, may reveal important insights into motor learning-induced changes, particularly in older adults.

## 4.3 Motor learning and neurochemicals

While several studies in younger adults have explored GABA modulation in response to motor learning, showing an overall reduction in GABA with learning, other studies do not confirm this. In older adults, evidence is sparse. The limited available data suggests that GABA modulation does occur to a certain extent with motor learning in older adults, with reductions in GABA concentrations potentially benefiting learning. However, at the group level, the effects of GABA modulation are not pronounced.

A key observation in the reviewed literature is that structural and functional brain metrics have predominantly been examined in isolation. Although brain structure and function are inherently related, and both show training-induced changes, they have not yet been analyzed together in this field. However, integrating these modalities would require aligning the duration of practice across studies. Particularly, studies assessing brain structure typically involve several weeks of practice on complex motor skills, while studies on brain function often focus on the initial phase of learning—just minutes of motor sequence practice. This dissociation likely stems from the traditional view that structural brain changes can only occur after extended periods of practice—a notion that recent studies have challenged, particularly in young adults. Combining structural and functional analyses could provide critical insights

into how these are modulated synchronously during motor learning. This recommendation applies not only to aging studies but to research across the lifespan as well.

However, when synthesizing evidence from the different modalities, and accounting for variations in training durations and task paradigms, it is clear that older adults retain the ability to learn new motor skills. This learning is accompanied by changes in neural structures and functions, underscoring that older adults maintain the capacity for training-induced neuroplasticity.

## 4.4 Optimizing motor learning

We examined the impact of NIBS techniques, such as tDCS, tACS, PAS, and rppTMS, as well as practice schedules (specifically the CI effect) on optimizing motor skill learning in older adults. Contrary to our initial expectation that NIBS might have more pronounced effects in older adults compared to younger adults (whose brains might already be functioning optimally), current literature does not (yet) support this hypothesis. Although individual studies do not provide compelling evidence and often present mixed results, there is emerging support for the efficacy of NIBS in enhancing brain function and motor learning in older adults. Nevertheless, further research is needed to clarify the effects of brain stimulation, refine stimulation techniques, and tailor them to the specific characteristics of individual brains. Additionally, the general absence of young control groups in many studies complicates drawing age-specific conclusions about the effects of NIBS on optimizing motor learning. Finally, regarding tACS, which currently yields mixed results in older (and younger) adults, the question arises whether the frequency should be tailored to each participant's individual dominant frequency. Given the observed inter-individual variation in preferred frequency within each of the frequency bands, determining a participant's optimal frequency, through a prior EEG session, could help in setting the target frequency for stimulation, and thereby enhance the effectiveness of stimulation.

With regard to optimizing practice schedules, both young and older adults benefit from the more demanding randomized practice over blocked practice, especially during the retention phase. Overall, random practice tends to stimulate more brain activity, which is associated with improved performance. Aging affects these outcomes, with older adults often engaging different or additional brain regions compared to younger adults, which is likely the result of

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age-related declines in particular brain structures. Thus, older adults can adjust their brain activation and FC to enhance motor learning, suggesting that more complex training programs are beneficial for skill acquisition at any age.

Among methods to enhance motor skill learning, physical exercise is also gaining attention as a neuromodulatory approach. In young adults, exercise shows promise for boosting motor learning by influencing neural mechanisms crucial for consolidation (Ostadan et al., 2016; Robertson et al., 2017; Roig et al., 2012; Roig et al., 2016; Singh et al., 2015; Stavrinos et al., 2017). However, in older adults, the use of cardiovascular exercise to improve motor learning and memory consolidation is still emerging. While acute exercise has demonstrated neuromodulatory effects, its translation into significant behavioral improvements has not yet been demonstrated. Future research should focus on standardizing exercise protocols and addressing variations in timing, intensity, and duration to establish effective interventions. Moreover, a significant body of research highlights the advantages of sleep over wakefulness for consolidating procedural memory tasks, especially motor sequencing skills, in young adults (Diekelmann et al., 2010; King, Hoedlmoser, et al., 2017). Since aging affects both sleep architecture (Hornung et al., 2005; Li et al., 2022) and motor memory consolidation (King et al., 2013; Roig et al., 2014), there is uncertainty about whether these benefits apply to older adults. A review by Backhaus et al. (2016) found limited evidence of sleep-related benefits in older adults, with notable exceptions in studies on gross motor skills like walking (Al-Sharman et al., 2014) and hand sequences (Gudberg et al., 2015). Overall, the impact of sleep on motor learning in older adults is complex and further research is needed to determine under what conditions older adults might benefit from sleep for motor skill consolidation. Factors such as task type, performance level, and encoding depth require additional investigation.

