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Early motor skill acquisition in healthy older adults: functional MRI and connectome correlates

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par

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“Mind and cognition is fundamentally about being embodied into actions in the world. Very simple sensory motor tasks are absolutely key”

Francisco Varela – 1983

Tête dans les nuages…
Pieds sur terre…

Hugues Allamargot - 2010

Acknowledgments

This thesis constitutes the summary of the work I accomplished in the past four years and a half. It also represents the culmination of my academic studies (for now) in which I learned to learn, and most importantly fell in love with the amazing field which is science. I am proud to be part of the scientific community, searching for truths and being humble to recognize what we do not know. Throughout my scientific studies, I had the chance to meet amazing people. The last four years do not deviate from this rule, I had the incredible chance to evolve in an amazing context, within the EPFL laboratory of Professor Hummel based in Geneva.

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Abstract

The capacity for motor learning is impaired in healthy aging. Possible mechanisms explaining this decrement have been proposed, such as weakened acquisition of the motor skill. While the processes at play during the initial acquisition phase have been well-characterized in young adults, they were only scarcely investigated in older adults. The goal of this thesis was to assess the neural processes occurring during the acquisition phase of motor learning in older adults. Successful functioning of the brain is complex and relies on complementary types of organization, i.e. the principles of segregation and integration. In other words, the brain is composed of segregated and specialized brain regions that interact with each other by exchanging information. Motor learning, considered as a key function of the brain, does not deviate from this organization scheme. As such, the investigation of motor learning beneficiates from the study of both functional segregation and integration.

The results of this thesis are based on the acquired data of a multiple-day experiment aiming at characterizing motor learning acquisition and improving sleep-dependent motor memory consolidation in older adults and stroke patients. 43 older adults and 15 stroke patients were included in this project and completed multiple measurements involving, among other methods, a novel motor learning task performed concurrently with functional magnetic resonance imaging.

In the first study of this thesis, we examined the functional specialization of the brain during acquisition of the motor skill by investigating the within-session dynamics and their relationship with behavioral change. The results demonstrated that motor learning ability relied on the parallel involvement of motor-related cortical areas responsible for action selection and associative parietal areas involved in visuomotor processing. In the second study of this thesis, we assessed the integration of information transfer within functional subnetworks by looking at the changes in functional topology and structure-function correspondence in relation to motor learning ability. We were able to show that motor learning ability was associated with higher flexibility in visual and cognitive/associative networks suggested by increased modularity of the functional subnetworks and a detachment of the functional connectome from the structural connectome.

In conclusion, this thesis demonstrates that the acquisition of a motor skill in healthy aging relies on the involvement and flexibility of distributed brain regions organized in networks. The achieved results expand on the existing knowledge of motor learning and offer an indication that multimodal studies are important to comprehend the functional processes of the brain.

Keywords

Motor learning, Acquisition phase, Healthy aging, Magnetic Resonance Imaging, Functional networks, Connectomics

Résumé

L'apprentissage moteur est altéré chez les personnes âgées. Plusieurs mécanismes expliquant ce déclin ont été proposés, tels qu'une acquisition affaiblie de l'habileté motrice. Alors que les processus en jeu lors de la phase initiale d'acquisition ont été bien caractérisés chez les jeunes adultes, ils n'ont été que très peu étudiés chez les adultes plus âgés. L'objectif de cette thèse était d'évaluer les processus neuronaux qui se produisent pendant la phase d'acquisition de l'apprentissage moteur chez les personnes âgées. Le bon fonctionnement du cerveau est complexe et repose sur des types d'organisation complémentaires, à savoir les principes de ségrégation et d'intégration. En d'autres termes, le cerveau est composé de régions cérébrales distinctes et spécialisées qui interagissent entre elles en échangeant de l'information. L'apprentissage moteur, considéré comme une fonction clé du cerveau, ne déroge pas à ce principe d'organisation. Ainsi, l'étude de l'apprentissage moteur et de ses mécanismes a du sens à être conduite en étudiant la ségrégation et l'intégration fonctionnelle du cerveau.

Les résultats de cette thèse sont basés sur les données acquises lors d'une étude visant à caractériser l'acquisition de l'apprentissage moteur et à améliorer la consolidation de la mémoire motrice dépendante du sommeil chez les personnes âgées et les patients victimes d'un accident vasculaire cérébral (AVC). Quarante-trois personnes âgées et quinze patients AVC ont été inclus dans ce projet et ont effectué de multiples mesures impliquant, entre autres, une nouvelle tâche d'apprentissage moteur effectuée simultanément à de l'imagerie par résonance magnétique fonctionnelle.

Dans la première étude de cette thèse, nous avons examiné la spécialisation fonctionnelle du cerveau pendant la phase d'acquisition de l'apprentissage moteur en étudiant la dynamique d'activation cérébrale au fil de la session ainsi que la relation entre l'activation et le changement de performance. Les résultats ont montré que la capacité d'apprentissage moteur repose sur l'implication parallèle des aires corticales liées à la motricité et responsables de la sélection de l'action et des aires pariétales associatives impliquées dans le traitement visuo-moteur. Dans la deuxième étude de cette thèse, nous avons évalué l'intégration du transfert d'information au sein de sous-réseaux fonctionnels en examinant les changements dans la topologie fonctionnelle et la correspondance entre la structure et la fonction en relation avec la capacité d'apprentissage moteur. Nous avons pu montrer que l'apprentissage moteur était associé à une plus grande flexibilité des réseaux visuels et cognitifs/associatifs, suggéré par une plus grande modularité des sous-réseaux fonctionnels et un détachement du connectome fonctionnel par rapport au connectome structurel.

En conclusion, cette thèse démontre que l'acquisition d'une compétence motrice dans le vieillissement en bonne santé repose sur l'implication et la flexibilité de régions cérébrales distribuées et organisées en réseaux. Les résultats obtenus élargissent les connaissances existantes sur l'apprentissage moteur et indiquent que les études multimodales sont importantes pour comprendre les processus fonctionnels du cerveau.

Mots-clés

Apprentissage moteur, Phase d'acquisition, Vieillissement en bonne santé, Imagerie par résonance magnétique, Réseaux fonctionnels, Connectomique

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Chapter 1 Introduction

Motor learning is fundamental to every aspect and point in life. From the moment we are born to older age, we need to continuously acquire new skills to be able to interact with our environment efficiently. With the advancement of medicine and generally healthier life styles and economic conditions, the human population is significantly aging (Brown, 2015). Already in 2000, 11% of the world's population was over 60 years old and it is expected that this percentage will increase to 22% by 2050 (Kanasi et al., 2016). In addition to this overall aging of the human population, the society we are living in can be characterized as fast-paced with a fast and continuous appearance of new tools for everyday life. Consequently, older adults are today required to learn the usage of new tools very fast and accurately to keep up with our changing environment and stay integrated into society. Efficient manipulation of objects is learned through motor learning processes, which however are reduced in older adults. In particular, older adults learn at a slower rate, with reduced quality, and with higher difficulty to retain successfully the acquired motor memory (Voelcker-Rehage, 2008). The underlying processes of the age-related changes in motor learning ability have gained interest in the last years; the field gathered significant insights with the advancement of neuroimaging techniques (King et al., 2013; Nackaerts et al., 2019). However, due to the diversity of paradigms and tasks used in the field, the studies have reported mixed results (Onushko et al., 2014; Bindra et al., 2021; Bootsma et al., 2021). Especially, very little amount of information is available in regard to neural correlates of the acquisition phase in older adults, i.e. the brain correlates while the new motor skill is acquired. In the next sections, I will introduce motor learning processes and stages as well as associated neural correlates in young adults, describe the age-related differences in motor learning, and finish by providing background information on the technique of magnetic resonance imaging (MRI), the main modality used in this thesis.

1.1 Motor learning

Motor learning can be generally defined as a complex process during which a motor skill is acquired by practice with increasing spatial and temporal accuracy (Willingham, 1998). It is a broad term that covers a wide range of phenomena, occurs over multiple timescales, and involves multiple brain processes (Krakauer et al., 2019). Due to the complexity of the processes, a large number of theories of motor learning have been formulated using information processing principles (Adams, 1971; Schmidt, 1975) or using dynamical systems theory (Newell, n.d.). All theories are attempting to explain the processes at play between the selection of external stimuli that will require action (called subsequently the "environment goal") and the resulting execution of the action (Figure 1 right). Krakauer and colleagues recently proposed an operational definition of motor learning in two parts. Motor learning refers to 1: skill acquisition during which the three steps, shown in Figure 1, are performed rapidly and accurately, and 2: skill maintenance which is the capacity "to maintain performance levels of existing skills under changing conditions" (Krakauer et al., 2019). In the research field, many different kinds of relatively simple motor tasks are used to study motor learning principles (left of Figure 1). In the next subsections, I will provide a short description of these motor learning tasks studied in the field, followed by a description of the different stages of the process, and finish with a review of the neural correlates of motor learning.

1.1.1 Types of motor learning

The research domain of motor learning has been dominated by two types of motor learning: motor sequence and motor adaptation learning (for a review see Doyon & Benali, 2005). Before detailing those, two other types that are gaining interest in the field are briefly described (Figure 1). *De novo* learning is the process by which individuals learn from scratch arbitrary relationships between actions and consequences (Costa, 2011). It usually involves the usage of a new object, such as learning to steer the wheel of a car for instance (Haith et al., 2021). Though probably more relevant for daily life tasks, the literature on this type of learning is still sparse (Krakauer et al., 2019). Similarly, motor acuity has been very sparsely studied in humans (Shmuelof et al., 2014) but more in animals (Krakauer et al., 2019). It is a process solely focusing on the improvement of action execution rather than on goal or action selection (Figure 1) (Shmuelof et al., 2012). Instead, the motor learning field has rather focused on the two first phases of motor planning, namely goal and action selection.

Motor adaptation learning is a process by which individuals learn to adapt to a new perturbation in the environment in order to perform as well as when the perturbation was absent (Izawa et al., 2008). In this type of task, the action selection step needs to be revised to be able to perform accurately (knowing that the skill was previously learned). It is an error-based learning in which individuals realize the perturbation exists while doing the movement and thus correct for it online (Seidler et al., 2013). The first task using this kind of paradigm involved prism goggles that shifted the visual field (Cohen, 1973) while nowadays, the main task implementing this kind of learning is force-field adaptation task (Shadmehr & Mussa-Ivaldi, 1994). I will not further elaborate on this type of motor learning as the main focus of this thesis is sequence learning.

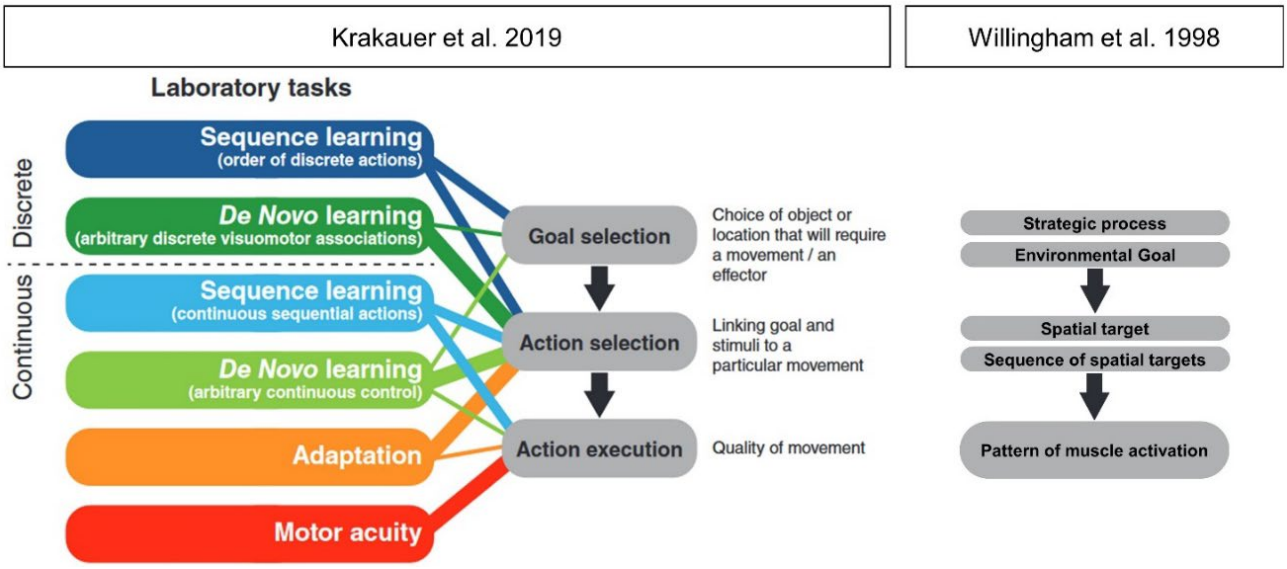

Figure 1. Existing motor learning paradigms in the field. Types of motor learning tasks (left) and their relationship to motor planning and execution pathway (right) according to Krakauer et al. 2019 and Willingham et al. 1998. The lines linking the type of motor learning tasks to the motor planning and execution pathway display different thickness according to the importance of the planning/execution stage in the type of task. Image adapted from the two papers.

Motor sequence learning refers to the execution of a coordinated sequence of actions built from the integration of single movements (Doyon et al., 2018). This type of task is relevant as many of our daily tasks, such as brushing our teeth, tying shoelaces, or typing on a keyboard for example, can actually be decomposed into a series of unitary actions. In experimental settings, different paradigms have been used with the most prevalent being the sequential finger-tapping task (SFTT) (Karni et al., 1995, 1998; Walker et al., 2002; Korman et al., 2003; Zimerman et al., 2013; Maceira-Elvira et al., 2022) and the serial reaction time task (SRTT) (Nissen & Bullemer, 1987; Doyon et al., 2002; Robertson, 2007; Beukema et al., 2019). These are discrete sequence learning tasks that usually involve key presses with four fingers. In SFTT the subjects are asked to perform the sequence of elements as fast and accurately as possible while in SRTT, they are required to react as fast as

possible to cues. The performance measure of these tasks is directly related to the instructions. On one hand, the performance in the SFTT can be quantified in terms of number of correct sequences within a fixed period (Karni et al., 1995, 1998), number of errors (Korman et al., 2003), time to complete correct sequences when the number of sequences is fixed (Orban et al., 2010; Barakat et al., 2013), or a compound of speed and accuracy (King et al., 2016). On the other hand, the performance in the SRTT is usually measured in terms of response time (Nissen & Bullemer, 1987; Robertson, 2007). The performance improvement on these tasks is due to several mechanisms such as better selection of environment goals and execution of individual elements (Diedrichsen & Kornysheva, 2015), better motor planning before and concurrently to execution (Ariani & Diedrichsen, 2019), and a process of grouping individual movements in "chunks" known as chunking or binding (Verwey, 1996; Sakai et al., 2004). This binding operation means that individual movements are grouped and become represented as a single memory unit (Sakai et al., 2003; Yokoi & Diedrichsen, 2019).

Although pertaining to the same type of motor learning, the SRTT and SFTT show several differences. One of these is the aspect of pacing: internally-paced or externally-paced respectively. When the task is externally-paced, it entails that the response time to a stimulus comprises two components: the reaction time and the movement time. A drawback of this task is the impossibility to disentangle the two components of the response time (Krakauer et al., 2019). A self-paced task such as the SFTT does not include the reaction time to a stimulus and is thus more appropriate when considering the speed of learning. Another important difference to note is the question of whether the task involves explicit or implicit knowledge following the general scheme of memory formation (Tulving, 1985). In the context of sequence learning, it means whether the presence of a sequence is known consciously or not. In the SFTT, the knowledge of sequence is explicit while it is usually implicit in the SRTT.

In the literature on motor sequence learning, most of the tasks used are discrete tasks (Jenkins et al., 1994; Karni et al., 1998; Boyd & Winstein, 2003; Doyon et al., 2018), such as the SFTT and SRTT. As argued in the comprehensive review of Krakauer, discrete sequence learning tasks might have limited relevance for everyday life tasks (Krakauer et al., 2019). Furthermore, they seem to involve different processes as shown in one study where rest following practice was only beneficial for a continuous task (Catalano, 1978), or another study showing differential cerebellar activation (Spencer, Verstynen, et al., 2007). A few examples of continuous sequence learning tasks are the pursuit-tracking task (Lang et al., 2013), and grip force tracking task (Sterr et al., 2009). These tasks are usually implicit, but it is feasible to make the sequence explicit (Reis et al., 2009; Wessel et al., 2020).

Regarding the course of learning, motor adaptation processes occur relatively quickly, sometimes even within one single-session (Kitago & Krakauer, 2013). On the contrary, motor sequence learning can take days or weeks depending on the complexity of the task (Wulf & Shea, 2002). However, performance changes are already observable within-session (Karni et al., 1998). In the next section, I will describe in greater detail the time course of motor sequence learning.

1.1.2 Stages of motor learning

As described earlier, many theories of motor learning attempted to explain the mechanisms involved in the accurate and fast performance of an action or set of actions. Another set of theories focused instead on motor learning from a temporal perspective. The theories posited the existence of different stages for the acquisition and retention of skill. Fitts & Posner (1967) were the first to propose such a model composed of three stages: cognitive, associative, and autonomous stages (upper part of Figure 2). One precision to make is that these stages are not clearly distinct from each other; they gradually evolve from one to the other. The cognitive stage is the early acquisition phase during which individuals "understand" the constraints of the task. It thus involves the instructions and demonstrations of the instructor as well as continuous attention to cues and events. During this phase, cognitive resources are extensively recruited; the amount of error is initially high but drops fast, it is differently called the *fast learning stage* of the Doyon & Ungerleider (2002) model. According to the model

of Hikosaka and colleagues, a spatial representation of the actions is formed (Hikosaka et al., 2002) (yellow arrow of Figure 2), in other words, relevant spatial coordinates are selected and learned (Albouy et al., 2015).

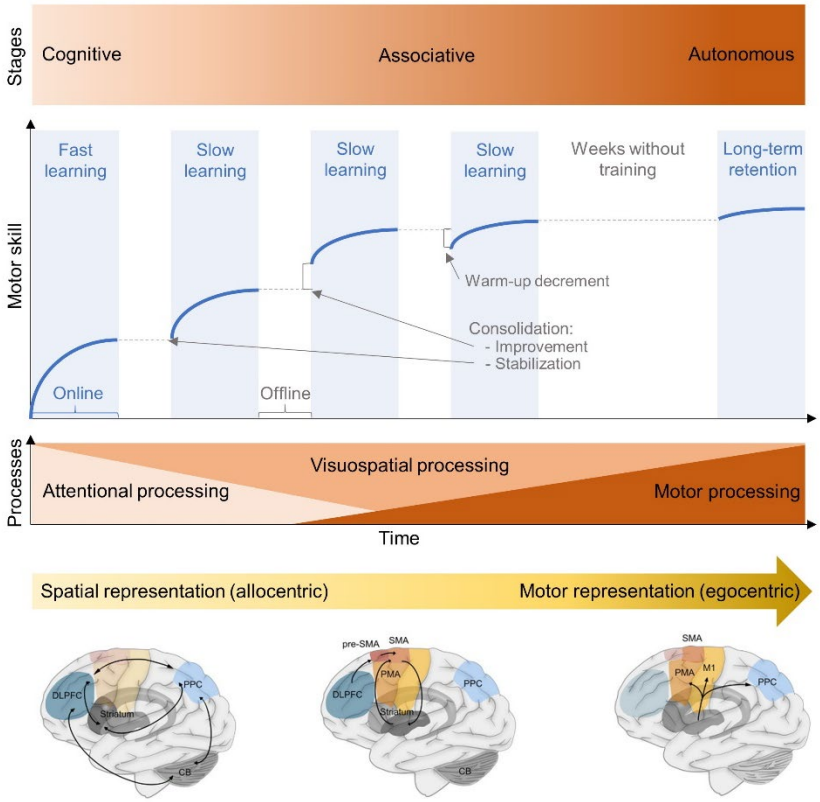

Figure 2. Schematic representation of the different stages of motor learning and the associated areas. Comprehensive view integrating the theories of Fitts and Posner (1967), Doyon and Ungerleider (2002), Eversheim and Bock (2001), Hikosaka et al. (2002). The neural correlates of motor sequence learning are presented at the bottom – the representations were adapted from Dahms et al. (2019). Abbreviations: CB, cerebellum; DLPFC, dorsolateral prefrontal cortex; M1, primary motor cortex; PMA, premotor area; PPC, posterior parietal cortex; pre-SMA, presupplementary motor area; SMA, supplementary motor area.

As learning progresses, subjects enter the associative stage, a phase during which individual units learned during the cognitive phase are associated to form new patterns. During this stage, gains in performance are small, but movements are getting more efficient and less variable (Weaver, 2015). While the initial cognitive phase usually occurs within the first session of training ("online learning"), this second stage shows varying length according to the complexity of the task, but usually occurs at least over multiple days in the context of motor sequence learning as described by Doyon and colleagues (Doyon & Benali, 2005). They refer to this stage as *slow learning*. In the view of Hikosaka's, this state includes the stabilization of the spatial-allocentric coordinates while the motor-egocentric coordinates are starting to be formed (Hikosaka et al., 1999; Eversheim & Bock, 2001; Hikosaka et al., 2002). This stage was initially thought of as the one during which consolidation processes appear (Walker et al., 2003; Robertson, Pascual-Leone, & Miall, 2004). Motor memory consolidation takes place when a "motor memory is transformed with the passage of time, and, in the absence of further practice, from an initial fragile state to a more solid state" (Brashers-Krug et al., 1996). It refers to two processes: the motor memory becomes resistant to interference (Krakauer & Shadmehr, 2006) and further performance improvements without practice are observable ("offline learning") (Robertson, 2005) (graph in Figure 2). This offline learning was considered as a process that occurs exclusively after the initial acquisition of a motor skill, however, a recent body of research has shown that consolidation processes also occur within seconds during the fast learning stage (Bönstrup et al., 2019; Robertson, 2019; Jacobacci et al., 2020; Buch et al., 2021). Later, the presence of sleep contributes to the consolidation of motor memory (Fischer et al., 2002; Walker et al., 2002; Laventure et al., 2016) although it depends on the studied task (Doyon et al., 2009).

The final stage called autonomous stage in Hikosaka's model and retention stage in Doyon's model is reached when no further improvement is made on the task, such that the performance has reached a stable plateau that is resistant to the passage of time without practice (Doyon & Benali, 2005). In this stage, the task is performed consistently and efficiently, the cognitive control is minimal and the performance is not impacted by environmental distractions (Hikosaka et al., 2002). The motor maps reorganize at this stage (Kleim, 2004) in specific brain regions. The stages of motor learning having been outlined, the neural correlates over the different stages of motor learning will now be described.

1.1.3 Neural correlates of motor learning

The first reports of imaging of motor learning in humans date back to the early 1990s with Positron Emission Tomography (PET) (Grafton et al., 1992; Kawashima et al., 1995) and with functional MRI (fMRI) (Karni et al., 1995). Since then, motor learning-related brain activation has been extensively studied in healthy populations (see Halsband & Lange, 2006 for a qualitative review and Hardwick et al., 2013; Lohse et al., 2014 for meta-analyses). Halsband & Lange, 2006 report successive activation of several brain areas as learning progresses (Figure 3). During the early phase of learning, there is significant activation of prefrontal areas, especially in the contralateral dorsolateral prefrontal cortex (DLPFC), bilateral premotor cortices (PMC), pre-supplementary motor areas (preSMA), posterior parietal areas and distributed cerebellar areas. Consistently with the cognitive stage of Fitts and Posner (Fitts & Posner, 1967), DLPFC is thought to be involved in coding the goal of a movement (Luria & Haigh, 1980; Willingham, 1998) and implementation of cognitive control (MacDonald et al., 2000).

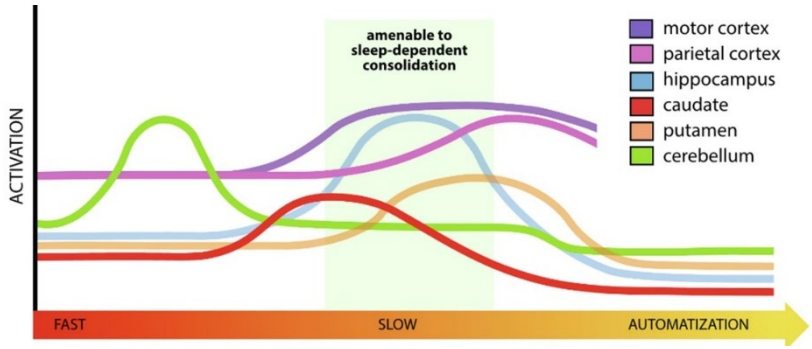

Figure 3. Time course of activation changes through the different phases of motor learning. Figure adapted from Fitzroy et al. (2021).

As practice advances, the supplementary motor area (SMA) proper, primary motor cortex (M1), and posterior parietal cortex show increased activation. The posterior parietal cortex seems involved in the development of the representation of the target, particularly in the transformation of sensory information into action plans (Eskandar & Assad, 1999; Grefkes et al., 2004). Animal studies in monkeys showed that it is especially involved in visually guided movements, acting as a sensory-motor hub for the interaction with the external environment (Taira et al., 1990; Passarelli et al., 2021). The basal ganglia and especially the caudate and striatum play a critical role throughout the course of learning (Albouy et al., 2013). A recent study showed that the caudate nucleus was dissociated in an anterior cognitive part and posterior sensorimotor part (Choi et al., 2020), respectively active during early versus late learning. Furthermore, in the late phase, motor learning has been related to significant activation in the primary motor cortex as well as the parietal cortex while activation in cerebellar areas decreases (Halsband & Lange, 2006; Doyon et al., 2018).

These reports and meta-analyses are consistent with the view of interacting cortico-cerebellar and cortico-striatal networks involved during different phases of motor learning (Doyon & Benali, 2005). While both networks seem involved in the early phase of motor learning, it appears that in later phases of learning, the contribution of these networks differs depending on the type of task studied with the cortico-cerebellar network

more involved in adaptation learning and the cortico-striatal more involved in sequence learning (Lohse et al., 2014; Doyon et al., 2015).