## 4.5 Conclusion

In conclusion, the emerging knowledge of lifelong brain plasticity induced by motor learning holds significant implications for our understanding of aging and the brain's adaptability across the lifespan. The reported findings open up new possibilities for developing new interventions, such as personalized treatments and home-based therapies like NIBS, to promote healthy aging, improve motor and cognitive abilities, and support recovery from

injuries or neurological disorders. As we continue our exploration of the intricate mechanisms underlying the brain's adaptive capacities, we should be better prepared to optimize motor function across the entire human lifespan and particularly improve healthspan (quality of life and independence) for older adults. This will undoubtedly also alleviate the serious socioeconomic consequences of aging and their increasing impact in years to come.

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# CONCLUDING STATEMENTS

- Older adults typically perform worse on motor tasks than younger adults but still show clear traininginduced improvements, though sometimes at a different rate. This demonstrates that the capacity for motor learning is preserved across the lifespan.
- In both older and younger adults, motor training-induced performance improvements are linked to interindividual variations in macro- and microstructural brain characteristics, with greater volume (gray matter) and higher fractional anisotropy (FA; white matter) values generally being predictive of greater improvements.
- Though evidence is limited to tasks like dancing, playing an instrument, and juggling, older adults show (transient) increases in gray and white matter volume and microstructural organization (higher FA values) after several months of practice. However, the temporal dynamics of neural changes remain unclear.
- Since aging implies a reduction of gray and white matter while learning can increase these, motor skill learning may help to counteract age-related brain structural loss. However, these effects might be task-specific, raising questions about their generalizability and whether other approaches, like physical activity, could promote more widespread neural benefits.
- Hyperactivation is prominent in older adults during the performance of motor tasks. Motor traininginduced reductions in functional activations occur in both young and older adults even though the findings are less consistent across studies in the latter group. Increases in activation can also be observed depending on the task features.
- Older adults show higher inter-network functional connectivity (i.e., reduced network segregation) compared to young adults, which is often linked to poorer motor performance. This effect is more pronounced than within-network FC differences. However, older adults can still modulate FC with motor training, although results are mixed and depend on several factors.
- Neurotransmitters play an important role in motor performance and learning. Neurotransmitter levels are lower in older than young adults and this may impact the modulatory capacity of these levels as a function of task training. Although some modulation of neurotransmitters is evident also in older adults, the question is how the baseline levels can be increased to boost task performance and learning at older age.
- Based on TMS research, complex motor tasks involving multisensory or sequential integration affect resting neurophysiological measures more than simpler tasks in both young and older adults. TMS shows increased cortical excitability with motor learning, linked to reduced inhibition, though results vary by age.
- Non-invasive brain stimulation techniques can be used for optimizing motor learning through enhancing cortical excitability, facilitating neuroplasticity, and improving synaptic plasticity. However, the current literature in older adults is limited and reveals inconsistent findings.
- For older learners, optimization of skill acquisition and neural plasticity might result from effective practice organization which may involve more frequent practice, enhanced visual feedback, increased trial-to-trial variation, and more challenging task conditions.

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**Figure 1.** A conceptual overview of the main conclusions on aging, brain plasticity and motor learning. A clear distinction is made between initial and late learning stages. The literature indicates that studies investigating the initial stage of learning are primarily focused on functional brain changes, demonstrating an overall reduction in brain activity and connectivity. Studies addressing the later stages of learning, especially after prolonged practice, predominantly assess brain structure, revealing a (transient) increase in grey and white matter volume and microstructural organization. Baseline measurements, taken before practice, assess individual differences in brain structure as potential predictors of future skill acquisition. We propose that longitudinal intervention studies, incorporating multiple time points and assessing both brain structure and function, would offer valuable insights into the temporal dynamics of motor training-induced neuroplasticity.

## **Declaration of interests**

□ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☑ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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