Apart from looking at patterns of activation changes related to motor learning, it is also possible to investigate the functional relationships (also referred to as *functional connectivity*) between these regions (Coynel et al., 2010). Indeed, looking at brain connectivity can get us valuable insight into how learning processes induce changes in the way regions interact with each other (Telesford et al., 2011; Stanley et al., 2015). Heitger and colleagues (Heitger et al., 2012) for instance showed that multiple days of motor learning induced increased functional connectivity in task-related networks, but more importantly reorganization of the network towards a de-centralization of network function. A more recent study showed that motor learning induced a decreased connectivity between the visual and the motor system (Bassett et al., 2015), revealing the autonomy in these systems in late learning compared with early learning. In the same vein, Mattar and colleagues reported that resting-state sensorimotor autonomy measured at baseline was able to predict faster motor learning during 6 weeks of training (Mattar et al., 2018). These results highlight the importance to investigate motor learning both in terms of patterns of activation and patterns of connectivity.

1.2 Age-related changes in motor learning

Healthy aging is accompanied by an overall decline in cognitive abilities (Bishop et al., 2010) and a reduction of motor learning capabilities (Voelcker-Rehage, 2008; Seidler et al., 2010). This effect goes along with significant functional and structural brain changes, at the level of local patterns as well as network patterns. I will further describe the differences between young and older adults and their possible underlying mechanisms in the next sections.

1.2.1 Behavioral changes

Older adults display several deficits in motor performance and motor learning compared with younger populations. First, they show motor slowing (Shea et al., 2006; Lamb et al., 2016) that has been related in part to a shift in the speed-accuracy trade-off (T. A. Salthouse, 1979); in the sense that older adults usually favor accuracy over speed (Forstmann et al., 2011). Moreover, they display more motor intra-individual variability in motor execution (Sosnoff & Newell, 2006) and force control (Vieluf et al., 2013; Vanden Noven et al., 2014; Critchley et al., 2014). Interestingly, the latter-mentioned study shows that force control variability is increased by the presence of visual feedback suggesting that feedback processing is less efficient in older adults (Critchley et al., 2014). This result was reproduced later for a similar force control task (Kenway et al., 2016) and a tracking task (Baweja et al., 2015). Thus, this points to the fact that decreased processing speed in aging (T. A. Salthouse, 2000) has a detrimental impact on motor performance.

Apart from reduced motor performance, older adults are also impaired in aspects of motor learning, although the results are not completely clear. Studies showed that older adults exhibit similar motor sequence learning (Seidler, 2006; R. M. Brown et al., 2009) compared with young adults while other research groups reported significant differences between the two groups (Daselaar et al., 2003; Shea et al., 2006; Zimerman et al., 2013; Maceira-Elvira et al., 2022). One hypothesis for the contradictory results is the variety of motor tasks used. Indeed, it appears that motor learning capacities in older adults depend on the complexity of the task (Onushko et al., 2014; Bootsma et al., 2020) as well as with which effector the task is done (fine finger skills or whole-hand skills for instance) (Voelcker-Rehage, 2008).

In the context of complex tasks, several studies showed that the acquisition of the sequence was carried out faster for the younger group (Shea et al., 2006; Zimerman et al., 2013; Maceira-Elvira et al., 2022). These results could be understood in relation to the previously mentioned impaired sensory feedback processing (T.

A. Salthouse, 2000; Critchley et al., 2014). The difference can also be related to the more general age-related cognitive decline (Bishop et al., 2010) and in particular the deficits in working memory processes (Bo et al., 2009; Anguera et al., 2011). Indeed, in both motor sequence learning (Bo et al., 2009) and motor adaptation learning (Anguera et al., 2011), visuospatial working memory deficits were related to the reduction in motor learning capabilities. Furthermore, a recently published study (Wang et al., 2020) showed that performance on a visuospatial working memory test predicted motor skill learning. Although deficits in working memory processes can explain part of the reduction of motor learning capacities in older adults, they cannot account for all differences observed between older and young adults. An alternative explanation was proposed by a recent study (Maceira-Elvira et al., 2022). In this report, they showed that young adults showed a sharp improvement in accuracy on an SFTT task followed by a gradual increase in speed, older adults instead displayed a gradual increase in both measures. This was interpreted as the fact that, following Hikosaka's model (Hikosaka et al., 2002), the development of spatial coordinates preceded the formation of motor coordinates in young adults, while these processes happened in parallel in older adults. This in turn impacted the temporal appearance of chunking patterns, in the sense that the chunking processes were slower to develop and consolidate in older adults consistent with other reports (Verwey, 2010; Bottary et al., 2016; Barnhoorn et al., 2019).

Another aspect of the reduction in motor learning abilities relates to poorer memory consolidation (Nemeth & Janacsek, 2011; Roig et al., 2014); this consolidation also depends on the complexity of the task (Onushko et al., 2014; Gudberg et al., 2015). Especially, the consolidation by sleep seems to be less efficient in older adults (Harand et al., 2012; Rasch & Born, 2013) with observable decrements or no changes in motor performance following a period of sleep in older adults whereas offline improvements were seen in younger adults (Spencer, Gouw, et al., 2007; R. M. Brown et al., 2009; Vien et al., 2016). Aging is accompanied by substantial sleep changes with macro sleep changes in terms of duration, latency to fall asleep, increased sleep fragmentation, and change patterns of sleep stages (Mander, Winer, et al., 2017). Furthermore, micro sleep changes are also seen in the sleep of older adults. The main sleep oscillations, namely slow waves and spindles, are substantially impacted by aging (Crowley, 2002; Mander et al., 2013). Slow waves are low-frequency oscillations (<1 Hz) that occur during the deep sleep stage (Steriade et al., 1993) and have been related to sleep-dependent memory consolidation (Wei et al., 2018). Spindles are characteristic events occurring during specific stages of sleep (De Gennaro & Ferrara, 2003). This sleep oscillation is a transient burst of approximately 2 seconds that occurs every 5 seconds on average (Achermann & Borbély, 1997) and has a frequency between 12-16 Hz (Werth et al., 1997). Spindles are sleep oscillations that have been related to motor learning in many reports (Tamaki et al., 2009; Vahdat et al., 2017; Boutin et al., 2018; Lutz et al., 2021, p. 202; see Boutin & Doyon, 2020 for a mechanistic review). Spindles in particular have previously been associated with sleep-dependent motor memory consolidation (Fogel et al., 2017; Boutin & Doyon, 2020).

The motor learning differences between older and young adults could stem from multiple factors ranging from working memory deficits to sleep physiology changes. Differences are observable at both the level of acquisition and offline consolidation, however, it was pointed out that most of the differences were stemming from distinct improvement dynamics during the first training day (Maceira-Elvira et al., 2022). In addition, multiple functional and structural changes in the brain occur with age and could be related to motor learning deficits. I will outline these age-related changes in brain organization in the next section.

1.2.2 Structural and functional changes

Multiple structural changes occurring in the brain were related to the change in behavior (Hirsiger et al., 2016). Several cortical areas comprising frontal, motor, and posterior parietal areas exhibit shrinkage (Raz et al., 2005; Berghuis et al., 2019) and thinning (Fjell et al., 2009) with older age (see Figure 4 for comparison with a younger brain). As for the relationship between region volume and motor learning, Kennedy & Raz, 2005

found a strong association between the volume in the lateral prefrontal cortex and the acquisition of a perceptual-motor skill. Furthermore, they also report a positive correlation between the volume of the caudate nucleus and better performance, in late learning especially. The structure of the cerebellum was also associated with motor performance in older adults (Bernard & Seidler, 2013; Koppelmans et al., 2015). A recent study found a correlation between the grey matter volume of the cerebellum and offline changes in performance (Fogel et al., 2017).

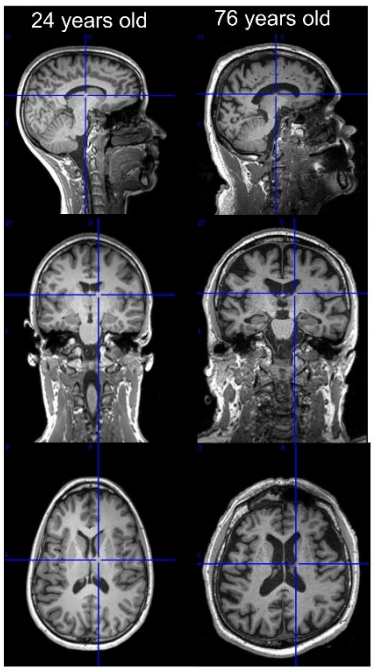

Figure 4. Differences in the structure of a young compared with an older brain.

White matter also undergoes substantial modifications with aging (Jeon et al., 2012), such as reductions in white matter integrity (Salat et al., 2005). This loss of integrity was related to motor learning in several studies. For instance, degradation of the tract linking the caudate to DLPFC explained the differences in late sequence learning in an older population (Bennett et al., 2011). Schulz et al., 2014 found a positive correlation between the integrity of interhemispheric tracts connecting the primary motor and secondary motor areas with skill acquisition. Later, evidence showed that the integrity of the corpus callosum and the corticospinal tract was related to the learning rate of a motor sequence learning task in older adults (Vien et al., 2016). When investigating sleep-dependent consolidation, Mander and colleagues showed a moderation effect of white matter for the efficacy of sleep spindles to promote motor memory consolidation (Mander et al., 2017). Similarly, a recent study showed that the integrity of thalamocortical tracts was indirectly related to offline gains in motor performance. This relationship was mediated by spindle density (Vien et al., 2019).

The investigation of functional changes related to age-related motor learning changes is more common. Generally, the reduction in motor learning capabilities has been related to hyperactivation in extensive brain regions (Heuninckx et al., 2008; Goble et al., 2010). Although similar circuits are recruited when comparing with young adults (Turesky et al., 2016), more widespread activation in the same areas and additional bilateral frontal, motor, and temporal areas seem involved in the process of motor learning in older adults (King et al., 2013; Fogel et al., 2014; Berghuis et al., 2019). The more extensive pattern of activation has been interpreted as a compensation process in the sense that wider activation is needed to reach comparable performance when compared with younger adults (Sala-Llonch et al., 2015). In particular, the bilaterality of brain activation has been interpreted by Cabeza and colleagues who formulated the Hemispheric Asymmetry Reduction in Old Adults (HAROLD) model (Cabeza, 2002). This model states that older adults show more bilateral activation during task execution, especially in frontal areas (Cabeza et al., 2002; Berghuis et al., 2019). It is in accordance

with the Posterior-Anterior Shift in Aging (PASA) in which Davis and colleagues argue that the deficits of posterior activation are compensated by increased activation in frontal areas (Davis et al., 2008). These models have been generated to explain the general changes in diverse cognitive tasks. When investigating motor learning specifically, a differential pattern in the activation of cortico-striatal networks has been reported and continued involvement of the hippocampal complex is observed (Rieckmann et al., 2010; King et al., 2013). The changes in the striatum have been related to the depletion of dopaminergic systems observable in older age (Kaasinen & Rinne, 2002). Interestingly, dopaminergic activation upregulation by intake of levodopa was beneficial for motor memory encoding in young and older adults suggesting the importance of this neurotransmitter in motor learning (Flöel et al., 2005). Moreover, the sustained involvement of the hippocampus has been interpreted as a compensatory mechanism to counteract the reduced efficacy of the striatum (Rieckmann et al., 2010). Hippocampus has been shown to play a crucial role in learning and memory and particularly in declarative memory (Eichenbaum, 2001). This suggests that, in addition to the reports of hyperactivation in frontal and parietal areas (Lin et al., 2012), older adults recruit more cognitively-related neural systems to compensate for the motor-related regions deficits. This interpretation is in accordance with the Compensation-Related Utilization of Neural Circuits (CRUNCH) model that posits that neural cognitive systems are more recruited in older compared with young (Reuter-Lorenz & Cappell, 2008; Reuter-Lorenz & Park, 2014). The model relates to the dedifferentiation hypothesis that states that brain functional activation is less specialized and segregated in the older brain (Sala-Llonch et al., 2015).

The CRUNCH model introduces the importance of different interacting circuits or networks to produce motor outputs. As mentioned in the last section, aging is accompanied by decreased processing speed that could in part explain motor learning differences (T. A. Salthouse, 2000) and we know that processing speed relies on coordinated activation of multiple neural networks (Ruiz-Rizzo et al., 2019). Similarly, for motor learning, several studies have reported relationships between connectivity and motor learning in older adults. First, studies have investigated the relationship between baseline resting-state connectivity and subsequent motor learning. Mary and colleagues found that lower connectivity between sensorimotor and dorsal-attentional and default mode network (DMN) was predictive of better motor learning during one session of a motor sequence task (Mary et al., 2016). Furthermore the next year, the same research team reported increases in young but decreases in connectivity between the somatomotor area and the superior temporal gyrus, inferior frontal gyrus, cerebellum, visual areas, and parietal areas that were associated with better motor learning in older adults (Mary et al., 2017). This suggests that learning is associated with a decreased necessity for compensatory circuits. Likewise, Solesio-Jofre and colleagues observed decreases in a task-specific motor network following the acquisition of a motor task in older adults while the same network showed increased connectivity in young adults (Solesio-Jofre et al., 2018). These changes were not related to motor performance changes. A recent study showed that middle-aged adults displayed increased connectivity in visuospatial processing areas during the task compared with rest (Aznárez-Sanado et al., 2022). Furthermore, a correlation analysis showed a decrease in coupling between the posterior putamen and parietal areas that are consistent with previous literature regarding the loss of efficiency in the cortico-striatal network (Rieckmann et al., 2010). Apart from functional connectivity studies based on temporal correlations of time series, recent literature focused on looking at the relationship between brain functional topology and motor learning with the use of graph theory principles. Lin et al., 2016 found that older adults differed in the way network centrality was related to motor learning retention performance compared with young adults. While younger adults beneficiated from a redirection of information towards hub nodes, older adults did not. They argue that older adults lack the flexibility to reorganise functional networks during the processes of memory consolidation (Lin et al., 2016).

Reviewing the literature on the neural correlates of motor learning in older adults, we can notice a gap of knowledge regarding the dynamics of activation during the initial training session. Indeed, although the dy-

namics of acquisition are important for overall motor learning as pointed out by Maceira and colleagues (Maceira-Elvira et al., 2022), the previously mentioned studies use a design where the initial practice session is performed before imaging (Heuninckx et al., 2008; Goble et al., 2010), outside of the scanner with pre and post sessions (Berghuis et al., 2019) or analyze the data looking at average activation over the entire training session (Fogel et al., 2014; King et al., 2016). This thesis is in consequence aiming to fill this gap by looking at the dynamics of brain activation during the initial learning process. Furthermore, apart from the dynamics of brain activation, changes in the connectivity of functional networks have only been sparsely studied when looking at the relationship with performance changes. Therefore, the second aim of this thesis is to investigate how a single training session would impact brain connectivity and whether we could observe network changes correlates of performance changes. Before outlining in greater detail the motivation of this thesis, an overview of the main technique used in this thesis to acquire brain imaging data, MRI, is provided.

1.3 Magnetic resonance-based neuroimaging

MRI is a medical imaging technique that allows analyzing non-invasively and in vivo the anatomy and functional processes of the body. The technique is widely used in the medical and research field and has the advantage that it can be employed without any radioactive tracers (such as Position Emission Tomography) or without releasing ionizing radiation (such as Computed Tomography scans). Instead, the technique uses a strong magnetic field and radiofrequency pulses to generate high spatial resolution images of tissues. The possible side effects of MRI are mild and include dizziness, headaches, magnetophosphenes, and nausea due to the extended time in the scanner as well as the risk of claustrophobic sensations due to the confined space (Weintraub et al., 2007). One drawback of this technique is a large number of contraindications, most of them due to the usage of a strong magnetic field. Subjects with metal implants, prosthetics devices, electronically-activated devices, and other implants cannot be tested with MRI, except if the metal is paramagnetic (the latest prosthetics in titanium for example are safe for MRI (Kim et al., 2019)). Pregnant women are also not allowed to perform an MRI (Ghadimi & Sapra, 2022). Following this brief introduction to the technique, I will give a more precise overview of the principles of MRI, the different types of images that we can acquire and that I use in this thesis and I will finally introduce a recent analysis technique that gained particular interest in the brain imaging field: the brain connectome.

1.3.1 History and basic principles

MRI technique stems from the physical phenomenon of nuclear magnetic resonance (NMR) discovered in 1938 by Isidor Rabi and colleagues (Rabi et al., 1938). The nuclei of atoms have magnetic properties (called magnetic moment) that make them react to a strong magnetic field. If a second oscillating magnetic field (a radio frequency pulse in particular) is applied, the nuclei will be perturbed, i.e. driven out of equilibrium. After the oscillating perturbating field stops, the nuclei will return to equilibrium through a process called relaxation. The time of relaxation is the most important measure in MRI as it can differ according to the properties of the nuclei.

Following these principles, Lauterbur was the first one in 1973 to produce 2D and 3D images thanks to the NMR technique and the use of magnetic field gradients to encode spatial information (Lauterbur, 1973). He called this technique ‘zeugmatography’, derived from the Greek term ζενγμα, ‘that which joins together’ (Lauterbur, 1974). He first tested the technique on tubes filled with water, as water molecules contain hydrogen protons that satisfy the magnetic properties needed for nuclear magnetic resonance. The human body contains a large proportion of water molecules as well as fat molecules, both containing hydrogen protons (Popkin et al., 2010). This property allowed Mansfield and Maudsley to perform the first *in vivo* image of a human finger in 1977 (Mansfield & Maudsley, 1977) while Damadian and colleagues acquired a chest scan in the same year (Damadian et al., 1977). A whole-body scan was acquired one year later by the team of Mansfield (Mansfield

et al., 1978), which also developed the echo-planar imaging (EPI) technique considerably reducing the time of scanning and improving the quality of images (Mansfield, 1977; Poustchi-Amin et al., 2001).
After this, the NMRI technique flourished for clinical use in the 1980s and the "nuclear" term was removed from the denomination as the word "nuclear" scared patients (Joyce, 2006). The technique improved constantly from this point and is now widely used in clinics as well as research settings. In these settings, MRI produces a strong constant magnetic field called B_0 of usually 1,5 or 3 Tesla for clinics and up to 7 Tesla or higher in research settings (see an MRI scanner on the left and its modelization on the right of Figure 5). Different coils are used to send multiple different radio-frequency pulses and to receive the output signal from the element being scanned. We can use MRI to characterize the structure of the body parts and in particular the brain. Moreover, thanks to EPI imaging, we can assess the real-time function of the brain. I will briefly describe the different techniques used in this thesis work.

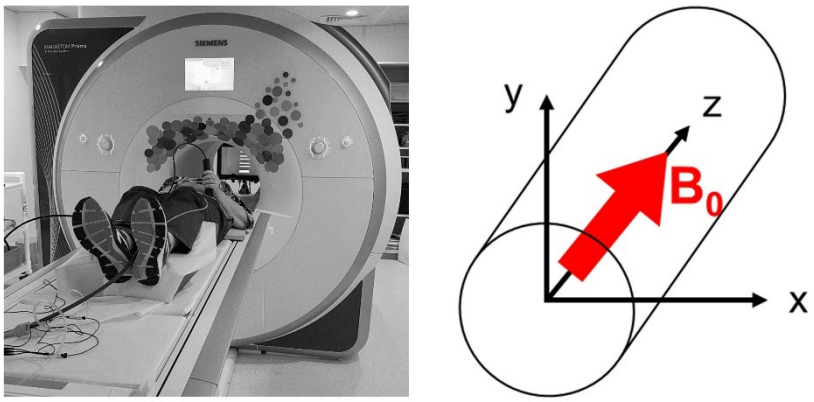

Figure 5. MRI environment. Picture of an MRI scanner (left) with its modelisation with orientation axes and orientation of B_0, the main magnetic field (right).

1.3.2 Structural measures

Two common types of structural measures acquired in clinical MRI are called T1-weighted and T2-weighted images (Hashemi et al., 2012). The names refer to the type of relaxation time measured when observing the net magnetization of the hydrogen protons in the tissue. As explained before, after applying a radiofrequency pulse, the protons will change their orientation so that the net magnetization is flipped 90° and thus find itself in the transverse plane (the x-y plane in Figure 5 right). The T1 relaxation time is the longitudinal relaxation time that refers to the amount of time it takes for the net magnetization of the tissue to come back to its initial state, meaning in alignment with B_0 (Figure 5 right). The T2 is the transverse relaxation time: it is the length of time for the net magnetization to decay. The variability in relaxation times will produce different contrasts in the brightness of the resulting image. Different tissues will have different relaxation times resulting from variations in the density of water molecules and in the way water interacts with other molecules. These characteristics permit the differentiation between the tissues (see Table 1).

Tissue type	T1-weighted	T2-weighted
Water	dark	bright
Fat	bright	bright
Cerebrospinal fluid (CSF)	dark	bright
White matter	light	dark grey
Grey matter	dark gray	light gray

Table 1. The brightness of tissue types according to the type of image acquired.

T1-weighted images are high-resolution 3D images that allow observing in great detail the different structures of the brain such as grey matter, white matter, and cerebrospinal fluid (CSF) (Figure 6 left). The typical resolution of a T1-weighted image is about $1mm^3$. This property makes it the common structural image used as template for other images displaying lower resolution such as functional images (see next section for a description). In addition to having a high-resolution 3D image of the brain, the T1 anatomical scan enables to perform volumetric segmentation of grey and white matter (Kennedy, 1998). T2-weighted images display the water and fluid as very bright as we can see in the middle image of Figure 6, this type of image is thus valuable in clinics to observe unhealthy tissue and diagnose diseases (Bitar et al., 2006).

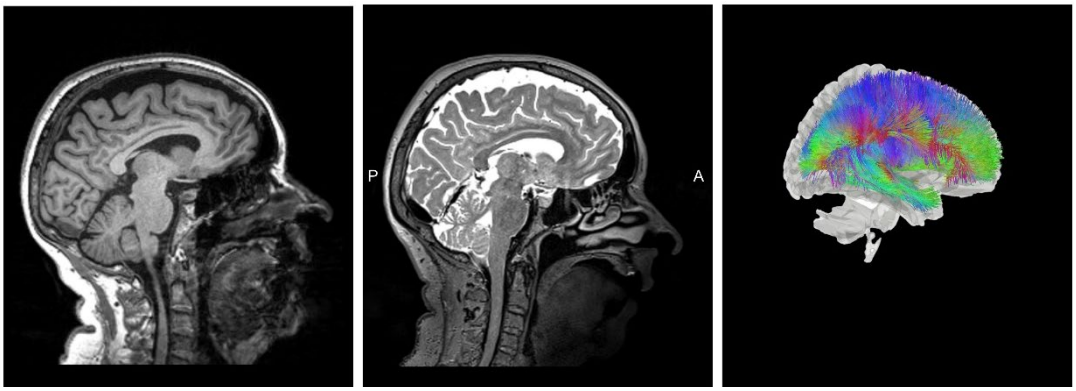

Figure 6. Images showing different types of structural images possible with MRI. Left: T1-weighted image. Middle: T2-weighted image. P corresponds to posterior and A to anterior. Right: Reconstructed fibres from the tractography measure of diffusion-weighted image.

Another type of image that gained interest in the last years is diffusion-weighted images. Diffusion-weighted imaging is a technique that allows studying white matter structure (Le Bihan & Breton, 1985). More specifically, it allows measuring the direction of diffusion of the water molecules that are moving along white matter tracts. Fibers and neuronal membranes restrict the molecules' diffusion in axons such that the molecules can only move in restricted directions (Chenevert et al., 1990). This process allows the mapping of white matter structures of the brain, i.e. the myelinated fiber bundles linking the different brain areas. Interestingly, the integrity of white matter has been characterized as a predictor of age and disease-related decline (Chanraud et al., 2010) and has also been associated with recovery and learning (Johansen-Berg et al., 2010). The most commonly used measure for white matter integrity is the fractional anisotropy (FA) value (Basser & Pierpaoli, 1996). It can be derived from the diffusion-tensor model that considers in each voxel the direction of maximum diffusivity (Basser et al., 1994). Other models that reconstruct multiple fiber orientations within a voxel are available such as the ball and stick model or the nonparametric q-ball technique (Hagmann et al., 2006). These models allow to perform tractography analyses, a way to represent white matter tracts of the brain and thus visualize and quantify how brain areas are structurally interconnected (Basser et al., 2000) (Figure 6 right). This analysis is named structural connectivity, and it permits the evaluation of the anatomical organization of the brain and how they are structurally connected (Babaeeghazvini et al., 2021).

1.3.3 Functional measures

In addition to being able to study the structure of the brain, the MRI technique offers the exciting possibility to investigate the real-time functioning of the brain (among other organs). The technique of fMRI was introduced in the early nineties. The first report on imaging the human brain was published in 1991 by a team of researchers, who observed the change in cerebral blood volume in the active visual cortex compared with rest (Belliveau et al., 1991) thanks to the application of an external contrast agent. In the same year but reported later, another group succeeded in eliciting visual activation with intrinsic blood contrast (Kwong et al., 1992; see the history in Kwong, 2012): the MRI contrast of oxy/deoxyhemoglobin, more commonly known as the

blood-oxygen-level-dependence (BOLD) contrast (Ogawa, Lee, Kay, et al., 1990; Kwong, 2012). This technique was developed by Ogawa and colleagues in 1990 and first tested on rodents (Ogawa, Lee, Kay, et al., 1990; Ogawa, Lee, Nayak, et al., 1990). It is of more interest as it does not need an external agent application and is an endogenous measure of oxygen consumption in the brain (Ogawa, Lee, Kay, et al., 1990). More precisely, the contrast of these images originates from the fact that deoxygenated hemoglobin has different magnetic properties compared with oxygenated hemoglobin, i.e. deoxygenated hemoglobin has higher magnetic susceptibility and thus disrupts the local magnetic field, which induces the MRI signal (T2* signal) to drop faster (Gore, 2003). The T2* signal refers to the observed transverse magnetization decay that results from inhomogeneities of the magnetic field (Chavhan et al., 2009).

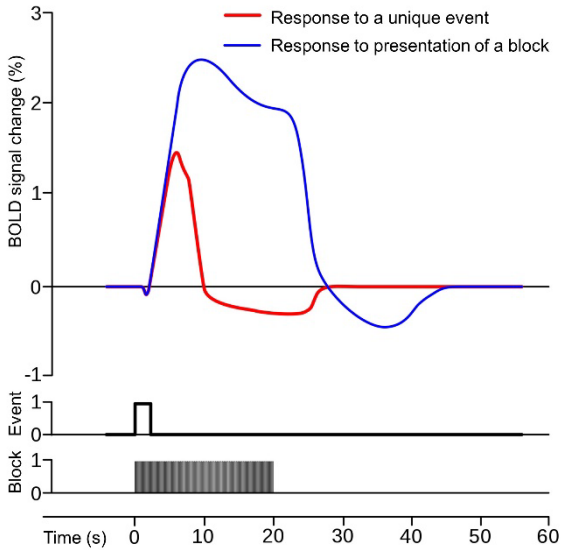

Figure 7. The hemodynamic response function. Graph depicting the hemodynamic response function after a short event (red curve) or after a block-type of stimuli.

When neurons activate in response to a stimulus (or sequence of stimuli) (Figure 7), the need for oxygen is increased causing more oxygen to be brought by increased blood flow in arterioles where the neurons are located. The amount of oxygenated blood in this area increases and actually exceeds the needed quantity thus inducing an increase in the ratio of oxygenated hemoglobin to deoxygenated hemoglobin. As this ratio increases, the magnetic field becomes more uniform and the BOLD signal increases (Gore, 2003). This metabolic response has been named the hemodynamic response and is modeled by the canonical hemodynamic response function (HRF) (see the legend of the red curve in Figure 7) (Buxton et al., 1998).

To be able to observe the dynamics of the BOLD signal, the MRI sequences for functional brain imaging are acquiring the images very fast thanks to the technique of EPI mentioned before (Mansfield, 1977). Consequently, the resolution of the images is less clear compared with structural images (one 3D volume of the brain for a 1mm^3-resolution T1-image takes about 5min to be acquired). Furthermore, due to the speed of acquisition, the signal is very sensitive to small disruptions of the magnetic field resulting in magnetic susceptibility artifacts. Especially regions in the vicinity of air pathways will show disrupted signal, i.e. geometric distortions or even sometimes signal loss (Weiskopf et al., 2006). We can compensate partially for these inhomogeneities in post-processing with the use of an acquired field map that helps in correcting the geometric distortions (Hutton et al., 2002).

The first experiments implementing fMRI used simple visual, sensory, or motor tasks to observe elicited activation in the brain (Kwong et al., 1992; Bandettini et al., 1992; Karni et al., 1995). The experimental tasks were usually implemented with multiple 20 to 30 seconds blocks in which the stimuli were repeated on multiple occurrences like in PET experiments, another type of functional imaging (Frackowiak & Friston, 1994; Bandettini, 2012). This design is called block design (see the depiction of one block at the bottom of Figure

7). This paradigm demonstrates a high signal-to-noise ratio as the analysis collapses across many trials and is suitable for discrete as well as continuous tasks (Petersen & Dubis, 2012). Another common design used in the field is the event-related design that consists in presenting several single stimuli with jittering delay between them (Boynton et al., 1996). This paradigm enables researchers to separate cognitive processes in events and accordingly disentangle the associated brain activation (Huettel, 2012). One drawback of this design involves a lower signal-to-noise ratio compared with block design (Miezin et al., 2000).

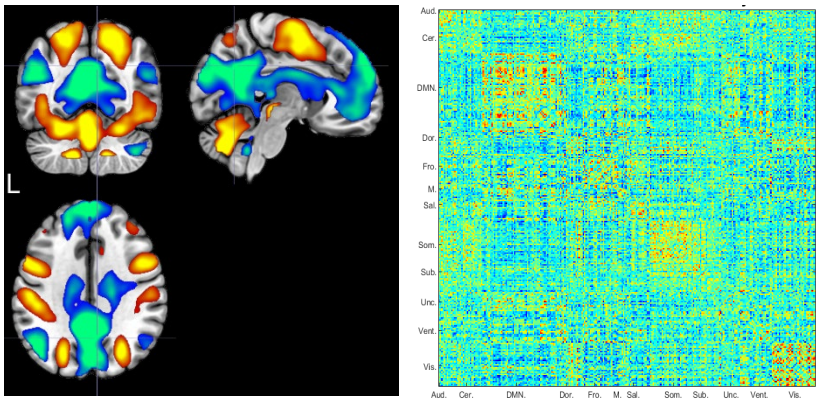

Figure 8. Examples of results computed from MRI data. BOLD activation analysis (left) and connectivity analysis in the form of connectivity matrix (right). Own data.

The fMRI technique is extremely relevant to the investigation of task-related processes as it enables investigators to localize precisely the brain areas involved in this process (example of a pattern of activation seeable for a motor task on the left of Figure 8). The analysis techniques are diverse. They comprise regions of interest (ROI)-based analyses which are the measure of specific local activation within a pre-defined region and are based on a priori hypotheses (Poldrack, 2007) while whole-brain analyses are the observation of brain activation within each volumetric unit of the images, the voxel (pixel in 3D) without a priori hypotheses. The activation analyses we just described are based on the principle of *functional specialization* of the brain, a concept dating from the nineteenth century, that states that brain functions can be attributed to specific brain areas (Friston, 2002; Friston, 2004). This principle originates from the study of brain-damaged individuals such as Phineas Cage (Bigelow, 1850) who had a frontal lobe lesion and lost his personality traits, and the case reported by Paul Broca on the region responsible for language (Broca, 1861).

The second fundamental principle of brain organization is *functional integration* which posits that several brain areas interact with each other to process information and generate a function (Friston, 2004). Initially, these two organization principles of brain function were distinct competing views, however, it became clear that they are actually complementary, i.e. they are only meaningful when both are considered (Friston, 2002). fMRI permitted to gain great insights into the field of functional integration with the techniques of effective and functional connectivity (Friston, 1994). Effective connectivity has been described as "the influence one neuronal system exerts over another" (Friston et al., 1993). It is informative of the causal influences of one brain region on another. Conversely, functional connectivity does not give information about the direction; it is quantifying how functionally related distributed brain regions are by looking at the statistical dependence between BOLD time-series averaged over ROI or between voxels (Babaeeghazvini et al., 2021). One can measure functional connectivity during a task *(task-based connectivity*) and can thus infer how brain regions interact with each other during task execution, but it is also possible to measure functional connectivity during rest in order to evaluate *resting-state networks* (Biswal et al., 1995). Indeed, as early as 1995, Biswal and colleagues discovered fortuitously that distributed regions related to motor function displayed highly correlated time courses of low frequency (<0.1 Hz) fluctuations in the resting brain (Biswal et al., 1995; Lowe, 2010). In other words, specific patterns of related activation were observed in the absence of any stimuli or goal-directed

actions (Damoiseaux et al., 2006). Furthermore, these patterns of activation revealed a set of networks (not just the motor-related network) that were differentially active during specific tasks and one network that was deactivated during any type of task; the DMN (seeable within the blue-green pattern on the left of Figure 8) (Damoiseaux et al., 2006). One of the main outputs of connectivity analysis is a representation of the results in the form of a matrix of connectivity (Figure 8 right), the basis for the brain connectome introduced in the next section.

1.3.4 The brain connectome

The human brain connectome is a concept that arose in 2005 (Hagmann, 2005; Sporns et al., 2005); it refers to a comprehensive representation of the brain in the form of a network composed of nodes and connections. It initially denoted the structural organization of the brain but is now referring to both the functional and structural aspects of connections (Seung, 2011). The main representation is in a matrix form (such as Figure 8 right). This view of the brain can capture the complex nature of the brain (Telesford et al, 2011); that is to say, the system is characterized by more than the sum of its parts, in this case, the nodes and the connections (Bassett & Gazzaniga, 2011). Indeed, to evaluate the characteristics of the system as a whole, complex network theory can be applied (Sporns, 2011) and this analysis technique has provided many insights into cognitive processes (Cohen & D'Esposito, 2016), and interestingly in our context, on aging (J. Sun et al., 2012; Stanley et al., 2015; Michely et al., 2018) and learning (Bassett et al., 2011; Heitger et al., 2012).

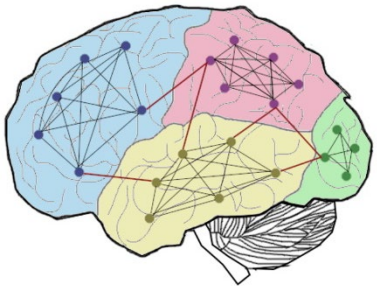

Figure 9. Representation of a globally efficient and modular brain network. Adapted from Leite et al. 2022.

Several global properties of graphs are especially relevant for the description of the brain and relate to the previously mentioned principles of segregation and integration (J. R. Cohen & D'Esposito, 2016). These properties are named *modularity* and *global efficiency*, respectively corresponding to segregation and integration (Figure 9) (Sporns et al., 2004). *Modularity* is a measure of how well the network is organized into local communities (called modules) of highly interconnected nodes (Newman & Girvan, 2004). *Global efficiency* is a proxy measure of global integration and represents the ability of information to flow efficiently between brain regions through short paths (Latora & Marchiori, 2001). This measure is inversely related to mean path length, i.e. the average minimum number of steps that must be taken from one node to another (Bullmore & Sporns, 2009). High modularity and high global efficiency of the brain guarantee that integration and segregation co-exist (Tononi et al., 1994). It should be noted however that for efficient behavior and learning in particular, the brain has to show plastic capacities (Green & Bavelier, 2008). This holds true when looking at the network properties of the brain (Shi et al., 2016).

We discussed the fact that the brain connectome is referring to either structural or functional connections. One recent subfield of research has tried to understand how these two types of networks are related (Suárez et al., 2020). Structural connectivity is known to shape functional connectivity (Honey et al., 2009, 2010) however the relationship between both is not fixed and can change due to age (Esfahlani et al., 2022; Pur et al., 2022) for instance. Furthermore, it is known that even when direct anatomical interconnections are lacking, we can

observe functional connections between brain regions (Honey et al., 2009). Computational models and correlational techniques have been used to relate functional and structural measures (Hagmann et al., 2008; Honey et al., 2009). Moreover, several studies looked at the strength of coupling or uncoupling between structure and function and how it relates to behavior (Preti & Van De Ville, 2019; Vázquez-Rodríguez et al., 2019).

Now that we have described the current knowledge of the literature as well as the basic methodological concepts used in this thesis, we will present the motivation for this thesis as well as the research questions it is answering.

1.4 Motivation

When reviewing the literature regarding the age-related neural correlates of motor learning, we observe that most papers are focusing on changes following motor learning acquisition or retention (Luft & Buitrago, 2005) rather than within-session changes. Indeed, the acquisition phase is usually performed outside the scanner before the MRI sessions or in between two MRI sessions (Heuninckx et al., 2008; Goble et al., 2010; Berghuis et al., 2019). However, the research field has shown the importance of the early motor acquisition phase for later consolidation of the motor skill (Albouy et al., 2008; Gabitov et al., 2014; King et al., 2016; Santos Monteiro et al., 2017; Maceira-Elvira et al., 2022). When the acquisition phase is performed in the MRI scanner, functional activation is usually averaged over multiple blocks (Fogel et al., 2014; King et al., 2016), thus not capturing the dynamics of online motor learning that occur specifically fast (Toni et al., 1998; Gabitov et al., 2014, 2015; Maceira-Elvira et al., 2022). Toni and colleagues for example reported that over 40 minutes of training, differential activation changes occurred in many cortical regions, the time course of changes having been modeled by a set of polynomial basis functions (Toni et al., 1998). Furthermore, the study of the relationship between single-session whole-brain activation and continuous behavioral changes is already sparse in the young adults literature (Orban et al., 2010; Gobel et al., 2011; Choi et al., 2020) and to our knowledge, not existent in the aging literature. The first study of this thesis **(Chapter 3**) addresses this gap of knowledge by investigating the neural correlates during the acquisition phase of a novel motor learning task in older adults. We looked at the changes across the entire session of training and assessed the neural correlates of performance changes. As behavioral dynamics during an initial training session of motor sequence learning are substantial in older adults (Zimerman et al., 2013; Maceira-Elvira et al., 2022), we wondered what would be the associated dynamics of whole-brain activation during the training. Our goal in this first study was to understand which brain regions are responsible for the improvement of performance during the fast "online" learning stage. Furthermore, the literature stresses the different speed-accuracy relationships in motor learning in older adults (T. A. Salthouse, 1979; Forstmann et al., 2011; Maceira-Elvira et al., 2022), and we consequently asked ourselves if different brain regions were responsible for the improvement in speed and/or accuracy.

In addition to investigating the functional dynamics of activation during the training session in older adults, the second goal of the thesis was to explore relationships between behavior and changes in functional topology of the brain after a single training session as well as the interplay between structure and function. A view of the brain as a complex graph with several topological functional characteristics is beneficial to understand further how the brain is functionally organized (Bassett & Sporns, 2017). As outlined before, older adults rely on more widespread activation for good performance and sometimes in differently relevant functional networks (Mary et al., 2016; Aznárez-Sanado et al., 2022), interpreted as compensatory mechanisms to achieve similar performance (Sala-Llonch et al., 2015). Therefore, studying how the brain seen as a network with different functional subnetworks changes as a function of motor learning can give us additional insights into the processes at play in the initial phase of motor learning in older adults. Furthermore, I outlined in the previous sections the importance of structural measures as predictors of motor learning. As reported previously, functional connectivity can be inferred from structural connectivity (Honey et al., 2009, 2010) however the

relationship between both is not fixed and can change due to age (Esfahlani et al., 2022; Pur et al., 2022). The research on the structure-function relationship and its association with motor learning in older adults is missing from the literature as it is a relatively new way to look at the organization of the brain. Yet, studies have shown the importance of structure-function correspondence as a biomarker for cognitive impairment (Wang et al., 2018; Webb et al., 2020) and as a relevant characteristic of brain integrity in aging (Romero-Garcia et al., 2014; Pur et al., 2022). Thus, investigating the structure-function correspondence in the motor learning process in older adults is of great interest and importance and could inform us on the reorganization of the functional connectome in relation to the structural connectome in an older population. Therefore, the second study of this thesis **(Chapter 4**) addressed the following questions: how does better performance during the initial acquisition phase relate to changes in the functional networks' topology, and whether these changes impacted the structure-function correspondence.

Chapter 2 General Methods

In this chapter, I will describe the experimental study performed during the course of my PhD project. The content of this thesis is part of a bigger project, named "*EconS: Enhancing sleep-dependent consolidation by non-invasive brain stimulation to boost motor skill acquisition in individuals after stroke*". In the next section, I will describe the rationale of the project, present the experimental design and detail the main analyses performed in the context of this thesis.

2.1 Rationale

As introduced in the first part of the thesis, older adults show difficulties in motor learning. The mechanisms of this decrement are thought to depend on multiple factors, such as decreased capacity during the acquisition process or the consolidation. This thesis aimed at characterizing the dynamic brain processes occurring during the initial acquisition phase of motor learning in older adults. To do so, we investigated the BOLD activation correlates of motor learning during the initial phase (Chapter 3), as well as the structural, and functional connectomes and their correspondence changes associated with higher motor learning ability (Chapter 4).

The second aim of this project was to target the sleep-dependent consolidation of the motor learning process by non-invasive brain stimulation and assess whether this intervention would facilitate the consolidation of motor memory in older adults. This aspect of the project is addressed in the thesis of my colleague Maëva Moyne. Stimulation during sleep has previously been applied over frontal areas to improve declarative memory consolidation by Marshall and colleagues (Marshall et al., 2006) or to improve motor learning consolidation (on a finger tapping task) by Lustenberger and colleagues (Lustenberger et al., 2016). Following the method of the latter study, we applied a placebo-controlled transcranial alternating current stimulation (tACS) protocol that resembles the natural spindle pattern of young adults. The rationale behind this stimulation is to induce spindles in the sleeping older brain, as it has been shown that tACS can entrain endogenous oscillations of the brain (Helfrich et al., 2014). The stimulation was applied during a short daytime nap since evidence exists regarding the fact that a nap is as efficient as a night to induce sleep-dependent learning (Mednick et al., 2003). In parallel, electroencephalography was measured to monitor the sleep states and to be able to analyze sleep physiological data. The results of the effects of stimulation on motor learning ability and sleep physiology are presented in the work of my colleague. As a secondary analysis of this thesis, we investigate the effects of stimulation compared with placebo in the online learning process by comparing the BOLD activation from the training period with the ones of the follow-up session. The results are presented in Appendix 1.

The third aim of this project consisted of a proof of concept for conducting the same motor and stimulation paradigm in a population of stroke patients. It is well-known that motor learning processes are crucial to motor recovery in patients who suffered from a stroke (Krakauer, 2006). Stroke is one of the leading causes of long-term disability worldwide. Moreover, it appears that most stroke survivors are above 60 years old (Kissela et al., 2012). Thus, there is a strong need to understand the mechanisms of motor learning in older adults to be able to more precisely tune motor therapies for stroke survivors. The behavioral results of the training phase of motor learning in the tested stroke patients are presented in Appendix 2.

2.2 Study design

The present study is a randomized, double-blinded, parallel trial implementing longitudinal assessments with training and post-nap period, and follow-ups at 24 hours and 7 to 10 days after the initial learning session (Figure 10). On Day 0, subjects were screened, and explained about the experiment in detail. After signing the informed consent, they filled out questionnaires to confirm the absence of MRI, transcranial electric stimulation (tES), and transcranial magnetic stimulation (TMS) contraindications as well as to assess cognitive abilities (the Montréal Cognitive Assessment (Nasreddine et al., 2005)), handedness (Edinburgh Handedness Inventory (Oldfield, 1971)) and quality of sleep (Pittsburgh Sleep Quality Index (Buysse et al., 1989)). On Day 1, subjects were asked to refrain from drinking caffeinated drinks to increase the probability that they would fall asleep during the afternoon nap. After arriving at the lab, the subjects were familiarized with the motor task with standardized explanations and by observing the experimenter performing it. They were then allowed to practice in a mock scanner for one block in supine position. After making sure they understood the task, subjects were brought to the MRI environment and prepared for the scanning session. The first MRI session comprised one resting-state scan of 8min (represented by the white-cross on black background in Figure 10) followed by two sessions of task and ended with one last resting-state scan (Figure 19). Before the lunch break, subjects underwent a short TMS session to determine the hotspot on the scalp above M1 to then place the stimulation electrode as precisely as possible. After the lunch break, subjects were brought to the sleep lab and were prepared for the rest period. The experimenters installed concentric stimulation electrodes and an electroencephalography-polysomnography setup to be able to monitor and record the sleep state during the rest period.

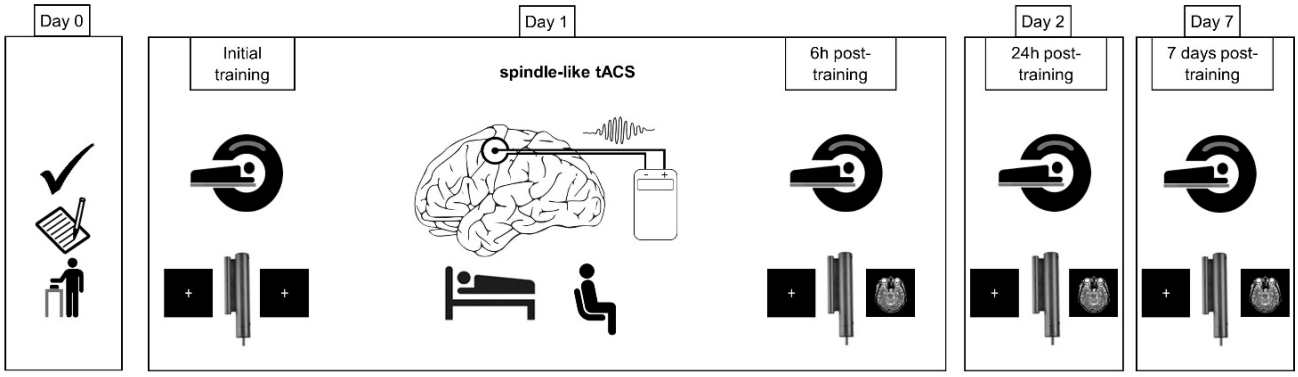

Figure 10. Experimental design. Day 0: screening day with signature of the informed consent, written questionnaires and motor abilities tests. Day 1: Main experimental day with the initial training session in the MRI, rest period comprising sleep or wake and real stimulation or placebo stimulation.

The stimulation was applied during non-rapid eye movement (NREM) 2 and 3 sleep. As soon as the subjects reached a stable NREM2 sleep stage (at least 4 minutes) the stimulation was applied. At that point a sleep experimenter was unblinded and launched the stimulation, checking simultaneously that the subject was still asleep. Following this rest period, a follow-up MRI session was performed with resting-state, task session, and brain structural image acquisition. Subjects came back on the following day and 7 to 10 days later to go through similar follow-up measurements.

2.2.1 Subjects

Forty-three older subjects were included in the study (N=27 female, mean age ± std = 69.5 ± 4.6, mean laterality quotient Edinburgh Handedness Inventory = 83.6 ± 20.5 (Oldfield, 1971)). The following inclusion criteria were respected: subjects were right-handed, healthy, and at least sixty years old, they did not have any

contraindication for tES, TMS, or MRI. These contraindications consisted in absence of neuropsychiatric diseases, history of seizures, intake of psychoactive medication that potentially interacts with tES or TMS, pregnancy, and intake of narcotic drugs. Furthermore, we excluded individuals who were unable to provide informed consent, were unable to follow the procedures of the study, and who requested to not be informed in case of incidental findings.

Fifteen chronic stroke patients were further included (N=7 female, mean age ± std = 66.6 ± 12.7). Left-handedness was not an exclusion criterion as our interest was in the investigation of motor learning of the affected hand. Within our cohort of stroke patients, 8 had the left hand affected, equivalent to right hemispheric stroke. The same inclusion criteria were applied regarding the contraindications for the procedures of the study. In addition, individuals suffering from stroke were at least 18 years old, and presented a mono-hemispheric stroke. The study could be performed at least six months after stroke onset. Furthermore, multiple stroke and cerebellar stroke were exclusion criteria.

2.2.2 Motor task design and implementation in the MRI environment

In our study, we chose to investigate motor learning with an explicit sequential grip force modulation task adapted for the MRI environment. We chose the task to be explicit to lower to the minimum the cognitive load and because previous evidence shows that implicit motor sequence learning was not impacted by sleep (Robertson, Pascual-Leone, & Press, 2004; Nemeth et al., 2010). Moreover, we implemented a whole-hand task to accommodate stroke patients who might not be dexterous enough to perform fine-grained finger movements such as key presses. A similar task was performed with stroke patients outside the scanner (Mooney et al., 2020). The task was modified based on a previous study of our lab (Wessel et al., 2020), it is a modified version of a pinch grip force task (Reis et al., 2009) on which subjects showed improvement over a prolonged period.

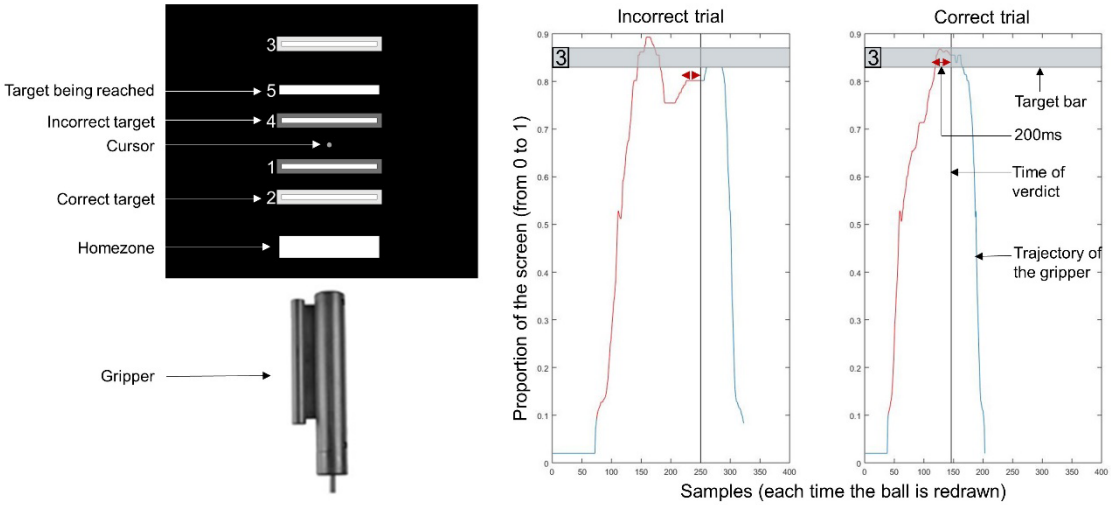

Figure 11. Depiction of the motor learning task used in the experiment. Upper left: Image visible on the screen by the subjects. Lower left: MRI-compatible gripper. Right: Depiction of an incorrect trial and a correct trial for the same target (n°3). The red curve corresponds to the trajectory of the gripper from departure to verdict. The time to travel this trajectory is the time of trial.

The setup consisted of an MRI-compatible gripper and a computer screen (Figure 11) placed behind the MRI scanner (see the photography in Figure 5). The gripper allowed to measure the gripping force applied. Depending on the force with which the gripper was pressed, a cursor moved along a vertical axis on a screen. Pressing the gripper strongly moved the cursor to the top of the screen whereas releasing the gripper moved the cursor to the bottom of the screen. The screen also displayed five horizontal bars, which are defined as targets. The targets were placed in relationship to each subject's grip maximum voluntary contraction (MVC) in ascending order: 20%, 30%, 45% 55%, and 70% of the MVC. 70% of the MVC corresponded to the upper bar placed at 85% of the height of the computer screen. The MVC was measured three times before the beginning of the

task and then averaged. The task required the subject to reach the targets in a predetermined order (following the sequence from 1 to 5) by pressing and releasing the gripper between each reach (Home-1-Home-2-Home-3-Home-4-Home-5-Home). They were asked to perform the task as fast and accurately as possible. If the subject kept the cursor more than 200ms outside of the target without moving, the target was labeled as incorrect (Figure 11). If the subject managed to maintain the gripper inside the target for at least 200ms the target was labeled as correct. The knowledge of result was made aware by the appearance of a grey frame for wrong targets and a white frame for correct targets (Figure 11).

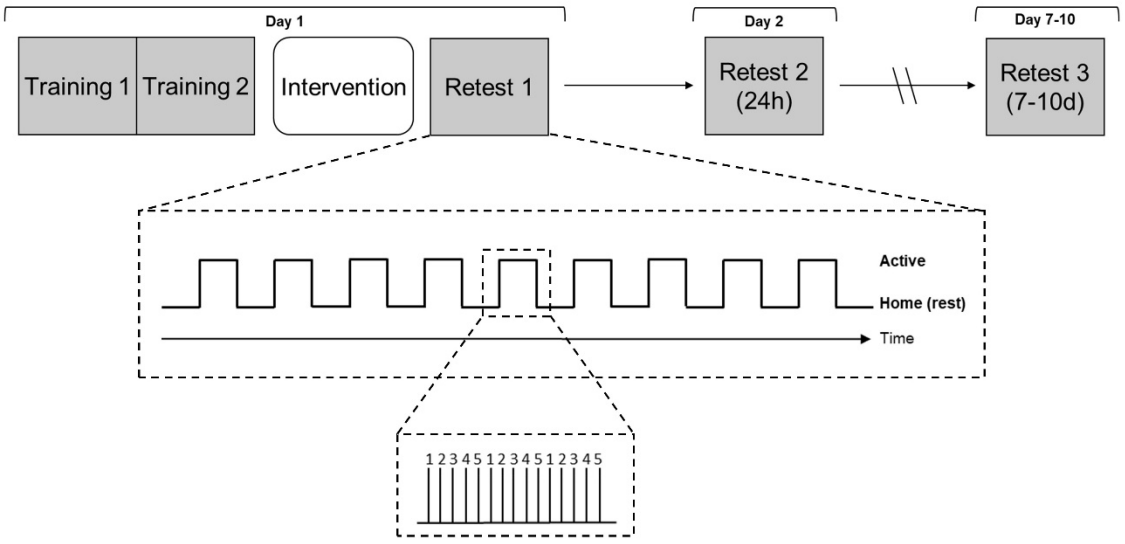

Figure 12. Experimental procedure of the motor task over the days of experiment. Design of the motor task adapted for the MRI environment.

The training session consisted of 18 blocks of practice divided into two sessions (Figure 12). The retest sessions consisted each of one session of 9 blocks. One session of task consisted of nine successive blocks, each comprising three sequences of 5 targets (named trials hereafter). A fixed number of trials was chosen according to the literature on finger-tapping paradigms assessed in the MRI environment (Barakat et al., 2013; King et al., 2016; S. Fogel et al., 2017) that also fixes the number of key presses per block to assure that all subjects trained on the same number of trials. All the sequences were the same across the blocks except for one block called a random block. The random block had the same amount of trials but the goal zones were in a different order.

2.2.3 MRI procedures

Imaging data were acquired with a 3T Magnetom Prisma scanner (Siemens Healthcare AG, Erlangen, Germany) with a 64-channel head coil. Multislice whole-brain T2*-weighted functional MRI images were obtained with an interleaved gradient-echo planar imaging (EPI) of 70 slices (TR= 900 ms TE=32 ms, FA = 50°, FOV read = 224 mm, receiver bandwidth= 2480 Hz/Px, acceleration factor=7 and voxel size of 2mm^3). T1-weighted sagittal anatomical brain image was acquired at the end of the first day, using a magnetization-prepared rapid gradient echo (MP-RAGE) sequence consisting of 192 slices (TR=2300 ms, TE=2.96 ms, TI=900ms, FA=9°, FOV read=256 mm, GRAPPA factor = 2, receiver bandwidth= 240 Hz/Px and voxel size of 1 mm3). For estimating magnetic field inhomogeneities, we additionally acquired a gradient echo field map. For diffusion-weighted MRI, the sequence we used is called the pulsed-gradient spin-echo sequence. Diffusion-weighted MRI (dMRI) data composed of 108 volume images, including 101 with diffusion weighting at multiple *b* values of 300, 700, 1000, 2000, and 3000 s/mm^2 and seven without diffusion weighting (*b*=0), The following parameters were used: number of slices = 84, slice thickness = 1.6 mm, matrix size = 146 × 146, and in-plane resolution = 1.6 mm × 1.6 mm. This value allows having a good contrast (better contrast with larger *b*) without losing too much signal.

2.3 Main analyses

2.3.1 Motor behavior analysis

Forty-one datasets were finally included in the analysis as two subjects did not understand well the motor task or had vision difficulties in the MRI scanner. The primary outcome of the study is the behavioral motor score. The motor performance was first computed in terms of accuracy and average time to reach targets across trials. When analyzing the behavioral data, we noticed that some trials were invalid because of a limitation of the gripper (see one example in Figure 13). These invalid trials comprised on average over all subjects 1.69% of all trials of the entire experiment, they were discarded from the analysis.

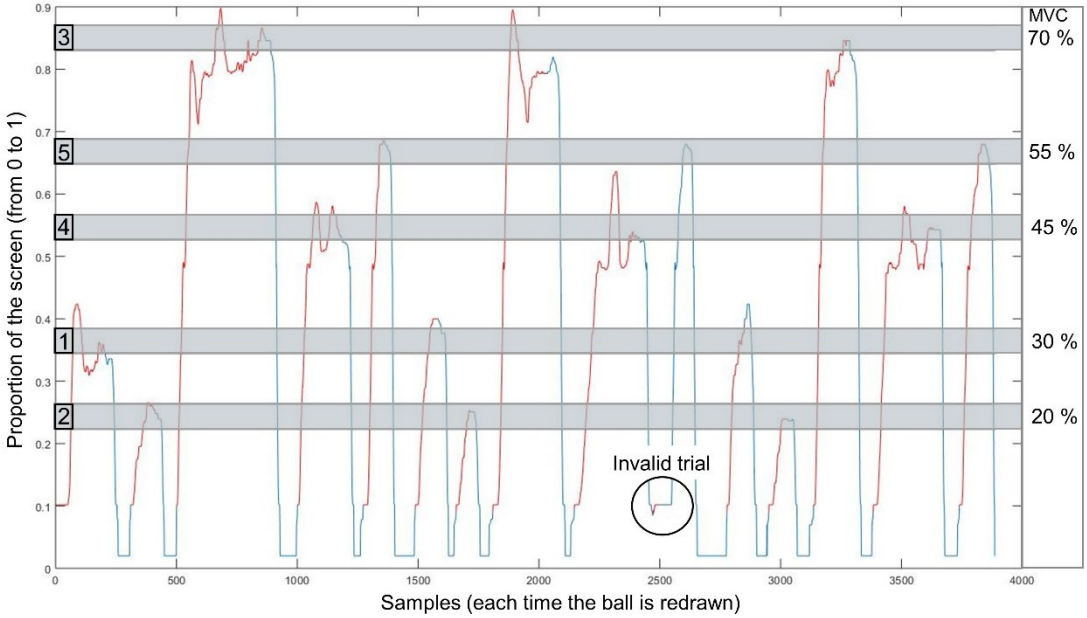

Figure 13. Depiction of the trajectory of the cursor during one entire block. The tenth trial is an invalid trial.

Following this quality check, accuracy was computed for each block as the percentage of correct trials per block. The average time per block was calculated as the mean time to reach each valid trial (the time spent from the moment the cursor left the home zone to the moment the cursor stopped depicted as red curves in Figure 13). To obtain a single compound score reflecting both speed and accuracy, we used a modified calculation as proposed by Townsend and Ashby (Townsend & Ashby, 1978) in which we computed the ratio of the accuracy to the average time per block (Figure 16).

2.3.2 fMRI analysis

Task-based functional data were preprocessed and analyzed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/; Welcome Department of Imaging Neuroscience, London, UK) implemented in Matlab (version R2018a). The preprocessing was performed on all sessions together and comprised the following steps: a two-pass realignment procedure was performed using rigid body transformations with realignment to the first image of the first session followed by a second realignment step to the mean functional image. After calculating a voxel displacement map from the field map, all functional volumes were corrected for magnetic field distortions. The mean functional image was then coregistered to the structural T1-image using a rigid body transformation optimized to maximize the normalized mutual information between the two images. This coregistration step was then checked for each individual and manually corrected if misalignment was observed. The coregistered T1-images were segmented into three types of brain tissues (cerebrospinal fluid, white matter, and grey matter) and normalized to standard MNI space. The normalization

parameters were subsequently applied to the individually coregistered BOLD times series, which were finally spatially smoothed using an isotropic 8-mm full-width at half-maximum (FWHM) Gaussian kernel. The following analyses consisted of the creation of first-level general linear models for each subject. Please refer to Chapter 3 for a more precise description.

For the resting-state functional data presented in Chapter 4, a similar processing pipeline was used. In addition, nuisance covariates regression was applied to model effects of low-frequency fluctuations, head movement using six movements regressors, and non-neuronal fluctuations on resting state fMRI signals. For 246 brain regions as defined by the Brainnetome atlas (Fan et al., 2016), a brain functional connectome was constructed by computing the correlation of signals between each pair of the 246 brain regions (Figure 14). To investigate the involvement of specific functional systems, seven cerebral networks were chosen to be assessed following the classification of Yeo and colleagues (Yeo et al., 2011). The assignment of brain regions to the networks followed suggestions from the Brainnetome website (https://atlas.brainnetome.org/download.html). To create a sparse connectivity matrix, we thresholded the binary network by considering that an edge is absent between a pair of regions when the correlation between functional signals did not survive after false discovery rate correction for multiple comparisons at the significant level of $p \leq 0.05$. Lastly, we then computed global efficiency and modularity for the whole-brain network and for the seven subnetworks using the Brain Connectivity Toolbox (https://sites.google.com/site/bctnet/) (Rubinov & Sporns, 2010) implemented in Matlab.

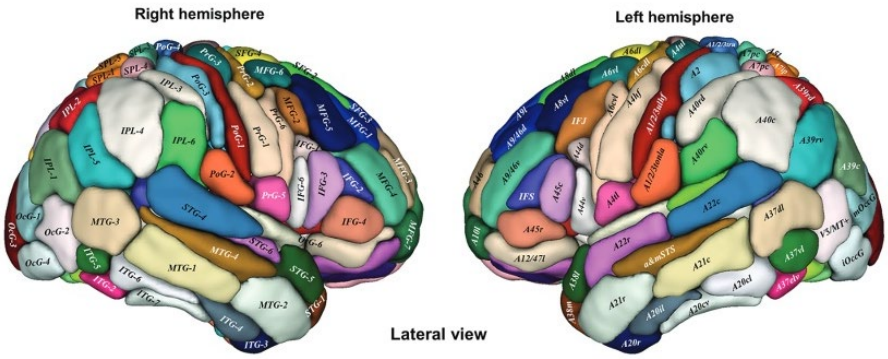

Figure 14. Parcellation scheme of the human brain of the Brainnetome Atlas in MNI space. Adapted from Fan et al. 2016.

2.3.3 Structural MRI analysis

Using tools in MRtrix3 (https://www.mrtrix.org/) and FSL (https://fsl.fmrib.ox.ac.uk/fsl/), images of diffusion-weighted MRI were corrected for Gibbs ringing artifacts, field inhomogeneity, susceptibility-induced off-resonance field, and head motion and eddy currents. By estimating the fiber orientation distribution function within each voxel via multi-shell multi-tissue constrained spherical deconvolution (Jeurissen et al., 2014), whole-brain tractography was conducted based on the probabilistic algorithm of the second-order integration over fiber orientation distribution (Tournier et al., 2019). A total of 10 million streamlines were generated by initiating them at each voxel of white matter. For the same 246 brain regions of the Brainnetome atlas (Fan, Li et al. 2016) in the standard space, a brain structural connectome was constructed by selecting fiber bundles that connected each pair of the 246 brain regions among those over the whole brain.

2.3.4 Structure-Function correspondence

The relationship between structure and function can be assessed in different ways depending on the model used to explain the structure-function coupling (Suárez et al., 2020). We chose to follow the technique described by Vázquez-Rodríguez and colleagues (Vázquez-Rodríguez et al., 2019). A multilinear regression

model was implemented to predict functional connectivity between two regions (otherwise called nodes) according to the geometry and topology of the pair within the structural network. For each pair of nodes, we computed three structural measures: the Euclidean distance between the node's centers, the path length defined as the shortest path of edges between two nodes within the structural network, and the communicability as defined in the weighted sum of all paths and walks between the nodes. Here is the equation for calculating the communicability C_{ij} between nodes *i* and *j*:

$$C_{ij} = [e^A]_{ij}$$

with A the adjacency matrix, i and j two different nodes

The measures were computed in Matlab and using Brain Connectivity Toolbox for the path length. Following these computations, the multiple linear regression model was constructed for each node as:

$$FC_i = b_0 + b_1 EU_i + b_2 PL_i + b_3 C_i$$

with FC the vector of functional connectivity from node i to all other nodes, b_0 the intercept and b_1, b_2, b_3 the regression coefficients, EU the euclidean distance, PL the path length, and C the communicability.

The regression coefficients and intercept were determined by ordinary least squares. Finally, the correlations with behavior were assessed with a multiple regression model using the goodness-of-fit measure R^2 as a measure of structure-function correspondence.

2.4 Research questions and hypotheses

To summarize, this thesis aimed at filling the gap in knowledge regarding the characterization of the dynamic brain processes during the initial acquisition phase of motor learning in older adults. To do so, we investigated fMRI correlates of motor learning during the initial phase (Chapter 3), as well as the structural, and functional connectomes and their correspondence changes associated with higher motor learning ability (Chapter 4).

Study 1: *Early motor skill acquisition in healthy older adults: brain correlates of the learning process*

Research questions: Which brain regions show activation changes involved in the early acquisition of a novel motor skill in older adults? Which brain regions are associated with the change of behavior in terms of compound measure or speed and accuracy? Are there commonalities and/or differences between the time-modulated activation and the performance-modulated activation?

Hypotheses: We expected to observe a wide range of brain cortical regions changing within the training session comprising frontal, parietal and motor-related regions in addition to subcortical areas and cerebellar regions. We specifically hypothesized that we would observe dynamics in visual, motor, and cognitive-related cortical networks. Investigating brain regions associated with the change of behavior during the training session was never done before in older adults during the training session, this analysis was thus explorative. Nevertheless, as the initial training session involves the formation of spatial coordinates, we expected the frontoparietal areas to play a role.

Personal contribution: Study design, data acquisition, data analysis, results interpretation, writing, and editing of the manuscript.

Study 2: *Brain Connectome Correlates of Short-Term Motor Learning in Healthy Older*

Research questions: How do functional brain networks change in terms of integration and segregation in relation to the change of motor performance during the acquisition of a motor skill in older adults? Does this change impact the structure-function correspondence? Additionally, does the structure-function correspondence changes also relate to performance change?

Hypotheses: We hypothesized that motor learning-induced brain connectome changes would be mainly driven by an associative frontoparietal circuit. As it is known that the aging brain is less segregated, we expected that the better the motor acquisition (closer to a young-like pattern), the more segregated the brain networks would become. Regarding the brain structure-function correspondence, the analysis was rather explorative as the relationship between motor skill acquisition and the structure-function correspondence is a new question of research.

Personal contribution: Study design, data acquisition, results interpretation, writing, and editing of the manuscript.

Chapter 3 Study 1: *Early motor skill acquisition in healthy older adults: brain correlates of the learning process*

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3.1 Abstract

Motor skill learning is a crucial process at all ages. However, healthy aging is often accompanied by a reduction in motor learning capabilities. This study characterized the brain dynamics of healthy older adults during motor skill acquisition and identified brain regions associated with changes in different components of performance. Forty-three subjects participated in an fMRI study during which they learned a sequential grip force modulation task. We evaluated the continuous changes of brain activation during practice as well as the continuous performance-related changes of brain activation.

Practice of the motor skill was accompanied by increased activation in secondary motor and associative areas. In contrast, visual and frontal areas were less recruited as task execution progressed. Subjects showed significant improvements on the motor skill. While faster execution relied on parietal areas and was inversely associated with frontal activation, accuracy was related to activation in primary and secondary motor areas. Better performance was achieved by the contribution of parietal regions responsible for efficient visuomotor processing and cortical motor regions involved in the correct action selection. The results add to the understanding of online motor learning in healthy older adults, showing complementary roles of specific networks for implementing changes in precision and speed.

3.2 Introduction

Motor learning is a process by which a motor skill is acquired with repeated practice. It is characterized by a succession of stages in which performance increases while functional and structural brain changes occur (Dayan & Cohen, 2011). These stages are described as an initial fast learning stage (sometimes referred to as "early online learning") that occurs within the first minutes of practice of the motor task, followed by a slow learning stage unfolding over multiple days and involving several sessions of practice interleaved with periods of rest (Doyon & Benali, 2005). With age, the ability to learn new motor skills is reduced (Brown et al., 2009; King et al., 2013), and these age-related differences have been associated with different mechanisms such as the degree of task complexity (Voelcker-Rehage, 2008; Onushko et al., 2014), a decrease in processing speed (Salthouse, 2000; Critchley et al., 2014) or a more general cognitive decline that would impact motor learning (Bo et al., 2009; Bishop et al., 2010; Anguera et al., 2011). Regarding the initial fast learning stage, while several studies reported similar improvements in older compared to younger adults (Seidler, 2006; Brown et al., 2009), other reports significant differences (Daselaar et al., 2003; Shea et al., 2006; Zimerman et al., 2013; Maceira-Elvira et al., 2022).

The neural correlates of the initial motor learning acquisition phase have been extensively studied in young adults thanks to functional magnetic resonance imaging (MRI) (see Dayan & Cohen, 2011 for review; Hardwick et al., 2013; Lohse et al., 2014 for meta-analyses). It is now well-accepted that the first acquisition of a motor skill relies on two different, but interacting networks, namely a cortico-cerebellar and a cortico-striatal network (Hikosaka et al., 2002; Doyon & Benali, 2005). Within the cortical correlates, fronto-parietal associative areas are thought to be recruited when the spatial coordinates of the motor skill are acquired, a process occurring fast, while sensorimotor areas are involved in the acquisition of motor coordinates, a process occurring on a slower timescale (Hikosaka et al., 2002). In addition to the cortical correlates, subcortical regions, i.e., the cerebellum and the basal ganglia, have been shown to be involved in a cortico-cerebellar and cortico-striatal circuit (Doyon et al., 2003), both recruited in the early motor learning phase. In the aging population, the circuits recruited during motor skill acquisition are similar (Lin et al., 2012; Fogel et al., 2014; Berghuis et al., 2019), but with more widespread patterns of activation and additional bilateral frontal, motor and temporal areas (Voelcker-Rehage, 2008; Turesky et al., 2016; Berghuis et al., 2019). Several cognitive models were

proposed in the recent years to explain the compensatory brain mechanisms in the aging population: the Hemispheric Asymmetry Reduction in Old Adults (HAROLD) model (Cabeza, 2002) states that more bilateral activation in motor and frontal areas allow to reach comparable performance to young adults, the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) (Reuter-Lorenz & Cappell, 2008) argue that higher neural recruitment of cognitive circuits occurs in older adults, finally the Posterior-Anterior Shift (PASA) model (Davis et al., 2008) explains age-related reduction in activation of posterior brain regions as a manifestation of the impairment in sensory processing that would be compensated by increases in activation of frontal regions.

Most of studies investigating single-session motor learning usually employ a pre-post design with a practice period performed outside of the MRI scanner (Boe et al., 2012), or compare an already-learned task to a new task (Jenkins et al. 1994). However, averaging activation over blocks may not capture faithfully the dynamics of online motor learning (Gabitov et al., 2015).

Within-session dynamic changes were only sparsely studied in young adults (Toni et al., 1998; Floyer-Lea & Matthews, 2005; Boe et al., 2012) and, to the best of our knowledge, not investigated in older adults. Furthermore, the relationship between single-session whole-brain activation and continuous behavioral changes is quite scarce (Orban et al., 2010; Gobel et al., 2011; Choi et al., 2020), and usually include one component of performance, i.e., either speed or accuracy. Improvement on the finger tapping task for example, one of the most used tasks in the motor learning field, is generally described in terms of speed (Orban et al., 2010). A few studies however, looked at different components of motor performance, but either in young adults (Lefebvre et al., 2012) or on multiple-day learning (Wadden et al., 2013).

Considering the limited amount of reports on the within-session brain changes and their relationship with performance during the acquisition of a motor skill in older adults, we designed a task-based whole-brain fMRI study involving a novel motor learning task and assessed practice-related and performance-related brain activation during the practice session. We expected to see behavioral improvements on the task and to detect concurrent distinct brain dynamics in visual, motor and cognitive areas. Among these dynamics in brain activation, we investigated the regions specifically involved in the change of performance. Furthermore, following the work of Wadden and colleagues (Wadden et al., 2013), we assessed if we could also observe different neural patterns associated with the different components of performance improvement, i.e. speed and accuracy.

3.3 Methods

3.3.1 Subjects

Forty-three healthy right-handed older adults participated in the study (N=27 female, mean age ± std = 69.5 ± 4.6, age range = 61 – 80 years old, mean laterality quotient Edinburgh Handedness Inventory = 83.6 ± 20.5 (Oldfield, 1971)). We included subjects with the following inclusion criteria: older than or equal to 60 years old, absence of contraindication for transcranial electric stimulation (tES), transcranial magnetic stimulation (TMS), or magnetic resonance imaging (MRI). These contraindications comprised neuropsychiatric diseases, history of seizures, intake of psychoactive medication that potentially interacts with tES or TMS, pregnancy, intake of narcotic drugs. Furthermore, we excluded subjects requesting not to be informed in case of incidental findings. The data of N = 41 subjects were finally included in the analysis as two subjects did not understand well the motor task or had vision difficulties in the MRI scanner. The study was carried out in accordance to the Declaration of Helsinki. Written informed consent was obtained from all subjects. Approval was obtained from the cantonal ethics committee Geneva, Switzerland (project number: 2017-00224).

3.3.2 Experimental design

The experiment was designed as a multiple-days study. On Day 0, subjects were screened and were explained the experiment in detail. They filled questionnaires to confirm the absence of MRI, tES and TMS contraindications as well as to assess the cognitive abilities (the Montréal Cognitive Assessment (Nasreddine et al., 2005)), handedness (Edinburgh Handedness Inventory (Oldfield, 1971)) and quality of sleep (Pittsburh Sleep Quality Index (Buysse et al., 1989)).

On Day 1, subjects were asked to refrain from drinking caffeinated drinks. After arriving at the lab, the subjects were familiarized to the motor task with standardized explanations and by observing the experimenter performing it (Figure 15A). They were then asked to practice in a mock scanner for one block in supine position. The first MRI session comprised one resting-state scan of 8 minutes followed by two sessions of task and ended with one last resting-state scan (Figure 15A). During the afternoon, subjects underwent a non-invasive brain stimulation, sham-controlled intervention associated with a period of sleep. Following the sleep period, follow-up behavioral sessions were performed over multiple days to assess the effect of the stimulation on behavioral improvement. As the main focus of the present study is understanding the neural dynamics during the initial fast learning session, results of the resting-state scans and of the effects of stimulation will be presented elsewhere.

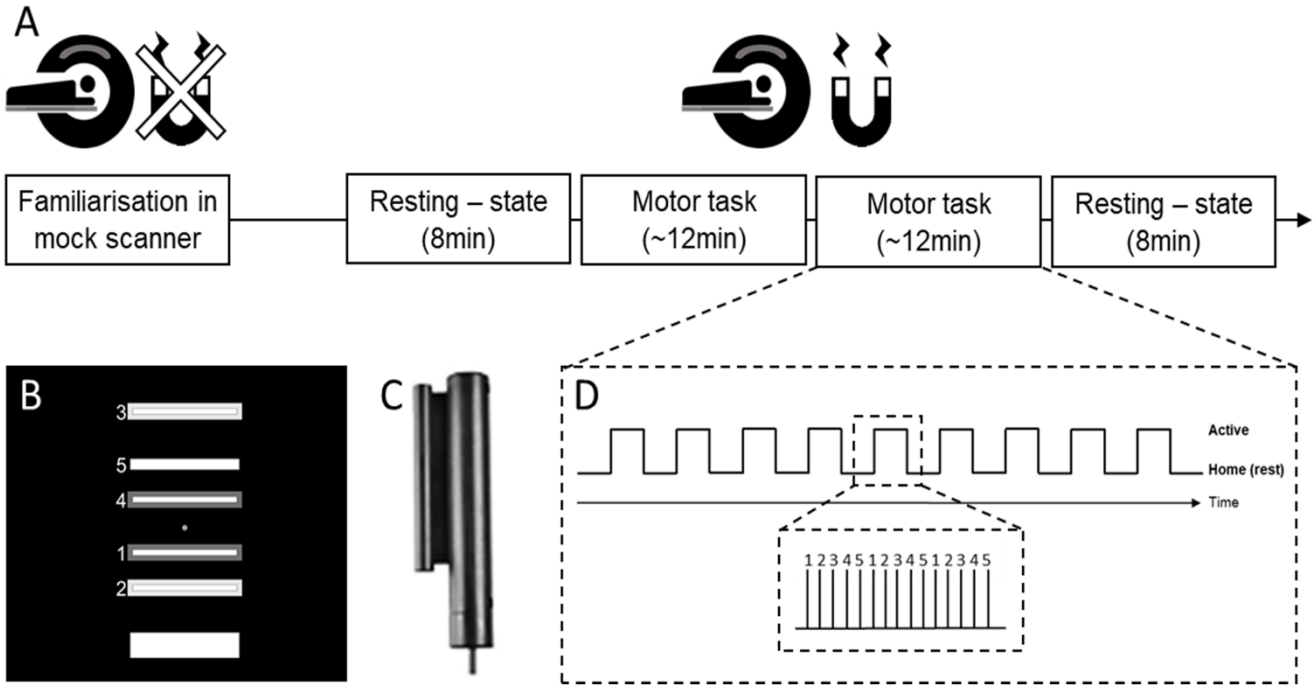

Figure 15. MRI training session. A: Subjects were familiarized to the task in the mock scanner and were then brought to the MRI environment for resting-state sessions and task-based fMRI. B: Screen of the sequential grip force modulation task (SGFMT). Subjects navigated a cursor as fast and accurately as possible by modulating their grip force between a homezone and each of five numbered target zones following a sequential order. C: MRI-compatible fibre optic grip force sensor used in the present study. D: Block design of one session of the fMRI motor task. The session consisted in 9 blocks of three sequences. The rest periods consisted in a fixation cross.

3.3.3 Motor learning task

The motor skill learning task consisted of a sequential grip force modulation task (SGFMT) adapted from Reis and colleagues (Reis et al., 2009) and from a previous study in the lab (Wessel et al., 2020). It was implemented in Matlab (version R2018a) and displayed in the MRI scanner with a screen behind the head of the subjects

who could see it thanks to a tilted mirror above their eyes. The grip forces were sampled with a fibre optic grip force sensor (Current designs, Inc., Philadelphia, PA, USA) compatible with the MRI environment (Figure 15C). Subjects controlled an onscreen cursor with the grip force sensor using their non-dominant left hand. The cursor moved vertically upwards with increasing force while it went back to the initial position at the bottom of the screen when the subject released the gripper. The subjects were asked to navigate the cursor between a homezone and 5 target zones (Figure 15B) scaled to individual maximal force measured before the start of the task. The topmost bar corresponded to 70% of the maximal force and placed at 85% of the height of the computer screen. The instruction was to place the cursor in each target by following the sequence from 1 to 5 as fast and accurately as possible and by releasing the gripper after reaching each target. When the cursor reached the correct target and was maintained in the target for 200 ms, the success was made aware by the appearance of a white frame on the target. If the cursor stopped for more than 200 ms outside of the correct target, the trial was labeled as being wrong and the failure was notified by the appearance of a dark grey frame (Figure 15B). Each session of task consisted of eight blocks of practice (Figure 15D) of the learning sequence and one block of random sequence placed at the 5th block. Each block was preceded by a countdown from 5 to 1 displayed on the screen. No other starting cues were given and the movements of the cursor were self-paced. Each block terminated when three sequences were performed (regardless of accuracy of the movements) and were followed by 15s of rest indicated by a white cross on black background.

3.3.4 Behavioral data analysis

The motor performance was first computed in terms of accuracy and average time to reach targets across trials (Figure 16). When analyzing the behavioral data, we noticed that some trials were invalid because of a limitation of the gripper. These invalid trials were removed from the analysis. Following this quality check, accuracy was computed for each block as the percentage of correct trials per block. The average time per block was calculated as the mean time to reach each valid trial (the time spent from the moment the cursor left the home zone to the moment the cursor stopped). In order to obtain a single compound score reflecting both speed and accuracy, we used a modified calculation as proposed by Townsend and Ashby (Townsend & Ashby, 1978) in which we computed the ratio of the accuracy to the average time per block. For the assessment of online learning, we performed a paired samples t-test analysis taking the average of the first and last two blocks of the training. Normality was tested with Shapiro-Wilk statistical test (Shapiro & Wilk, 1965).

3.3.5 fMRI Data Acquisition and Analysis

Imaging data were acquired with a 3T Magnetom Prisma scanner (Siemens Healthcare AG, Erlangen, Germany) with a 64-channel coil. Multislice whole-brain T2*-weighted functional MRI images were obtained with an interleaved gradient-echo planar imaging (EPI) of 70 slices (TR = 900 ms TE = 32 ms, FA = 50°, FOV read = 224 mm, receiver bandwidth = 2480 Hz/Px, acceleration factor = 7 and voxel size = 2mm3). A T1-weighted sagittal anatomical brain image was acquired at the end of the first day, using a magnetization-prepared rapid gradient echo (MP-RAGE) sequence consisting of 192 slices (TR = 2300 ms, TE = 2.96 ms, TI = 900ms, FA = 9°, FOV read = 256 mm, GRAPPA factor = 2, receiver bandwidth = 240 Hz/Px and voxel size = 1mm3). For estimating magnetic field inhomogeneities, we additionally acquired a gradient echo field map.

Functional data was preprocessed and analyzed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/; Wellcome Centre for Human Neuroimaging, University College London, London, UK) implemented in Matlab (version R2018a). The preprocessing comprised the following steps: realignment and correction for magnetic field distortions, coregistration of the mean functional image to the structural T1-image, segmentation of the T1 image into three types of brain tissues (cerebrospinal fluid, white matter and grey matter) and normalization to standard MNI space. The normalization parameters were subsequently applied to

the BOLD times series, which were finally spatially smoothed using an isotropic 8-mm full-width at half-maximum (FWHM) Gaussian kernel.

Statistical analysis consisted of general linear models (GLM) that account for fixed and random effects. The subject-level model included all sessions, each of them modelled with block regressors coding for the practiced sequence, for the preparation phase (countdown) and for the random sequence (fifth block). These regressors consisted of box cars convolved with the canonical hemodynamic response function. Global signals of cerebrospinal fluid and white matter and six movement parameters were included as covariates of non-interest. Spike regressors derived from thresholding the framewise displacement (FD) signal (Power et al., 2012) at 2 mm were also included. We adopted a liberal threshold for the FD considering the relatively large head movements in older adults (Savalia et al., 2017). High-pass filtering was implemented in the design matrix using a cutoff period of 128 s to remove low-frequency drifts from the time series. Serial correlations were estimated using an autoregressive (order 1) model and a restricted maximum likelihood (ReML) algorithm. Separate models were created to assess the time modulation effect (model 2) and the performance modulation effect (model 3), including each of them as orthogonalized parametric regressors. Only first order modulation was considered for the models. The main performance measure used was the compound measure. Separate secondary analyses were performed post-hoc to understand whether the brain regions found to be associated with the compound measure contributed differently to accuracy and speed. The other covariates of non-interest were the same as the first model described above.

To obtain significant activation induced by the task during the training session, a linear contrast tested the main effect of practice on the two training sessions in model 1. The same contrasts were computed for the time-modulated regressor in model 2 and the performance-modulated regressor in model 3. These contrasts allowed to generate statistical parametric maps [SPM(T)] at the individual level. The resulting contrast images were entered in a second-level analysis, accounting for intersubject variance and allowing inferences to be made at the population level.

In the second-level analyses of the training session, one-sample t-tests were run on the entire sample as subjects. This test was performed for execution-related activation, time-modulated activation and performance-modulated activation. Additional conjunction analyses were carried out to assess the distributional relationship between time-modulated activation and performance-modulated activation. To do so, we computed the one sample t-tests of the performance-modulated activation with inclusive or exclusive masks of the time-modulated activation, thresholded at $p<0.05$ uncorrected, and inversely. For all fMRI results presented in the next section, we adopted a voxel-wise threshold of $p<0.001$ uncorrected and a cluster-extent based threshold of $p<0.05$ corrected for multiple comparisons using family-wise error (FWE) rate. The anatomical automatic labeling (AAL2) atlas (Rolls et al., 2015) was used to label significant regions of activation.

3.4 Results

3.4.1 Motor learning task

Do older adults improve during the motor learning task?

To test whether the initial scores and end-of-training scores of the compound measure were different, we performed a paired sample t-test on the average of the first (mean ± std = 39.3 ± 15.1) and last (mean ± std = 59.5 ± 18.7) two blocks of the compound measure. This analysis showed a significant difference with $t(40) = -8.05$, $p < .001$. Cohen's d was estimated at -1.26 which is a large effect based on Cohen's guidelines (Cohen, 1992) (Figure 16). Secondary analyses also showed significant improvement between initial and end-of-training scores of accuracy $t(40) = -3.6$, $p < .001$, Cohen's $d = -0.56$ and average time to complete trials $t(40) =$

8.1, p < .001, Cohen's d = -1.27. We tested whether the learning was sequence specific (Supplementary information and Supplementary Figure 1, Supplementary Figure 2 and Supplementary Table 1). We could not observe a significant behavioral difference between the training and random blocks. However, when looking at the BOLD activation contrasts in Session 2 in particular, we observed significant difference in activation with more activation in cingulate middle areas, supplementary motor area, frontal opercular areas, cerebellar areas and right primary motor area. These two pieces of evidence are contradictory, they suggest that there are both a sequence-specific and sequence-independent learning occurring during the first acquisition phase.

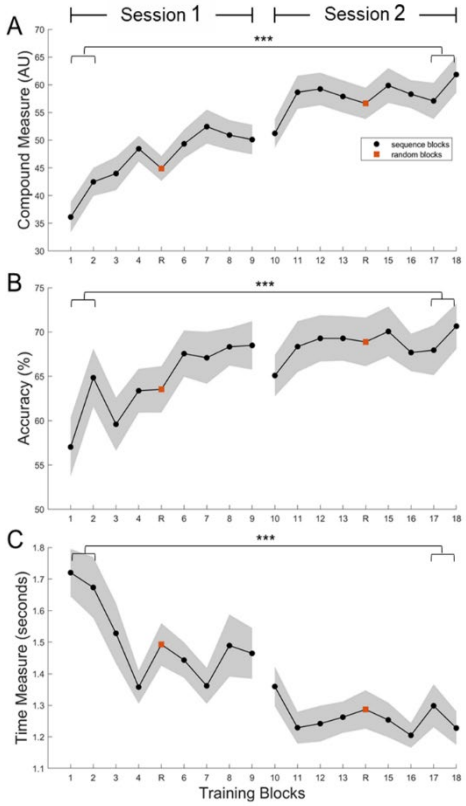

Figure 16. Evolution of performance measures throughout training. (A) a compound measure of (B) accuracy and (C) time. The training consisted of two learning sessions of 8 blocks of practice of the training sequence and two random blocks (depicted in orange in the figure). Shaded areas are the standard error of the mean (SEM). *** refers to statistical significance with p-value inferior to 0.001.

3.4.2 fMRI results

Which brain regions are involved in the execution of the task?

To assess which brain regions are activated during the initial encoding of the motor learning task, we computed a one sample t-test on the average contrast of the two learning sessions. This analysis revealed activation in a wide network comprising primary and secondary motor regions, subcortical nuclei, visual, associative and frontal areas (Supplementary Figure 3 and Supplementary Table 2).

Which brain regions show activation changes during the training session?

To investigate the dynamics of brain activation related to the task, we included a regressor modulated by time in the model. One sample t-tests were performed individually for each learning session. We observe specific patterns as training advances (Figure 17). Some regions increase linearly in both sessions, such as the bilateral

premotor cortices, contralateral (right) primary motor cortex, ipsilateral (left) superior parietal lobule (see Table 2A). Other regions decrease linearly in both sessions, contralateral ventromedial prefrontal cortex, bilateral anterior and middle cingulate areas and bilateral thalami (Table 2B).

In contrast, activation in some brain areas linearly changes only in the early or the later part of the learning (first vs. second session). In the first training session, we observe increases in bilateral inferior parietal areas, left visual middle occipital area, right hippocampus, right cerebellum and vermis and decreases in left somatosensory area and right rolandic operculum. In the second session, the results show increases in right supplementary motor area, left somatosensory area and left caudate. We further see decreases in this second session in multiple visual areas and cerebellar areas (Table 2).

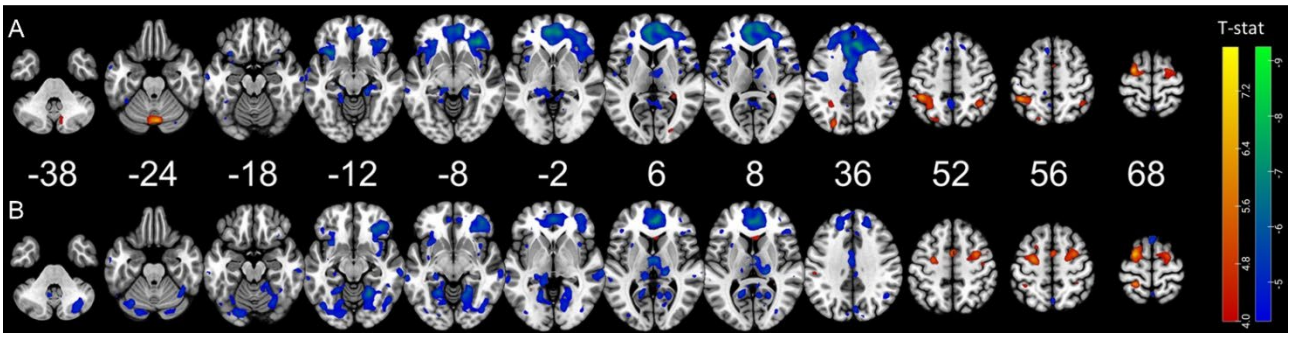

Figure 17. fMRI results of the time-modulated regions during the training sessions. First session depicted on top (A) and second session depicted below (B). Blue-green regions have their activation decreasing linearly during the session while red-yellow regions have their activation increasing during the session. Activation maps are depicted at p-unc<0.001.

A — Areas linearly increasing during the training

Region Label	Session 1				MNI Coordinates			Session 2				MNI Coordinates		
	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	x	y	z	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	x	y	z
Frontal_Sup_2_L	0.002	334	<0.001	7.32	-26	-4	68	<0.001	872	<0.001	7.81	-24	-2	66
Frontal_Mid_2_R	-	-	-	-	-	-	-	<0.001	1055	0.031	5.76	32	0	54
Frontal_Sup_2_R	0.001	348	0.386	4.72	22	-6	68	<0.001	1055	0.064	5.49	22	-4	66
Precentral_R	0.001	348	0.631	4.43	52	4	48	<0.001	1055	0.949	3.60	48	2	50
Supp_Motor_Area_R	-	-	-	-	-	-	-	<0.001	1055	0.073	5.44	0	0	52
Postcentral_L	-	-	-	-	-	-	-	<0.05	184	0.01	6.17	-24	-42	68
Parietal_Sup_L	<0.001	368	0.621	4.44	-30	-72	52	<0.05	184	0.894	4.11	-38	-46	56
Occipital_Mid_L	<0.001	368	0.095	5.32	-26	-78	36	-	-	-	-	-	-	-
Parietal_Inf_L	<0.001	1373	0.004	6.49	-44	-44	54	-	-	-	-	-	-	-
Parietal_Inf_L	<0.001	1373	0.008	6.24	-30	-54	46	-	-	-	-	-	-	-
Parietal_Inf_R	<0.05	190	0.094	5.32	36	-50	50	-	-	-	-	-	-	-
Caudate_L	-	-	-	-	-	-	-	<0.001	796	0.164	5.12	-12	-6	22
Hippocampus_R	<0.001	475	0.91	4.07	30	-38	4	-	-	-	-	-	-	-
Vermis_7	<0.001	405	0.002	6.78	4	-74	-24	-	-	-	-	-	-	-
Cerebelum_Crus2_R	<0.001	405	0.877	4.12	8	-78	-38	-	-	-	-	-	-	-
Cerebelum_8_R	<0.001	405	0.935	4.01	10	-68	-38	-	-	-	-	-	-	-

B — Areas linearly decreasing during the training

Region Label	Session 1				MNI Coordinates			Session 2				MNI Coordinates		
	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	x	y	z	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	x	y	z
Frontal_Sup_Medial_R	<0.001	17661	0.001	-6.86	8	50	6	<0.001	6869	<0.001	-7.19	4	48	4
Cingulate_Ant_L	<0.001	17661	<0.001	-8.03	-4	30	26	<0.001	6869	<0.001	-7.14	-4	42	12
Cingulate_Ant_R	<0.001	17661	<0.001	-8.46	12	38	22	<0.001	6869	0.007	-6.31	6	26	26
Cingulate_Mid_L	<0.001	17661	<0.001	-9.25	-10	26	32	<0.001	6869	0.011	-6.15	-2	4	32
Insula_L	<0.001	17661	0.001	-6.90	-34	20	-12	<0.001	402	0.078	-5.42	-32	14	-12
OFCpost_L	-	-	-	-	-	-	-	<0.001	402	0.717	-4.35	-42	28	-14
Postcentral_L	0.003	304	0.073	-5.42	-42	-12	34	-	-	-	-	-	-	-
Rolandic_Oper_R	0.002	323	0.007	-6.31	52	-10	18	-	-	-	-	-	-	-
Temporal_Mid_L	0.044	166	0.171	-5.09	-66	-12	-20	0.007	249	0.218	-5.00	-64	-34	-6
Temporal_Mid_R	-	-	-	-	-	-	-	<0.001	493	0.128	-5.22	66	-26	-2
Lingual_L	-	-	-	-	-	-	-	<0.001	7855	0.004	-6.49	-20	-54	-8
Lingual_R	-	-	-	-	-	-	-	<0.001	7855	0.024	-5.86	22	-50	-8
Calcarine_L	-	-	-	-	-	-	-	<0.001	7855	0.184	-5.07	-16	-54	8
Cuneus_R	-	-	-	-	-	-	-	<0.001	7855	0.226	-4.98	4	-78	38
Occipital_Inf_L	-	-	-	-	-	-	-	<0.001	7855	0.265	-4.91	-44	-72	-14
Fusiform_R	-	-	-	-	-	-	-	<0.001	7855	0.002	-6.80	22	-54	-14
Hippocampus_L	-	-	-	-	-	-	-	<0.001	7855	0.257	-4.93	-24	-34	-6
Thalamus_L	<0.001	17661		-4.32				<0.001	7855	<0.001	-7.26	-12	-32	2
Thalamus_R	0.043	167	0.199	-5.02	10	-4	6	<0.001	7855	0.001	-6.97	4	-10	4
Cerebelum_Crus1_L	-	-	-	-	-	-	-	<0.001	7855	0.167	-5.11	-32	-70	-28
Cerebelum_6_R	-	-	-	-	-	-	-	<0.001	7855	0.271	-4.90	26	-68	-18

Table 2. fMRI results of the time-modulated regions during the training sessions. Areas showing increasing activation (A) and areas showing decreasing activation (B). Results are reported at uncorrected p<0.001 at the voxel level, cluster level p-FWE<0.05.

Brain regions with BOLD activation associated with behavioral change

To investigate the association between brain activation and behavior, a parametric modulation analysis was performed by including the compound measure per block as a parametric regressor. The results at the group level indicate that areas associated with the improvement of performance (online learning aspect) are bilateral premotor areas, supplementary motor areas, part of the primary motor and superior parietal areas. In the significant cluster, voxels in the ipsilateral primary motor cortex are significant, the large part of the cluster is however located in the contralateral motor areas to the trained hand, as outlined in Figure 18A. In contrast, areas associated with worse performance comprise frontal and anterior cingulate areas (Figure 18A and Table 3B).

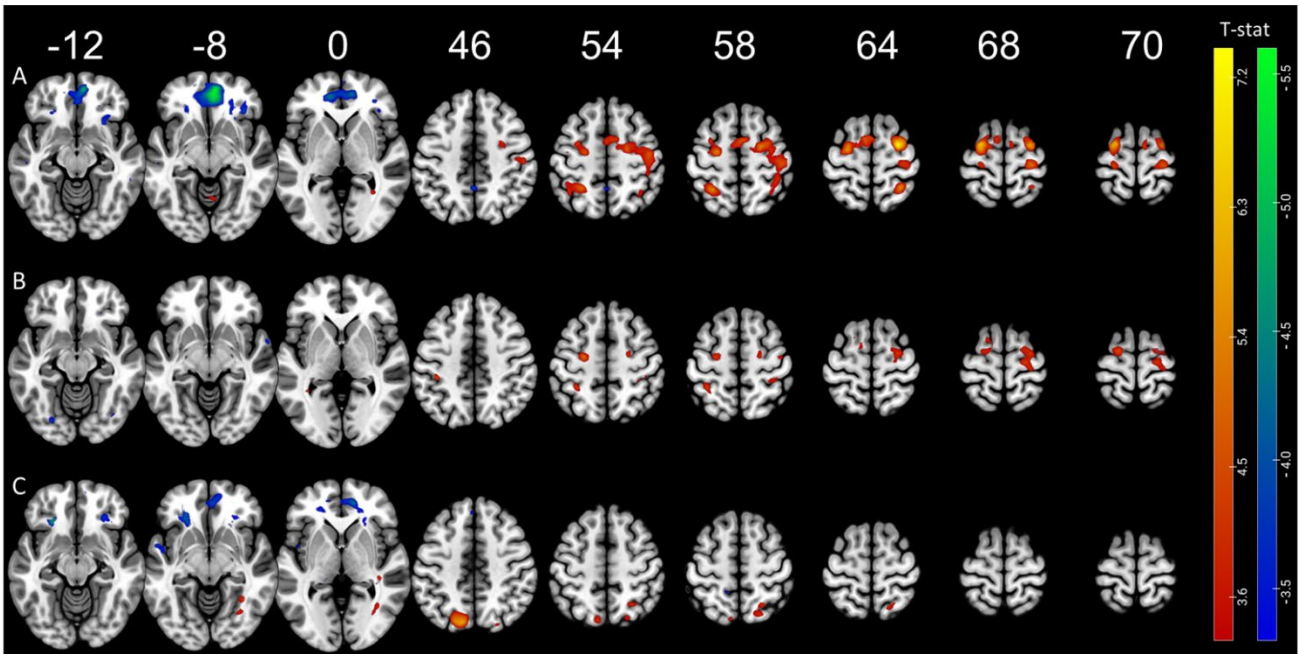

Figure 18. fMRI results of the performance-modulated regions during the training sessions. Regions associated with the compound measure depicted on top (A), the regions associated with accuracy in (B) and the regions associated with average time of trials in (C). In figure C, the color bars were reversed to be consistent with the other subfigures. Blue-green regions have their activation negatively associated with better performance and red-yellow regions are positively associated. Activation maps are depicted at p-unc<0.001.

A

	Areas positively associated with compound measure							Areas positively associated with accuracy							Areas negatively associated with average trial time						
Region Label	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates x	y	z	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates x	y	z	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates x	y	z
Frontal_Sup_2_R	<0.001	3104	<0.001	7.40	28	-4	64	<0.001	436	0.404	4.70	28	-8	66	-	-	-	-	-	-	-
Supp_Motor_Area_R	<0.001	3104	0.165	5.09	6	2	56	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Precentral_R	<0.001	3104	0.101	5.29	28	-24	68	<0.001	436	0.432	4.67	22	-18	68	-	-	-	-	-	-	-
Postcentral_R	<0.001	3104	0.309	4.82	44	-24	58	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Frontal_Sup_2_L	<0.001	3104	0.003	6.62	-24	-4	68	<0.001	369	0.214	5.00	-18	-6	72	-	-	-	-	-	-	-
Supp_Motor_Area_L	<0.001	3104	0.151	5.13	-8	2	64	<0.001	369	0.700	4.36	-10	0	66	-	-	-	-	-	-	-
Precentral_L	<0.001	3104	0.525	4.54	-24	-26	70	<0.001	369	0.097	5.32	-24	-12	52	-	-	-	-	-	-	-
Postcentral_L	-	-	-	-	-	-	-	0.014	215	0.445	4.65	-38	-34	46	-	-	-	-	-	-	-
Left ventricule	<0.001	419	0.078	5.39	-20	-36	14	<0.001	445	0.003	6.58	-20	-36	14	-	-	-	-	-	-	-
Right ventricule	<0.001	399	0.033	5.71	30	-40	12	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thalamus_R	<0.001	399	0.736	4.30	12	-22	20	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parietal_Sup_L	<0.001	468	0.049	5.57	-26	-50	58	-	-	-	-	-	-	-	0.001	365	0.013	6.06	-14	-78	46
Parietal_Inf_L	<0.001	468	0.787	4.24	-38	-54	54	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Parietal_Sup_R	<0.001	3104	0.033	5.72	30	-48	64	-	-	-	-	-	-	-	0.013	231	0.829	4.18	26	-58	54
Occipital_Sup_R	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0.013	231	0.402	4.68	28	-76	40

B

	Areas negatively associated with compound measure							Areas negatively associated with accuracy							Areas positively associated with average trial time						
Region Label	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates x	y	z	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates x	y	z	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates x	y	z
Frontal_Med_Orb_R	<0.001	2562	0.037	-5.68	4	48	-6	-	-	-	-	-	-	-	<0.001	389	0.941	-3.98	4	48	-8
Cingulate_Ant_R	<0.001	2562	0.508	-4.56	6	28	20	-	-	-	-	-	-	-	<0.001	389	0.866	-4.13	14	46	16
Frontal_Sup_Medial_R	<0.001	2562	0.840	-4.17	22	34	-10	-	-	-	-	-	-	-	<0.001	389	0.597	-4.46	12	48	0
Frontal_Inf_Orb_2_L	<0.001	2562	0.682	-4.36	-24	32	-12	-	-	-	-	-	-	-	0.02	207	0.387	-4.71	-24	28	-10
Fusiform_R	-	-	-	-	-	-	-	0.008	244	0.424	-4.68	32	-74	-18	-	-	-	-	-	-	-
Cerebelum_Crus1_R	-	-	-	-	-	-	-	0.008	244	0.985	-3.83	24	-80	-24	-	-	-	-	-	-	-

Table 3. fMRI results of the performance-modulated regions during both trainings. Areas positively associated with performance (A) and areas negatively associated with performance (B). Results are reported at uncorrected p<0.001 at the voxel level, cluster level p-FWE<0.05.

Brain regions with BOLD activation associated with speed and accuracy

Speed and accuracy as performance scores have been associated with different neural systems (Wadden et al., 2013; Perri et al., 2014). We aimed to investigate whether this was also the case in the SGFMT. Separate models with each performance measure revealed that the premotor and somatomotor areas were positively associated with accuracy while activation in frontal cingulate areas and parietal areas were related to time (Figure 18B-C). More specifically, longer average time of trials was associated with higher activation in frontal areas and lower activation in bilateral superior parietal areas.

Do we observe commonalities and/or differences between time-modulated activation and performance-modulated activation?

As a supplementary analysis, we looked at the conjunction between the practice and compound-related activation. We could observe that most brain regions associated with performance show a linear change in their activation over the course of practice (Supplementary Figure 4A). The exception was found for the activation of the contralateral postcentral area (S1), which showed a positive association with performance, but did not increase over time (Supplementary Figure 4B). Inversely, we could observe brain regions, such as visual areas and cerebellar areas changing over time, but were not related to the change of behavior (Supplementary Figure 5B).

3.5 Discussion

In this study, we examined the neural correlates of short-term online learning of a new motor skill performed in the MRI by healthy older adults. The implementation of the SGFMT was feasible in the MRI environment and older adults improved significantly on this task during the training sessions, showing that acquisition of the motor skill is possible in our aging cohort. In addition to practice-related dynamics of brain activation in a wide range of areas of the motor network, we determined here specific brain regions associated with the fast change in performance during the learning process. Worthy of note, we observed regions differentially associated with the change of accuracy or time. Increases in accuracy were associated with increased activation in parts of the cortical sensorimotor network: bilateral primary somatomotor areas and premotor areas. Conversely, decreases in time of execution were related to activation in a fronto-parietal network with increased activation in bilateral superior parietal areas and decreased activation in prefrontal and anterior cingulate areas associated with behavioral improvement.

Motor skill acquisition has been extensively studied with two types of paradigms, motor adaptation and motor sequence learning (Hardwick et al., 2013; Doyon et al., 2015; Seidler & Meehan, 2015; Maceira-Elvira et al., 2022). In the motor sequence learning literature, most studies investigate discrete sequence tasks (Karni et al., 1998; Hikosaka et al., 2002), but this paradigm has recently been critically reviewed (Krakauer et al., 2019) regarding its relevance to daily life activities. In contrast, it was posited that continuous tasks, such as the one used in the present study, are probably more comparable to real life skills (Reis et al., 2009; Wadden et al., 2013; Choi et al., 2020). In the present study, we show that a cohort of older adults, a population showing impairment in motor performance (Seidler, 2006; Voelcker-Rehage, 2008; Seidler et al., 2010), can improve significantly on this task. More specifically, although evidence exists regarding the impairment in the precision of force modulation in older adults (Voelcker-Rehage & Alberts, 2005), we show that a grip force modulation task could be even learned in a short session by older adults. Worthy of note, the sequential component of this task is not clear. Indeed, we could not observe a significant behavioral difference between the random blocks and the learned sequence blocks suggesting that our cohort might be learning an aspect of the task that is sequence-independent. Since our cohort were only explained the task and tried it briefly before the initial training it might be that our subjects are learning the visuomotor mapping between the amount of force to

apply to control the cursor. In that sense, the grip force modulation task might be closer to a de novo learning task as described by Krakauer and colleagues (Krakauer et al. 2019). Nonetheless, an additional analysis of the BOLD activation during the different blocks revealed that there is differential activation during the random blocks compared to the learned sequence blocks with more activity in visual areas suggesting that subjects rely more on visual feedback during random blocks. As such, the grip force modulation task could be seen as a mixture of different types of tasks, both sequence and de novo visuomotor learning task.

Activation elicited by the task

This is the first online evaluation of the SGMT by means of fMRI, therefore we firstly want to discuss the findings in the light of brain activation determined during other motor learning tasks. Consistently with the literature (Sterr et al., 2009; Hardwick et al., 2013; Doyon et al., 2015), a wide network comprising bilateral cerebellum, subcortical areas and especially basal ganglia and thalamic nuclei, cortical motor, visual and associative cognitive areas is involved in the first acquisition of the task. Furthermore, the observed bilaterality of activation is consistent with the HAROLD model (Cabeza, 2002).

Practice-related changes in brain activation

Changes in brain activation within a single-training session have been studied in young adults (Floyer-Lea & Matthews, 2005; Tang et al., 2009; Orban et al., 2010), but to the best of our knowledge, not investigated in older adults. Our results show similar results to the corpus of literature of young adults. Activation of the cerebellum, a region known to be involved in the early phase of learning when error is high and the movement needs to be corrected quickly (Doyon et al., 2003; Krakauer et al., 2019), first increases followed by decreases in the second session when the accuracy becomes more stable (Figure 16). This is consistent with the model posited by Doyon and colleagues (Doyon et al., 2003; Doyon & Benali, 2005; Doyon et al., 2018), which states that a cortico-cerebellar network is crucial to the early encoding of motor programs. In this model, the researchers present the dynamics of the cortical regions, which consist of constant involvement of motor cortical regions and parietal cortices while they report decreased involvement of hippocampus and frontal associative areas. Our results are partially consistent with this model, as we observe a decrease in the time course of activation of frontal areas and an increase in activation of parietal areas, suggesting that cognitive processes are less needed while procedural processes are increasing as training advances (Sakai et al., 1998). Activation of premotor areas is consistently increasing throughout the training while the supplementary motor area activation is especially increasing in the second session. These areas are thought to play a role in the integration of working memory and sensory information for the selection of action (Chen et al., 1995; Hernández et al., 2002; Floyer-Lea & Matthews, 2005; Tang et al., 2009). Differently to the model of Doyon, we find substantial decreases in the visual system, especially in the second session. This observation suggests more efficient visuospatial processing in the end of the training as in a report of Berghuis and colleagues (Berghuis et al., 2019) and stresses the difference between discrete sequence learning tasks and a continuous task with visual feedback, comparable to tracking tasks (Sterr et al., 2009). Finally, one unexpected result was a consistent decrease of activation in the thalamus observable in both sessions of the training which is rarely described. This result is probably associated to the presence of motor fatigue as suggested recently (Hou et al., 2016). One interesting aspect to point out in this analysis is that in contrast to other studies that assessed pre-post changes (Floyer-Lea & Matthews, 2005; Boe et al., 2012), we assessed the within session changes occurring in the brain while subjects performed the task. In summary, we demonstrated dynamical changes towards decreases in cognitive areas and visual areas and increases in associative and motor areas during the initial acquisition of a motor learning task.

Performance-related brain activation

In addition to looking at the overall changes in a single training, we investigated the relationship between activation and performance changes throughout the training. We observed that contralateral primary motor, bilateral secondary motor and somatosensory areas and bilateral superior parietal areas were positively associated with better performance, while medial frontal and anterior cingulate areas were negatively associated. As for the positive association, previous research reports similar results in finger tapping tasks (Orban et al., 2010, 2011; Albouy et al., 2012; Gabitov et al., 2015) and in tracking tasks (Kranczioch et al., 2008; Sterr et al., 2009). The association between performance and cerebellar activation suggested in several studies (Orban et al., 2010; Albouy et al., 2012; Wadden et al., 2013) is not clear in the present study. This differential result might be explained by the fact that in the second session of training, despite the fact that performance continues to increase, a decrease in cerebellar activation was observed. It might be that the cerebellum was strongly implicated in error correction leading to improvement of performance in the first session, but not in the second, when errors were already reduced and the performance improvement was relying on other mechanisms such as e.g., speed improvement. The cerebellum is thought to be involved in the generation of internal models (Shadmehr & Krakauer, 2008), which would be corrected at the early stages of training in order to reduce error. It could be that during the second session, the internal model is rather accurate thus leading to decreased involvement of the cerebellum. We also found negative modulation with performance in medial prefrontal and cingulate areas. These areas are known to be engaged in cognitive processes and effort (Devinsky et al., 1995; Pessiglione et al., 2018) indicating that poorer performance led to increased effort. Most of the above-mentioned areas were present in practice-related and performance-related activation (Supplementary Figure 4). The somatosensory area, however, was modulated by better performance, but not by time. A recent study has shown that the contralateral somatosensory cortex is involved in motor planning in order to achieve better movement control (Ariani et al., 2022). In our context, we hypothesize that, although activation in the somatosensory cortex did not change due to the sensory stimulus staying constant, higher activation in the area resulted in better motor planning and thus in better performance. Inversely, we could observe that activation in insula, visual, temporal and lateral frontal areas were decreased over time, but were not related to motor performance. This suggests that these areas are decreasing due to the effect of repetition, but their change is not strongly associated with the motor behavioral improvement.

Usually, improvement on motor sequence learning tasks is assessed in terms of changes in speed rather than accuracy, as accuracy ceils relatively quickly (Boutin et al., 2013; Fitzroy et al., 2021). However, this did not occur in the present task (see Figure 16), and it allowed to investigate whether different brain areas were involved in these specific aspects of motor performance. Similarly to Wadden and colleagues, who employ a joystick-tracking task (Wadden et al., 2013), we could disentangle different networks of brain activation related to the time to complete the task and the accuracy while performing the task. Improvement in accuracy was related to premotor and supplementary motor areas, whereas improvement in time was associated with higher activation in parietal areas and inversely related to medial frontal and anterior cingulate areas. Good accuracy in the present task involves selecting the good timepoint to stop increasing grip force, this is consistent with the view that premotor cortex and supplementary motor area are involved in the temporal control of movement (Halsband et al., 1993). Additionally, the involvement of somatosensory areas in the accurate maintenance of force has been reported before (Mayhew et al., 2017). Lower time to complete trials (better performance) has been suggested to be associated with effective visuo-motor processing implemented in parietal areas (Coull et al., 1996; Grefkes et al., 2004). Indeed, the superior parietal lobule is thought to act as a sensory-motor hub for the interaction with external environment (Passarelli et al., 2021) and has been shown to play a role in the rapid processing of visual information in particular (Coull et al., 1996). Inversely when the time to reach a target increases, it implies that a sustained effort is made by the subject and thus the anterior cingulate areas get more involved. This area has been proposed as a region responsible for the on-line detection

of processing conflicts that will lead to deteriorating performance (Carter et al., 1999). In other words, its activation reflects the level of conflict present in the response system. If the time to complete the task is high, it means that the initial representation of directing the cursor is wrong and thus the attention needs to be allocated to correct for this wrong representation, the anterior cingulate areas might be the region responsible for evaluating this conflict. To summarize, better performance was achieved by the interplay of distributed brain regions responsible for efficient visuomotor processing and correct selection of action. It is worthy to note that common regions, such as the cerebellum and the basal ganglia, usually involved in good performance on motor sequence learning tasks (Halsband & Lange, 2006; Lefebvre et al., 2012; Wadden et al., 2013) were not clearly associated with performance in this study. This discrepancy might be due to the difference in the motor learning task used; indeed it was posited that the basal ganglia are involved in the organization of individual elements into a sequence and to the automaticity of the execution of this set of actions (Krakauer 2019). As the present task is continuous, the relevance of the basal ganglia might not be so prominent. An additional explanation might be that this initial training period failed to induce a shift from allocentric-spatial strategy to an egocentric-motor one (Hikosaka et al., 2002; Albouy et al., 2013), thus not (yet) involving relevantly the basal ganglia in the production of good performance.

Conclusion

This work evaluated online learning and brain-behavior correlates during the acquisition of a novel motor learning task in older adults. Spatial precision was associated with higher activation in motor-related cortical areas responsible for action selection whereas speed of execution was related to associative areas involved in visuomotor processing. These results show the relevance of continuously monitoring brain activation changes during the acquisition phase of motor learning to understand which brain areas are recruited and associated with better behavior. Furthermore, this work adds to the understanding of underlying processes during motor learning in older adults and paves the way for characterizing potential targets for interventional approaches for older subjects or patients with motor deficits.

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Chapter 4 Study 2: *Brain Connectome Correlates of Short-Term Motor Learning in Healthy Older*

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4.1 Abstract

The motor learning process entails plastic changes in the brain, especially in brain network reconfigurations. In the current study, we sought to characterize motor learning by determining changes in the coupling behavior between the brain functional and structural connectomes on a short timescale. 39 older subjects (age: mean (SD) = 69.7 (4.7) years, men:women = 15:24) were trained on a visually guided sequential hand grip learning task. The brain structural and functional connectomes were constructed from diffusion-weighted MRI and resting-state functional MRI, respectively. The association of motor learning ability with changes in network topology of the brain functional connectome and changes in the correspondence between the brain structural and functional connectomes were assessed. Motor learning ability was related to decreased efficiency and increased modularity in the visual, somatomotor, and frontoparietal networks of the brain functional connectome. Between the brain structural and functional connectomes, reduced correspondence in the visual, ventral attention, and frontoparietal networks as well as the whole-brain network was related to motor learning ability. In addition, structure-function correspondence in the dorsal attention, ventral attention, and frontoparietal networks before motor learning was predictive of motor learning ability. These findings suggest that in the view of brain connectome changes, short-term motor learning is represented by a detachment of the brain functional from the brain structural connectome. The structure-function uncoupling accompanied by the enhanced segregation into modular structures over the core functional networks involved in the learning process suggests that facilitation of functional flexibility is associated with successful motor learning.

4.2 Introduction

Motor learning refers broadly to a change in the capacity to execute a motor task as a result of practice. It can occur across different timescales, leading from temporary gains in motor performance, often termed motor adaptation, to permanent acquisition of motor skills (Weaver, 2015). Since motor learning relies on the integrative contribution of brain cortical and subcortical systems to different aspects of the process (Graydon et al., 2005), it entails changes across multiple brain regions (Dayan & Cohen, 2011), which may be limited to functional changes or extended to structural changes depending on the timescale of motor learning (Scholz et al., 2009; Landi et al., 2011).

While brain functional changes were often observed for local activation during a motor task (Orban et al., 2010, 2011), it has been increasingly understood that motor learning-induced functional changes could be manifested in terms of task-related or resting state functional connectivity (T. Wu et al., 2008; Coynel et al., 2010) and collectively the brain functional connectome (Bassett & Mattar, 2017). In particular, the support of the brain functional connectome for motor learning has been assessed in terms of network topology, specifically efficiency (Heitger et al., 2012; Sami & Miall, 2013; Zang et al., 2018) and modularity (Bassett et al., 2011), but behaviorally-relevant changes in network topology that underlie motor learning ability have yet to be further clarified according to different timescales of motor learning.

The patterned brain functional connectome tends to be promoted or constrained by the architecture of the brain structural connectome, as can be simulated by generative models (Messé et al., 2015), so that there are relationships between the brain structural and functional connectomes. Given dynamic changes in the brain functional connectome in motor learning (Bassett et al., 2011, 2015), it is likely that the correspondence between the brain structural and functional connectomes would evolve as well. Especially, in short-term motor learning during which the brain structural connectome could be supposed to remain static, adaptive changes in the brain functional connectome would directly shape alterations in brain structure-function correspondence. In that regard, motor learning could be characterized by whether brain functional changes would lead to a coupling or uncoupling of the brain functional connectome from the brain structural connectome.

In the current study, for short-term motor learning with a visually guided sequential hand grip learning task, we sought to examine brain functional changes in terms of network topology of the brain functional connectome and, moreover, parallel changes in the correspondence between the brain structural and functional connectomes. Considering regional differences in brain structure-function correspondence (Zimmermann et al., 2016; Vázquez-Rodríguez et al., 2019), we assessed the motor learning-induced changes across distinguished cerebral networks, as well as the whole brain network. Short-term learning tends to rely on an associative/premotor network that is involved in the formation of the spatial representation of motor skill (Hardwick et al., 2013; Lohse et al., 2014). Consequently, we hypothesized that motor learning-induced brain connectome changes would be mainly driven by an associative circuit, rather than by a motor circuit that tends to be engaged later in the motor learning process (Kleim, 2004). In particular, for older adults, who may have been accompanied by progressively impaired motor learning ability (Voelcker-Rehage, 2008; King et al., 2013; Maes et al., 2020), we expected to explain diverse individual differences in motor learning ability by brain connectome changes.

4.3 Methods

4.3.1 Subjects

Forty-three healthy older subjects initially participated in the study, with exclusion criteria of psychoactive medication use, drug or alcohol abuse, pregnancy, inability to follow study procedures, or contraindications to MRI. Among those, 39 subjects (age: mean (SD) = 69.7 (4.7) years, men:women = 15:24) were finally included in the analysis, whereas the other four subjects were excluded due to missing or abnormal MRI data. Handedness of the subjects was confirmed to be right-handed according to the Edinburgh handedness inventory questionnaire (mean laterality quotient (SD) = 83.6 (20.5)) (Oldfield, 1971). The study was approved by the cantonal ethics committee Geneva (project number: 2017-00224), and the written informed consent was obtained from all the subjects. The study conformed to the standards according to the Declaration of Helsinki.

4.3.2 Motor learning ability

Inside an MRI scanner, the subjects performed two subsequent sessions of a visually guided sequential hand grip learning task adapted from the previously developed one (Wessel et al., 2020), with each session composed of nine training blocks containing 15 hand grip trials (three repetitions of a sequence of five hand grip trials) each (Figure 19A and C). With each session lasting around 12 minutes dependent on individual subjects' reaction times, the total time spent for the task was within half an hour by including a short break between the two sessions. The task involved applying force on a gripper (Figure 19B) that controlled the height of a cursor on a computer screen to match the height of a target bar. The absolute height of a target bar was adapted according to each subject's maximum hand grip force, such that 70% of the maximum force corresponded to 85% of the height of the computer screen. During the task, the subjects were instructed to move a cursor to target bars in sequence as swiftly and accurately as possible by pressing and releasing the gripper, and they were expected to learn to track a sequence of hand grip trials demanding variable isometric force contraction with the non-dominant (left) hand.

Accuracy was evaluated by the proportion of hand grip trials that successfully reached target bars within a block. The elapsed time per trial was measured from the onset of cursor movement at the baseline to the stop of cursor movement at a target bar in successful trials or to the continued pause of cursor movement at least for 200 ms outside a target bar in unsuccessful trials. Motor task performance for each block was computed by the ratio of accuracy to the average elapsed time per trial. While it appears not to be consistent in the literature what motor learning ability refers to (Krakauer et al., 2019), we defined motor learning ability as a summary

measure representing a change in motor task performance based on the capability to respond appropriately in the process of motor learning. Across the two sessions, individual subjects' motor learning ability was calculated by the ratio of the difference between later motor task performance (measured for the last two training blocks of the second session) and earlier motor task performance (measured for the first two training blocks of the first session) to earlier motor task performance: motor learning ability = (later motor task performance – earlier motor task performance)/(earlier motor task performance).

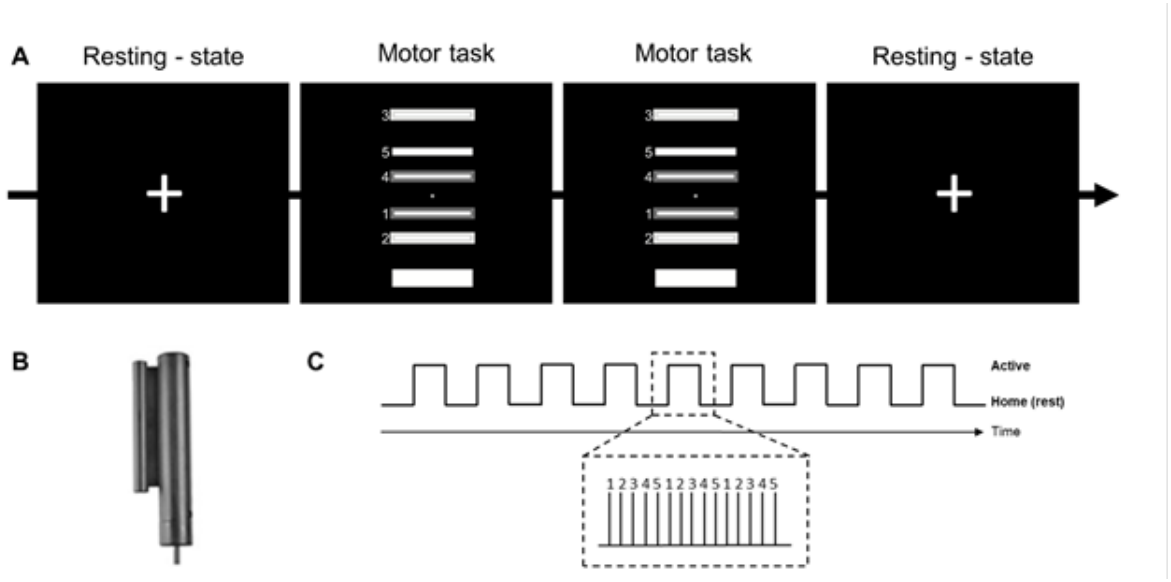

Figure 19. Experimental protocol and motor task design. (A) Description of the fMRI session. A first 8-minutes resting state scan was followed by two sessions of task. The fMRI session was completed after a last resting-state scan. (B) MRI-compatible fiber-optic grip force sensor used in the present study. (C) Block design of the motor task.

4.3.3 MRI data acquisition

MRI data were collected using a 3T MAGNETOM Prisma scanner (Siemens Healthineers, Erlangen, Germany). Diffusion-weighted MRI (dMRI) data composed of 108 volume images, including 101 with diffusion weighting at multiple b values of 300, 700, 1000, 2000, and 3000 s/mm2 and seven without diffusion weighting, in axial planes were acquired with a pulsed gradient spin echo sequence: number of slices = 84, slice thickness = 1.6 mm, matrix size = 146 × 146, and in-plane resolution = 1.6 mm × 1.6 mm. Resting state functional MRI (fMRI) data consisting of 540 volume images in axial planes were acquired with a multi-slice interleaved gradient echo planar imaging (EPI) sequence that was sensitive to blood oxygen level dependent (BOLD) contrast at every 0.9 s: number of slices = 70, slice thickness = 2.0 mm, matrix size = 112 × 112, and in-plane resolution = 2.0 mm × 2.0 mm. T1-weighted structural MRI (sMRI) data composed of one volume image in sagittal planes were acquired with a 3D magnetization prepared rapid gradient echo (MPRAGE) sequence: number of slices = 192, slice thickness = 1.0 mm, matrix size = 240 × 256, and in-plane resolution = 1.0 mm × 1.0 mm. For each subject, dMRI and T1-weighted sMRI data were obtained once after the hand grip learning task, whereas resting state fMRI data were acquired twice, before and after the hand grip learning task each (Figure 19A).

4.3.4 MRI data processing

Using tools in MRtrix3 (https://www.mrtrix.org/) and FSL (https://fsl.fmrib.ox.ac.uk/fsl/), images of dMRI data were corrected for Gibbs ringing artefacts, field inhomogeneity, susceptibility-induced off-resonance field, and head motion and eddy currents. By estimating the fibre orientation distribution function within each voxel via multi-shell multi-tissue constrained spherical deconvolution (Jeurissen et al., 2014), whole-brain tractography was conducted based on the probabilistic algorithm of the second-order integration over fibre

orientation distribution (Tournier et al., 2019). A total of 10 million streamlines were generated by initiating them at each voxel of the white matter.

Using tools in SPM12 (https://www.fil.ion.ucl.ac.kr/spm/), images of resting state fMRI data were corrected for different acquisition time across slices, field inhomogeneity, and head motion, and they were spatially smoothed with a 6 mm full-width at half-maximum (FWHM) Gaussian kernel. In addition, nuisance covariates regression was applied to model effects of low-frequency fluctuations, head movement, and non-neuronal fluctuations on resting state fMRI signals.

4.3.5 Brain connectome analysis

For the registration between the dMRI or resting state fMRI data native space and the standard space, T1-weighted sMRI data were used to estimate transformation parameters. For 246 brain regions as defined by the Brainnetome atlas (Fan et al., 2016) in the standard space, a brain structural connectome was constructed by selecting fiber bundles that connected each pair of the 246 brain regions among those over the whole brain. For the same 246 brain regions, a brain functional connectome was constructed by computing the correlation of signals between each pair of the 246 brain regions. That is, nodes were commonly defined by the 246 brain regions, while edges between the nodes were estimated by fiber bundles for the brain structural connectome and by signal correlation for the brain functional connectome.

Given the brain structural connectome at one time point (after the hand grip learning task) and the brain functional connectome at two time points (before and after the hand grip learning task), we assumed that the brain structural connectome remained static on the short timescale of motor learning, such that the brain structural connectome could be regarded not only as a baseline, but also as being unchanged thereafter. Thus, in addition to functional network topology measured for the brain functional connectome, the correspondence between the brain structural and functional connectomes was measured at each time point, so that changes in structure-function correspondence as well as functional network topology over the two time points could be assessed.

For a brain structural connectome, a sparse binary network was defined by considering that an edge is not existent between a pair of nodes when there was no fiber bundle tracked between the two nodes. For a brain functional connectome, a sparse binary network was defined by supposing that an edge is not existent between a pair of nodes when the correlation of signals between the two nodes failed to pass the false discovery rate correction for multiple comparisons at the significant level of $p \leq 0.05$. Given a sparse binary network derived from a brain structural connectome or a brain functional connectome, network topology was evaluated in terms of efficiency and modularity. Efficiency, as a measure of how efficiently a network exchanges information (Latora & Marchiori, 2001), was computed by averaging inverse shortest path lengths between nodes. Modularity, as a measure qualifying community structure in a network (Newman & Girvan, 2004; Newman, 2006), was computed by comparing the number of edges included in nonoverlapping groups in a given network against an equivalent network with edges connected at random.

The correspondence between the brain structural and functional connectomes was assessed by the multilinear regression fit of an observed brain functional connectome to a predicted brain functional connectome, as proposed before (Vázquez-Rodríguez et al., 2019). The predicted brain functional connectome was generated by the linear combination of the Euclidean distance, path length, and communicability in the brain structural connectome. The goodness of fit in terms of the coefficient of determination (R^2 value) between the observed and predicted brain functional connectomes provided structure-function correspondence at each node.

For the brain structural and functional connectomes, in order to address variable involvement of different functional systems in motor learning, seven cerebral networks that have been divided according to the similarity of signals between brain regions (Yeo et al., 2011) were considered, so that network topology and structure-

function correspondence were measured for the seven cerebral networks as well as the whole brain network. The seven cerebral networks included the visual, somatomotor, dorsal attention, ventral attention, limbic, frontoparietal, and default mode networks.

4.3.6 Brain connectome changes and association with motor learning ability

To assess whether functional network topology and structure-function correspondence at the group level significantly changed following the motor learning task compared to before, linear regression models were computed, using the change in the studied measure as response variable and adding age and sex as adjusting variables. The outcome measure (referred as coefficient in the figures) was the t-statistic for the intercept of the linear model. Statistical significance was determined at $p \leq 0.05$, specifically corrected for multiple comparisons by a false discovery rate approach in the case of considering the seven cerebral networks.

The changes in functional network topology and structure-function correspondence between before and after the hand grip learning task were then correlated to each other to test whether changes in functional network topology could be directly transferred to changes in structure-function correspondence.

In addition, brain connectome correlates of motor learning ability were evaluated from two perspectives. Firstly, the association of changes in functional network topology and structure-function correspondence during the hand grip learning task with motor learning ability was assessed to check what changes in the brain connectome could support motor learning ability. Secondly, the association of network topology and structure-function correspondence before the hand grip learning task (at baseline) with motor learning ability was assessed to check what substrates of the brain connectome could be predictive of motor learning ability. The strength of associations was again assessed with linear regression models, including the motor learning ability measure as response variable and the change in either functional network topology or structure-function correspondence as predictor variable. All statistical inferences were conducted by adopting permutation tests, in which the null distribution of a test statistic was obtained by repeatedly computing the test statistic through 1000 times of rearrangements of the subjects' labels, after adjusting for the effects of the subjects' age and sex. Statistical significance was determined at $p \leq 0.05$, specifically corrected for multiple comparisons by a false discovery rate approach in the case of considering the seven cerebral networks.

4.4 Results

4.4.1 Motor learning ability

Among the 39 subjects, later motor task performance (mean (SD) = 59.0 (20.1)) was improved compared with earlier motor task performance (mean (SD) = 39.6 (15.1)) in 35 subjects (Figure 20). Therefore, the subjects' motor learning ability (mean (SD) = 0.64 (0.68)) was generally shown as positive values, while interindividual variations in them were large.

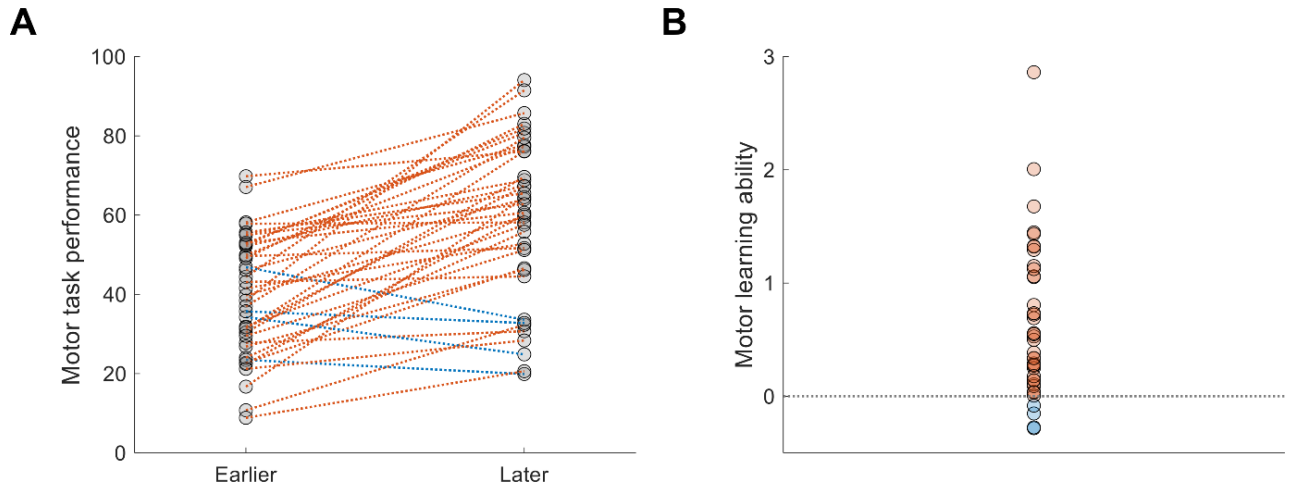

Figure 20. Motor learning of the hand grip learning task. (A) Motor task performance. Earlier and later motor task performance was assessed by averaging the two first blocks of the first training session and the two last blocks of the second training session. (B) Motor learning ability was evaluated based on the ratio of the difference between earlier and later motor task performance. The majority of the subjects shows an increase of motor task performance from the first to the second training session (orange). Subjects showing a decrease of motor task performance from the first to the second training session are represented in blue.

4.4.2 Brain connectome change

While changes in functional network topology between before and after the hand grip learning task were not significant in the whole brain network and neither in the seven cerebral networks (Supplementary Figure 6A), efficiency and modularity showed trends for opposite directions in their changes, as seen before for a different form of short-term motor learning (Sami & Miall, 2013). Brain structure-function correspondence exhibited different relationships between the brain structural and functional connectomes across the seven cerebral networks, as observed previously (Vázquez-Rodríguez et al., 2019), at both time points (Supplementary Figure 7). Although there were changes in structure-function correspondence in some brain regions, significant changes were observed in neither the whole brain network nor the seven cerebral networks (Supplementary Figure 6B). Between functional network topology and structure-function correspondence, efficiency positively correlated with structure-function correspondence ($r = 0.72$, $p < 0.01$), whereas modularity negatively correlated with structure-function correspondence ($r = -0.66$, $p < 0.01$) for their changes in the visual network (Supplementary Figure 8).

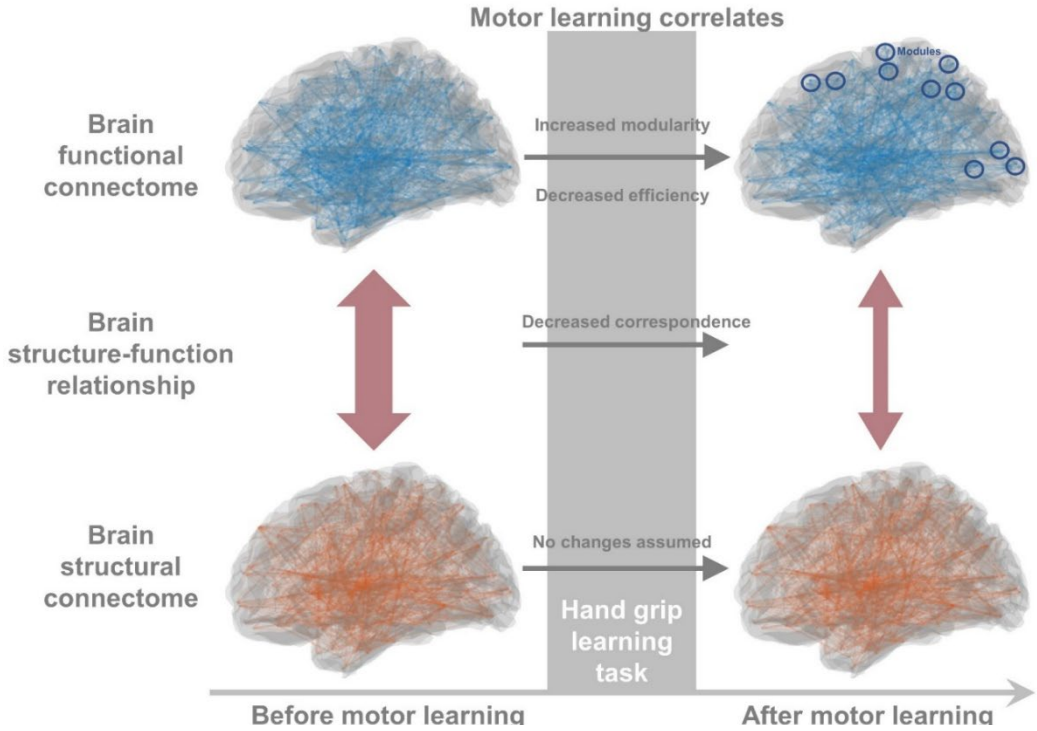

Figure 21. Schematics of behaviorally-relevant brain connectome changes during short-term motor learning. Motor learning related-changes in the brain functional connectome, featured by a decrease of efficiency and an increase of modularity (blue circles), are accompanied by a decrease in the brain structure-function correspondence over specific networks. The brain structure-function relationship correspondence decreases with motor learning (as shown by the thinner red arrow).

4.4.3 Brain connectome association with motor learning ability

The association of changes in functional network topology with motor learning ability was in different directions depending on the topology measures. Motor learning ability was related to decreased efficiency and increased modularity in the visual (efficiency: $t = -3.14$, $p < 0.01$; modularity: $t = 2.52$, $p = 0.01$), somatomotor (efficiency: $t = -2.61$, $p < 0.01$; modularity: $t = 3.73$, $p < 0.01$), and frontoparietal networks (efficiency: $t = -1.80$, $p = 0.04$; modularity: $t = 1.89$, $p = 0.04$) (Figure 22A). With respect to brain structure-function correspondence, motor learning ability was related to reduced correspondence in the visual ($t = -2.58$, $p < 0.01$), ventral attention ($t = -2.81$, $p < 0.01$), and frontoparietal networks ($t = -2.17$, $p = 0.02$) as well as the whole brain network ($t = -1.85$, $p = 0.02$) (Figure 22B), representing a possible connection of behaviorally-relevant brain connectome changes between functional network topology and structure-function correspondence, specifically over the visual and cognitive networks (Figure 21).

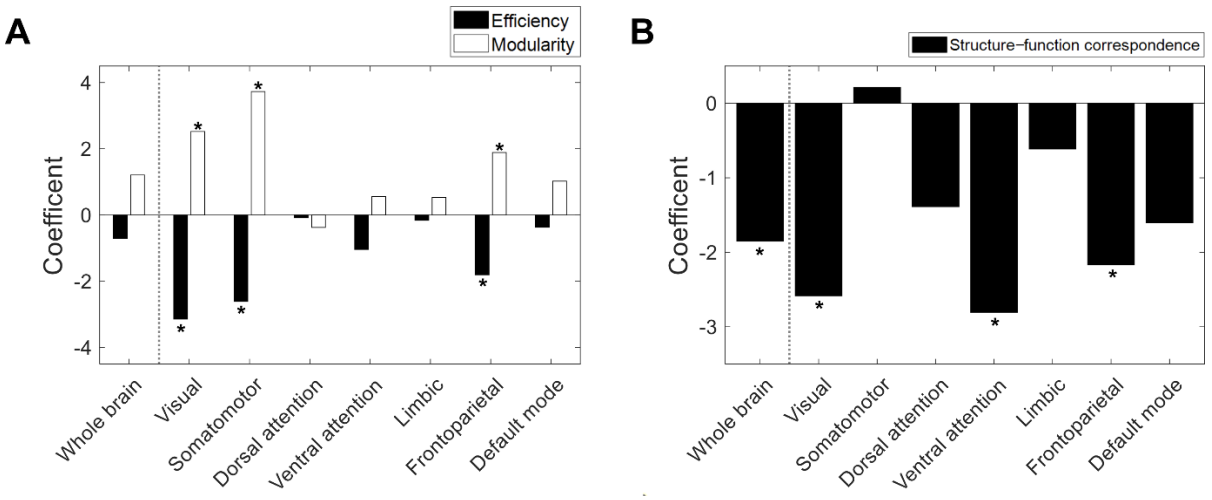

Figure 22. Brain connectome changes in association with motor learning ability. (A) Changes in network topology of the brain functional connectome featured by the efficiency (black) and the modularity (white). (B) Changes in brain structure-function correspondence between before and after motor learning. Both changes were measured for the whole brain network and seven cerebral networks. *, statistical significance.

Motor learning ability was not related to network topology of the brain structural and functional connectomes before the hand grip learning task (Supplementary Figure 9). In contrast, greater structure-function correspondence in the dorsal attention ($t = 1.90$, $p = 0.04$), ventral attention ($t = 2.33$, $p < 0.01$), and frontoparietal networks ($t = 2.24$, $p = 0.01$) as well as the whole brain network ($t = 1.96$, $p = 0.03$) before the hand grip learning task was related to motor learning ability (Figure 23).

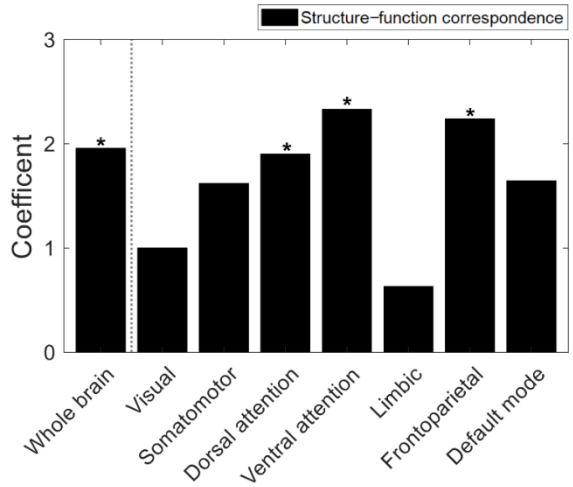

Figure 23. Brain connectome bases of motor learning ability. Brain structure-function correspondence before motor learning was measured for the whole brain network and seven cerebral networks. *, statistical significance.

4.5 Discussion

In short-term motor learning, correspondence between the brain structural and functional connectomes changes most likely due to learning-related changes of the functional connectome, while the brain structural connectome remains unchanged. In this study, we sought to track changes in the brain functional connectome and its effects on changes in brain structure-function correspondence after a short period of motor learning. Motor learning ability was attributable to decreased efficiency and increased modularity of the brain functional connectome and correspondingly decreased correspondence between the brain structural and functional connectomes over the visual and cognitive networks (Figure 21). In addition, motor learning ability could be predicted by the connectome determined before starting the motor learning task. Interestingly, only the structure-function

correspondence over cognitive networks, but not structural or functional network topology alone, allowed to predict motor learning ability. Indeed, higher baseline structure-function correspondence was related to superior motor learning ability.

The connection matrix of the brain, referred to as the brain connectome, has been suggested as either a structural (Sporns et al., 2005) or a functional (Achard, 2006) description of the brain. The rationale behind increasing attention to the notion of the brain connectome is that the brain can be seen as a network machine (Sporns, 2013) and there is a strong need of knowledge about the different processes occurring within this network. In this context, the network interconnections are key elements in understanding brain functioning (Bargmann & Marder, 2013), specifically with respect to connectivity patterns, for instance, the interplay between segregation and integration (Tononi et al., 1994). New insights have been offered by brain connectomics for plastic changes in the brain, such as during normal development (Tymofiyeva et al., 2014), after brain diseases (Griffa et al., 2013), especially in recovery after stroke (Guggisberg et al., 2019; P. J. Koch et al., 2021; Egger et al., 2021) and during training and learning (Taya et al., 2015). Here, we focused on plastic changes in the brain during a short period of motor learning from the perspective of brain connectome changes. While average changes in the brain connectome across the subjects were not clearly seen on the short timescale, changes in the brain connectome in association with individual differences in motor learning ability were revealed.

While higher efficiency at baseline has been suggested as a predictor of motor learning ability (Zang et al., 2018), intelligence (Langer et al., 2012), and robustness to cognitive impairment (Tuladhar et al., 2016), we show here that changes in motor learning performance are related to changes towards a decrease in efficiency, representing the reduction of integration of information transfer within the visual, somatomotor, and frontoparietal networks. The modulation of integrity within the functional systems may reflect less demand for information exchange in consequence of more practice, while a need for integration between different functional systems may be arisen as motor learning progresses (Coynel et al., 2010).

In contrast, motor learning ability-related changes in modularity were in the opposite direction, indicating enhancement of the quality of modular structure over the same networks. The contribution of increased modularity to motor learning ability appears to represent selective adaptability or flexibility required for motor learning that could be furnished by modular structure (Bassett et al., 2011). Besides, a shift of functional network topology towards a modular organization may not be limited to motor learning, but might be a more general mechanism, e.g., also described for working memory functions (Stevens et al., 2012).

Although the brain functional connectome is at least partially shaped by the brain structural connectome (Honey et al., 2009), brain structure-function correspondence is not fixed due to dynamic changes in the functional part of the connectome that can occur even on a short timescale. Indeed, here we revealed that changes in the brain functional connectome led to changes in brain structure-function correspondence in short-term motor learning, such that decreased correspondence in the visual, ventral attention, and frontoparietal networks contributed to motor learning ability. According to the notion that relatively low structure-function correspondence could promote functional flexibility (Baum et al., 2020), decreased correspondence may reflect enhanced flexibility in the functional systems that supported motor learning based on successful brain dynamics. Considering that flexibility could be a main attribute to drive desired motor learning (Bassett et al., 2011; Reddy et al., 2018), a demand for flexibility in motor learning appears to be represented in this study by detachment of the brain functional connectome from the brain structural connectome, along with a shift of functional network topology towards a modular organization. A demand for flexibility specifically in the visual and cognitive systems may be related to the establishment of new associations between environmental targets and motor actions for the development of automaticity in motor learning (Hardwick et al., 2013).

Assuming the static brain structural connectome during short-term motor learning, we suppose that increased segregation and decreased integration in the brain functional connectome generally led to its uncoupling from the brain structural connectome. However, in the somatomotor system, unlike the visual and cognitive systems, motor learning ability-related changes in functional network topology did not lead to decreases in structure-function correspondence, reflecting a possibly reduced demand for flexibility. This may be related to the continued involvement of the somatomotor system in the process of motor learning, while the visual and cognitive systems tend to be more dynamically involved probably only in an early stage of motor learning (Hardwick et al., 2013; Berghuis et al., 2019). Besides, it would be notable that functional network topology is only a facet of the brain functional connectome, so that its changes may not comprehensively explain changes in structure-function correspondence.

In the context of this study, the evaluation of brain connectomics did not only allow to reveal connectome changes that underlie inter-individual variability in motor learning ability, but also to identify basic connectome information for predicting the magnitude of motor learning. It is of interest that only structure-function correspondence, but not structural and functional network topology of the connectome, allowed to predict motor learning ability. This suggests the value of relationships between structure and function in explaining individual differences in the potential ability of motor learning, not only in specific brain regions (Tomassini et al., 2011), but also over more wide-spread brain networks.

Brain structure-function correspondence appears to contain information distinguished from the sourced brain structural and functional connectomes, providing signatures for the network organization of individual brains (Griffa et al., 2022). In particular, the frontoparietal network has been suggested to include information for individual fingerprinting and, moreover, individual differences in cognitive traits in terms of brain structure-function correspondence (Petrovic et al., 2020). In a similar vein, it may be proposed that brain structure-function correspondence specifically over the cognitive networks including the frontoparietal network could serve as substrate of individual subjects' motor learning ability.

The current study was performed with healthy older subjects; thus, we cannot exclude that the changes in structure-function correspondence and its relation to motor learning might be confounded by aging effects. For instance, age-related alterations in functional network topology and brain structure-function correspondence, specifically decreases in efficiency (Achard & Bullmore, 2007; L. Wang et al., 2010; J. Sun et al., 2012) and brain structure-function correspondence (Esfahlani et al., 2022), may be noted. Furthermore, the possibility of overexpressed involvement of the cognitive networks due to a need for greater brain resources in older subjects (T. Wu & Hallett, 2005) may be taken into account. In future investigations, it needs to be checked whether the current findings regarding enhanced flexibility in motor learning in the view of brain connectome changes apply across the lifespan or they may be rather specific to older age.

In summary, here we showed that ability in short-term motor learning was attributable to higher brain structure-function correspondence in the cognitive networks at baseline and reduced brain structure-function correspondence in the visual and cognitive networks, which have been induced by topological reorganization of the functional connectome, during motor learning. These findings underscore brain connectome correlates of motor learning, in terms of a demand for flexibility in the visual and cognitive system, as supported by increased segregation and decreased integration over the systems. While we are motivated to examine brain connectome correlates of motor leaning on a longer timescale in future studies, the value of brain structure-function correspondence on top of the sourced brain structural and functional connectomes stresses the importance of multimodal views on brain functioning.

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Chapter 5 General Discussion

The world population is aging and this tendency is expected to be increased in the future. Aging is accompanied by a general decline in functioning, ranging from reduced cognitive (T. Salthouse, 2012) to motor capacities (Seidler et al., 2010). However, adapting to novel tools and ways to behave in the external world is important for the aging population in order to stay integrated into society. In this context, motor learning is a crucial component. Yet, the capacity for motor learning is impaired in older adults (Voelcker-Rehage, 2008; Maceira-Elvira et al., 2022). Possible mechanisms explaining this decrement have been proposed, especially considering the different stages of motor learning (Dahms et al., 2019; Maceira-Elvira et al., 2022). The literature underscores the critical importance of the acquisition phase of motor learning for later consolidation of motor memory in young adults (Korman et al., 2003; Diekelmann et al., 2009; Fitzroy et al., 2021) and older adults (King et al., 2016; Fitzroy et al., 2021; Maceira-Elvira et al., 2022). However, while the processes occurring during the initial acquisition phase have been well-characterized in young adults (Hikosaka et al., 2002; Doyon & Benali, 2005; Dayan & Cohen, 2011), they were only sparsely studied in older adults (King et al., 2013; Maceira-Elvira et al., 2022). Hence the main aim of this thesis was to characterize better the neural processes at play during the early acquisition phase of motor learning in older adults. To perform such with an integrative view of the brain, we explored changes in the brain in a multimodal way, considering the organization of the brain in terms of *functional specialization and integration* (K. J. Friston, 2004) and by looking at the relationship between function and structure (Koch et al., 2002; Honey et al., 2009). More specifically, we explored in the first study (Chapter 3) entitled "*Study 1: Early motor skill acquisition in healthy older adults: brain correlates of the learning process*" the functional specialization by investigating the dynamics of brain activation during the initial acquisition phase and their relationship with behavioral change. I would like to underscore that in this study, we assessed the within-session brain activation changes related to time and behavior. The results revealed that motor learning ability relied on the parallel involvement of motor-related cortical areas responsible for action selection and associative parietal areas involved in visuomotor processing. As for the functional integration of the brain, the second study (Chapter 4) entitled "*Study 2: Brain Connectome Correlates of Short-Term Motor Learning in Healthy Older*" aimed at assessing changes in segregation and integration of information transfer within functional subnetworks with graph theory measures in addition to changes in structure-function correspondence. We reported that increased segregation, decreased integration, and decreased structure-function correspondence in relevant networks were related to motor learning ability. Specifically, we showed that better motor learning ability was associated with higher flexibility in visual and cognitive/associative networks in the direction of a detachment from the structural network and increased modularity. In the following sections, I will detail further the results, provide general interpretations in view of the existing literature and present possible future developments of the work presented in the thesis.

5.1 Summary and discussion

5.1.1 Behavioral improvement

Motor learning ability was defined in this thesis as a change in motor performance based on the capability to execute successfully the motor skill. To probe motor learning in a population of older adults and assess neural correlates, we implemented the following motor learning task in the MRI. The task consisted of a grip force modulation task adapted from two previous studies on young adults (Reis et al., 2009; Wessel et al., 2020). The initial study implementing this type of task utilized the pinch grip (Reis et al., 2009); we instead implemented the task with whole-hand gross movements as in the study of Wessel and colleagues. It was designed as such for two reasons: so that the task resembles everyday life movements like holding a glass and to be feasible in a population with motor disabilities for fine movements such as stroke populations. The motor task was successfully adapted for the MRI environment and a proof-of-concept study revealed that stroke patients improved significantly during the acquisition of the motor skill in the MRI (Appendix 2).

Older adults showed significant improvement after training for a short time on the motor skill learning task. This result confirms previous reports showing learning ability in older adults (Berghuis et al., 2019; Fitzroy et al., 2021; Maceira-Elvira et al., 2022), although the capacity to learn in a single session is different compared with young; the motor learning dynamics of older adults are more gradual (Berghuis et al., 2019) and thus demands additional training to reach comparable performance to young adults (Fitzroy et al., 2021). The absence of a young control group in our design prevents us from investigating age-related differences in this motor learning task. Nevertheless, we could show that twenty minutes of acquisition were enough to elicit behavioral changes. The main performance outcome for assessing motor learning ability was a compound score including both accuracy and completion time. Previous studies have used different outcomes combining speed and accuracy in a single measure (Townsend & Ashby, 1978; Reis et al., 2009; Bruyer & Brysbaert, 2011; King et al., 2016) to get an overall measure of performance and to account for inter- and intra-individual variability in the speed-accuracy trade-off (Heitz, 2014; Liesefeld & Janczyk, 2019). When observing the average behavior of our older cohort, we could see that they improved both in accuracy and speed. Conversely, stroke patients showed improvement on the compound measure difference of first to last blocks of acquisition (Appendix 2), but not when looking at accuracy and time, probably due to low sample size and high interindividual variability. The compound measure allows us to give an integrative view of behavior by integrating two components of performance and might permit smoothing out differences among patients in the strategy of prioritization between accuracy and time.

Finally, the motor learning task has been defined as a sequential force modulation task, however, the investigation of sequence specificity revealed that sequence-independent learning was also present in our task (Supplementary Figure 1 in Supplementary Material for Chapter 3). Thus, in contrary to SRTT and SFTT which show sequence-specific learning (Krakauer et al., 2019), the grip force modulation task used in this study seems to entail a sequence-independent learning component. Our interpretation is that during the initial learning process, the subjects are learning a novel visuomotor mapping, that is understanding the relationship between the force and the control of the cursor. In that sense, the task used in these studies might relate to a *de novo* learning task where the goal is to learn the association between the use of the gripper and its consequences in terms of cursor movement. Nevertheless, we cannot conclude with certainty that the task is not a sequential motor learning task. Indeed, first at the behavioral level, we observe a trend in the difference between sequence and random blocks (Figure 16 and Supplementary Figure 1). Secondly at the brain activation level (Supplementary Figure 2 and Supplementary Table 1), we observed a significant difference in activation in several brain areas. As such the grip force modulation task is probably a mixture of a sequence learning task and a *de novo* learning task. In the context of the motor planning and execution pathway presented in Figure 1, *de novo*

motor learning is related to the three parts of the pathway. Our grip force modulation task requires goal selection (which target to reach), action selection (which force to apply), and action execution (adapting the amount of force in real-time according to the visual feedback). The grip force modulation task thus is relevant to study the full pathway of motor learning and its relevant neural correlates. Our MRI design was not performed to disentangle between the different steps, but we observed relevant neural correlates related to the execution and performance improvement of the task. The neuroimaging results presented in this thesis can be divided into two different types, namely time-related changes and behavior-related changes. I will discuss them in the next sections.

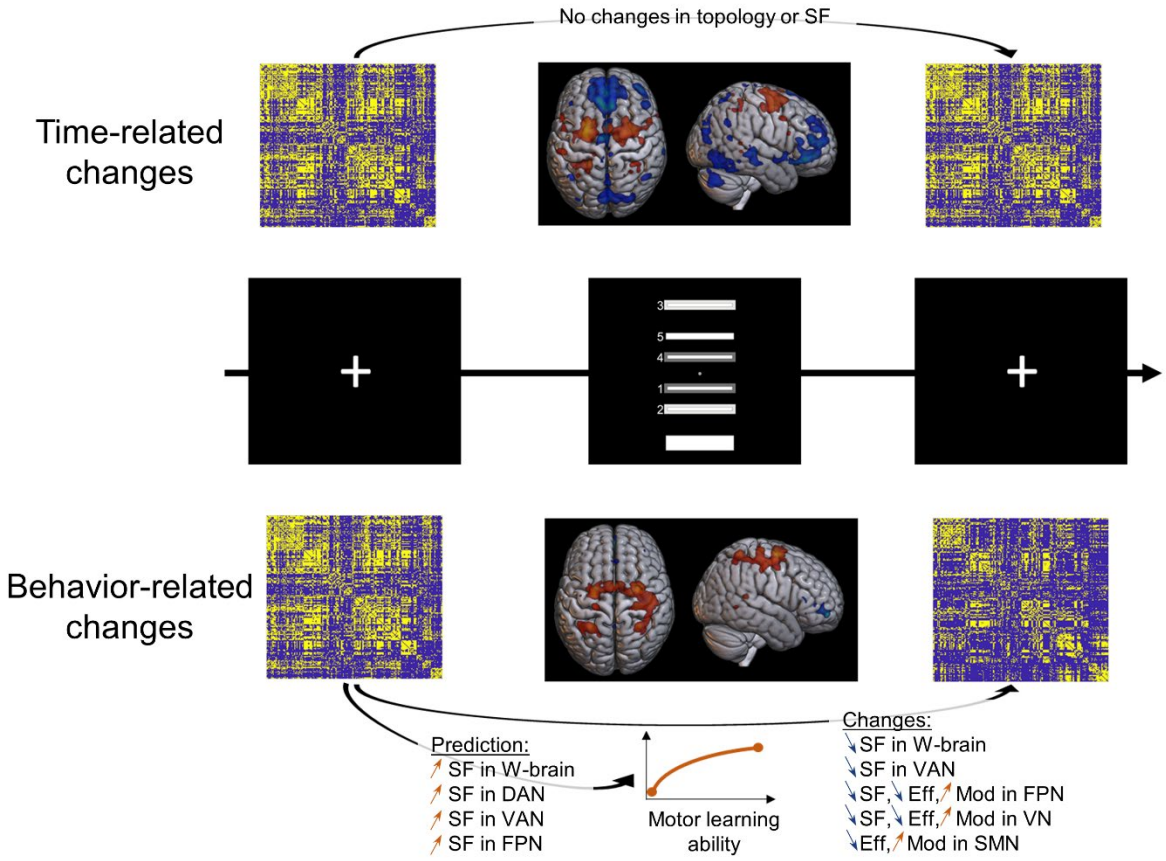


Figure 24. Schematic summary of the results of this thesis. The time-related changes are displayed on top and the behavior-related changes at the bottom. In the center top and bottom, activation changes are depicted on glass brains. Red regions are positively associated with time or performance while blue regions are negatively associated. The functional topology changes and structure-function correspondence prediction results and changes are listed at the bottom. The upward orange arrow signifies positive correlation with motor learning ability and the blue downward arrow negative correlation. Abbreviations: SF, structure-function correspondence; Eff, global efficiency; Mod, modularity; W-brain, whole-brain network; DAN, dorsal attention network; VAN, ventral attention network; FPN, frontoparietal network; VN, visual network; SMN, somatomotor network.

5.1.2 Time-related functional brain changes

One of the aims of this thesis was to investigate the time-dependent changes occurring in the brain during acquisition of a motor learning task in older adults. Time-dependent changes were defined as the observed changes in brain activation occurring while practicing the task and in resting-state networks' functional topology comparing post to pre-measurements. We assessed the within-session changes in activation throughout the acquisition phase instead of performing a pre-post training comparison as usually performed (Poldrack, 2000). To summarize the first study (Chapter 3), here we observed an increase of activation in bilateral secondary motor and associative parietal areas, while cognitive frontal and visual areas decreased as acquisition progressed (Figure 24). Furthermore, the cerebellum, a region known to be important for motor learning

(Doyon & Ungerleider, 2002), displayed increased activation during the first part of learning and decreased afterward. It is important to point out that we observed an overlap of brain activation changes in regard to time-related and performance-related changes (see Supplementary Figure 4B and Supplementary Figure 5B). One interesting aspect of the first study (Chapter 3) was to attempt to disentangle between the regions changing over time, but not involved in better performance and those that showed both relationships. In the following paragraph, I will focus on the areas that solely changed over time, but were not related to behavioral changes, such as anterior prefrontal and inferior frontal areas, cerebellar and fusiform and lingual areas (see Supplementary Figure 5B). These areas show a decrease in activation due to the repetition of the task but are not directly associated with behavior. These decreases might be related to reduced neural processing as training advances or to the sharpening of neural responses which induces a reduction in brain activation since the extent of activation gets smaller (Poldrack, 2000). This does not mean that they do not have a role in the motor learning process, but they are not directly involved in the production of good performance.

In accordance with the available literature, we report a decreased involvement of cognitive frontal areas (Floyer-Lea & Matthews, 2005; Dayan & Cohen, 2011) suggesting that cognitive control is less needed as practice advances *(*Miller & Cohen, 2001*).* The cerebellum is believed to be a key region for early motor learning (Doyon et al., 2002) and is usually associated with good performance (Lefebvre et al., 2012; Wadden et al., 2013). This region is thought to be involved in error correction and especially in the generation of internal models of the motor skill that needs to be updated in the early acquisition (Doyon et al., 2002; Shadmehr & Krakauer, 2008). We would thus expect that activation of this region is clearly related to performance. Although we observed a small cluster in the right cerebellum (but with peak voxel in the right fusiform) negatively correlated with accuracy in Table 3, the main part of the cerebellum showed activation changing over time, but not in relation to behavior (Supplementary Figure 5). One interpretation of this unexpected result could be related to the dynamics of performance. According to Figure 16, the performance gets already more stable at the end of the acquisition phase inducing a relatively low number of errors. It could be that the internal model formed in the cerebellum during the first learning session was accurate enough to induce a decreased involvement of the cerebellum in the second session while the performance was maintained or continued to improve.

Regions usually not mentioned in the models of motor learning (Hikosaka et al., 2002; Doyon & Benali, 2005) are visual regions. As models are usually considering motor sequence learning, the importance of continuous visual feedback is low. Conversely, in visually-guided grip force tasks and tracking tasks (Halder et al., 2007; Sterr et al., 2009; Berghuis et al., 2019), an involvement of visual regions is consistently reported. In our study, we observed a decrease in activation in the visual system (secondary visual areas) with the progress of the training, specifically in late acquisition. An extensive review of animal and human studies similarly reports that when visual cues are repeated throughout time, the literature also reports consistent decreases in activity (Grill-Spector et al., 2006). Our results are also consistent with a recent study that showed decreases in visual regions after a period of training on a visuomotor tracking task (Berghuis et al., 2019). A similar decrease in visual areas was found in a serial interception sequence learning task when comparing a practiced sequence to a new sequence (Gobel et al., 2011). This convergence of results can be interpreted as a more efficient visuospatial and visual motion processing with the progress of the training and especially at the end of the training (Berghuis et al., 2019). As the internal models and spatial coordinates got more precisely defined by the cerebellum (Shadmehr & Krakauer, 2008) and parietal regions (Hikosaka et al., 2002) respectively as learning progressed, the reliance on visual feedback was less needed. Therefore, the visual processing system is relevant for the execution of the task in the very early acquisition phase, when the visual coordinates of the targets are encoded by the visual system (Kawato et al., 1987; Hikosaka et al., 2002). As training continues, these visual coordinates are getting transformed into spatial coordinates by the associative parietal areas (Hikosaka et al., 2002; Grefkes et al., 2004) thus inducing reduced involvement of the visual system.

Finally, as for time-related changes, one of the goals of the second study (Chapter 4) was to assess the changes in resting-state functional network topology and changes in structure-function correspondence from before to after the motor skill acquisition phase. It is now well accepted that short-term motor learning induces immediate changes in resting-state functional connectivity with the first report dating from 2009 (Albert et al., 2009) and many other results reported later (Vahdat et al., 2011; Sami & Miall, 2013; Tung et al., 2013; Gregory et al., 2014; Elton & Gao, 2015). Interestingly, Sami & Miall investigated the graph properties of resting-state activity comparing a baseline resting-state with post-motor learning resting-state activity (Sami & Miall. 2013). They reported significant changes at the level of the whole-brain network going in the direction of increases in global strength and degrees and local efficiency suggesting increased local connectivity in the network. Decreases were also seen in path length and betweenness centrality indicating more direct information transfer following learning. These results were not reproduced in our study. In fact, no time-related changes were seen in the efficiency or modularity of resting-state functional networks. We interpret this discrepancy in light of the different populations tested. It could be that the inherent variability of the brain of older adults (Caspers et al., 2014) and the variability seen in the motor learning ability (see Section 4.4.1) prevented from observing significant time-related changes in the resting state networks topology. Indeed, aging is characterized by great variability in how the brain reorganizes and this stems from multiple factors such as nutrition (Jannusch et al., 2017) and many other lifestyle characteristics (Bittner et al., 2019). Concerning brain network topology, recent research studied functional network reorganization in older adults with graph network measures (Stumme et al., 2020), and a subsequent review focused on resting-state networks changes in the course of aging and the characterization of the increasing inter-individual variability of the networks associated with increasing age (Jockwitz & Caspers, 2021). The study of Stumme and colleagues, for example, used a dataset of 951 older adults and reported very small effect sizes, results interpreted in terms of inter-individual variability (Stumme et al., 2020). In our study, we observed quite a large variability in motor learning ability during the training session in our sample of older adults, with subjects getting way better on the task compared to others (Figure 20). In light of this individual variability and considering our relatively limited sample size, the analysis of time-related changes in the averaged network topology over all subjects might not capture common dynamics. Conversely, when we consider the behavior-related changes, we take into account the variability in motor learning ability to explain functional changes. It is thus of great relevance to look at changes in brain function and structure in association with individual motor learning ability in older populations. The results of these associations are presented in the following section.

5.1.3 Behavior-related functional brain changes

The two studies presented in this thesis allow us to gain significant insight into the dynamics of brain activation and brain network connectivity associated with motor learning ability. Specifically, we characterized which brain regions showed concurrent changes in activation with the changes in motor performance during the motor acquisition phase in the first study. In the second study, we were interested in the changes in resting-state networks' topology in terms of segregation and integration in relation to motor learning ability. While brain activation changes were assessed on the whole brain, the brain connectome changes were evaluated both at the level of the whole brain network and at the level of subnetworks, namely somatomotor, frontoparietal, visual, dorsal and ventral attention, limbic, and default mode networks (Figure 24). I will discuss the results regarding the behavior-related brain changes focusing on the relevant functional regions and will subsequently provide a more general interpretation of the results.

Somatomotor network

Regions of the somatomotor network comprising contralateral S1, M1, part of the PMC, and bilateral SMA showed activation associated with better performance indicating the involvement of these regions in the correct execution of the task. In particular, we showed that better accuracy was associated with more activation in

these regions. In the grip force modulation task, good accuracy relates to the correct selection of actions, that is applying the right amount of force and selecting the correct moment to stop increasing force and instead maintain a stable force on the target. This is consistent with the view that secondary motor areas are involved in the temporal control of movement (Halsband et al., 1993; Chen et al., 1995) as well as in the integration of visual and sensory information for the selection of action (Hoshi & Tanji, 2000; Hardwick et al., 2013), and that S1 is important for accurate maintenance of force (Mayhew et al., 2017). According to the models of motor learning (Hikosaka et al., 2002; Doyon & Benali, 2005), somatomotor areas are usually involved later in the motor learning process, when the motor coordinates are being formed. We show here that accurate performance during the acquisition phase of a novel motor skill already relies on the somatomotor system. This is consistent with the view of Maceira and colleagues, who posit that already in the acquisition phase of a motor skill performed by older adults, the motor coordinates are developed in parallel to the spatial coordinates (Maceira-Elvira et al., 2022). The behavior-related pattern of activation we observed during the practice of the motor skill was also inducing changes in the functional network topology as measured by resting-state connectivity. Indeed, we report in the second study a reduction in the global efficiency and increased modularity in the somatomotor network in relation to the change in motor performance. As a parallel of efficiency, Sun and colleagues report greater coupling in the motor network in early learning compared with late learning on a single, 20 minutes learning session (Sun et al., 2006), it thus seems that the somatomotor network undergoes functional reorganization in relation to correct acquisition of a motor skill.

Frontoparietal network

In the same way as the somatomotor network, activation of regions comprised in the frontoparietal network was positively associated with the improvement in performance during the acquisition. The dorsal PMC has been included in this network before (Wise et al., 1997; Hikosaka et al., 2002) and has been shown to play a role in the integration of working memory and sensory information for the selection of motor action (Chen et al., 1995; Hernández et al., 2002). Additionally, the parietal region is key in the network as it is a sensorymotor hub for the interaction with the external environment (Passarelli et al., 2021) and has been shown to play a role in the rapid processing of visual information in particular (Coull et al., 1996; Grefkes et al., 2004). In our task, activation in parietal areas is negatively associated with completion time, consistent with the view that their recruitment leads to fast sensorimotor processing and thus faster task execution. In the context of the motor learning models, the frontoparietal network is also called an “associative” circuit (Penhune & Steele, 2012) that contributes to the formation of the spatial representation of the motor skill (Hikosaka et al., 2002; Hardwick et al., 2013; Lohse et al., 2014). Apart from its continuous involvement throughout the motor learning process (Doyon & Benali, 2005; Dayan & Cohen, 2011), frontoparietal areas have been associated with spatial and goal-directed attention (Corbetta & Shulman, 2002; Husain & Nachev, 2007), with working memory processes (Coull et al., 1996) and recently with a newly described aspect of motor learning: the offline micro-consolidation of the motor representation occurring within seconds (Bönstrup et al., 2019). A final characteristic of this network is that it contains regions operating as flexible hubs in the sense that they can rapidly change their pattern of functional connectivity with other hubs according to task demands and in order to implement task switching (Cole et al., 2013). Considering the behavior-related topological changes in this network, we also found decreased global efficiency and increased modularity associated with motor learning ability. Considering all these results, the frontoparietal network seems to play a crucial role in the acquisition of motor skill in the grip force modulation task. Its functional role in our task is probably to develop the spatial coordinates, transitioning from the visual coordinates formed at the beginning of training (see interpretation in section 5.1.2) to the motor coordinates that are formed later (Grefkes et al., 2004).

Visual network

As discussed before, brain activation of visual areas changed over time but was not related to the changes in performance within the acquisition phase. However, as for the somatomotor and frontoparietal networks, the visual network topology changes were also related to the motor learning ability in terms of decreased efficiency and increased modularity. These results point towards the conclusion that the successful acquisition of the motor skill induced reorganization of the visual network resting-state network topology without inducing a behavior-related change in activation during the task. The reorganization of the visual network into a modular structure may represent how well visual coordinates are encoded in the visual areas. Indeed, the visual system is thought to be involved in the formation of the visual coordinates, especially in early acquisition (Kawato et al., 1987; Hikosaka et al., 2002). The disengagement of the visual system with practice seen in the functional activation patterns might be related to the establishment of stable visual coordinates in the visual network in the form of a modular organization of the visual network. Furthermore, this interpretation is supported by the results presented in Appendix 1. The analyses presented in this appendix demonstrate that the subjects who displayed worse performance after the intervention showed higher activation in a visual processing area involved in object recognition and visually-guided movement compared with pre-intervention activation. In other words, higher forgetting overnap was related to higher activation postnap. We interpreted this result as the fact that the involvement of this visual processing area after the nap is a compensatory mechanism for the poor consolidation of the visual coordinates.

Other areas and networks

Regarding other areas showing brain activation correlates of better performance, we reported a negative association with performance in medial frontal and anterior cingulate areas. These regions are involved in cognitive processes and effort (Devinsky et al., 1995; Pessiglione et al., 2018) indicating that poorer performance led to increased effort. More specifically, these areas were positively associated with time, meaning that faster execution (shorter time) is accompanied by decreases in activation in these regions. When the time to reach a target increases, it implies that a sustained effort is made by the subject and thus the anterior cingulate areas get more involved.

We did not find any association between the change in behavior and other functional networks' topology changes, such as the dorsal and ventral attention, limbic, default mode, or whole-brain networks. This result is different from the literature on young adults for the whole-brain network (Zang et al., 2018). They found in young adults a positive association between motor learning ability and global efficiency, small-worldness, and a negative association with characteristic path length and transitivity as measured by post-training resting-state networks (Zang et al., 2018). Their results go in the direction of a more efficient network in terms of information transfer associated with short-term learning ability. Several differences such as a different age group and the fact that they did not look at the prepost network changes, but at the association between behavior and post-training network topology could explain the discrepancy in results. It might also be that our measures of topological changes might not capture all changes occurring in the networks. Another explanation might be that in our older subjects, the task-related networks involved in the acquisition of the motor skill undergo topological reorganization associated with the behavior while the other networks, i.e. dorsal, ventral attention, limbic and default mode might stay stable throughout the task and not be related to the change of behavior.

One astonishing result of the second study was that we showed no significant association between baseline resting-state network topology and subsequent motor learning ability. In contrast, several reports (Wu et al., 2014; Mary et al., 2016; Mattar et al., 2018; King et al., 2018) found a significant predictive value of resting-state functional organization. For example, Mattar and colleagues found that visual-motor connectivity was

inversely related to learning rate meaning that sensorimotor autonomy at baseline corresponded to faster learning in the future (Mattar et al., 2018). Similarly, King and colleagues found that stronger internetwork connectivity, or in other words decreased segregation between networks was related to worse motor performance in older adults (King et al., 2018). We interpret this discrepancy as the fact that in the mentioned studies, they investigated internetwork connectivity. Instead, our design aimed at investigating the regional differences within the relevant functional networks. Consistent with our results, the reduction of integrity within a motor-related network was reported before for a motor learning paradigm over a longer period (Coynel et al., 2010). This result may reflect less demand for information exchange within the network as a consequence of more practice, while a need for integration between different functional networks may arise as motor learning progresses. The relationship between the networks in our study should thus be assessed in future studies.

General functional topology changes

Segregation and integration of information transfer in functional networks are key aspects of their characterization (Sporns et al., 2004). Decreased integration as measured by global efficiency has been usually associated with abnormal behavior or diseases (Wang et al., 2018; Novaes et al., 2021) while higher integration has been related to intelligence (van den Heuvel et al., 2009; Langer et al., 2012), working memory performance (Alavash et al., 2015; Stanley et al., 2015), and motor learning ability (Zang et al., 2018). In our study, we show that changes in motor learning performance are related to decreases in efficiency within the visual, somatomotor, and frontoparietal networks, revealing that the reduction of integration of information transfer within these subnetworks was beneficial for better learning.

One aspect that could explain our result of decreased behavior-related global efficiency stems from a study investigating cognitive efforts in a working memory task (Kitzbichler et al., 2011). We have seen before that frontal areas as well as anterior cingulate areas, regions associated with cognitive effort, showed decreased activation as practice advanced and improvement increased. Therefore, we can argue that our older subjects displayed a reduction of cognitive effort during our task. In the study of Kitzbichler and colleagues, they found that as the cognitive demand and thus effort to provide on the task increased, the network integration also increased as probed by increased global efficiency. Following their results, a reduction in the information transfer in the relevant functional networks observable in our task could be interpreted as reduced cognitive demand (Kitzbichler et al., 2011). Breckel and colleagues reported similar results on an attentional task with a sharp increase in global efficiency at the beginning of the task execution from rest to task, followed by a slow decrease with ongoing time-on-task and a final drop lower than the initial pre-task level (Breckel et al., 2013). A different study that tested working memory performance is in accordance with our results (Stanley et al., 2015). They reported that lower local efficiency from rest to task was predictive of higher working memory performance in young and older adults. They interpreted this result of low local efficiency as an indication that a high degree of specialization in local areas is beneficial for better performance. These studies are supporting evidence and help for the interpretation of our results, although they are investigating different tasks that aimed to test working memory. The relevance of working memory for motor learning has been suggested before for young (Maxwell et al., 2003; Anguera et al., 2010) and older adults (Bo et al., 2009; Anguera et al., 2011). In our task framework, working memory processes might be involved in the successful acquisition of the motor skill in the sense that the position and order of the targets might be kept in memory for faster execution of the task. This type of short-term memory is referring to visuospatial working memory that is defined as the temporary maintenance of visuospatial information to guide actions (Jiang & Leung, 2021). Thus, instead of relying constantly on the visual stimuli throughout the learning process, the subjects are recruiting visuospatial working memory processes to be faster on the task.

Concurrently with the decrease in global efficiency, we demonstrate a significant association between an increase in modularity and motor learning ability. The previously mentioned studies also report similar results suggesting that, as task demands decrease, the network gets more clustered and modular (Kitzbichler et al., 2011; Breckel et al., 2013). Modules correspond to functionally defined brain regions with dense intra-modules connections for efficient local information processing (Taya et al., 2015). In accordance with our data, Bassett and colleagues posited that learning involves a change in the modular structure of brain networks (Bassett et al., 2011). Although probing motor learning on a longer timescale (3 days), they found dynamical changes in the configuration of functional modules during the course of motor learning (Bassett et al., 2011, 2015). In particular, they showed that motor learning was relying on changes in the modular structure of visual and motor modules as well as disengagement of cognitive control regions (Bassett et al., 2015). Conceptually, the change in modular structure appears to represent the selective adaptability of neurophysiological processes to drive desired behavior required for motor learning (Bassett et al., 2011). Our results are comparable to their conclusions in terms of the involvement of the different networks in the learning process. We add on their knowledge by specifically investigating the acquisition phase of motor learning and by looking at the modular structure within visual and motor modules. Our results thus help to understand the short-term changes in functional topology following a single session of motor learning in older adults, highlighting the rapidity of functional reorganization and the importance of the frontoparietal network in the acquisition process of motor learning in older adults. One aspect introduced in their seminal paper that we did not investigate was the aspect of network flexibility defined as "the number of times that each node changes module allegiance, normalized by the total possible number of changes" (Bassett et al., 2011). They found that there were two types of nodes consisting of low-flexibility and high-flexibility nodes. The individual flexibility of the entire network was predictive of motor learning ability.

Aging-related functional topology changes

The previously mentioned studies, although relevant for the interpretation of our results, were done in young adults. Interestingly, a growing amount of research demonstrates differences in the functional network topology of the older brain compared with the younger brain. Decreased efficiency of functional networks has been extensively reported in healthy aging (Achard & Bullmore, 2007; L. Wang et al., 2010; J. Sun et al., 2012). In relation to behavior, Stanley and colleagues (Stanley et al., 2015) showed that older adults beneficiated from lower global efficiency for working memory. In the second study of this thesis, although changes in whole-brain efficiency were not related to behavioral change, subnetworks changes and specifically the frontoparietal network engaged in working memory processes (Coull et al., 1996) were associated with the behavior. The convergence of our results with previous ones indicates that better motor performance is achieved by a reduction in information transfer in older adults. In terms of modularity, aging is also accompanied by decreases in modularity (Onoda & Yamaguchi, 2013), but more importantly by changes in the composition and topological roles of modules (Meunier et al., 2009). For example, the fronto-cingulo-parietal module present in the young brain network is segregated into a fronto-striato-thalamic and a medial posterior module in the older brain network. Furthermore, the fronto-striato-thalamic module receives fewer intermodular connections from the posterior module while the intermodular connections between posterior modules are increased (Meunier et al., 2009). Decreased modularity is one clue proving a decrease in the segregation in the older brain as reported by other studies (Antonenko & Flöel, 2014; King et al., 2018; Kong et al., 2020). Our results of increased modularity associated with motor learning ability could thus mean that the brain of older adults tends towards a young-like pattern of functional network organization, but this interpretation is to be taken with great caution as we do not have a young control group to verify the statement.

5.1.4 Behavior-related structure-function correspondence

In the second study, we assessed the change in segregation and integration of functional networks in relation to motor learning ability, and we also investigated the correspondence between structure and function at baseline and by comparing baseline and post-learning in association with behavior. Structure-function correspondence is the relationship between the structural and functional organization of the brain. It is now well-accepted that although the brain structure shapes the functional structure (Honey et al., 2009), part of the functional connectivity cannot be explained solely by the structure (Batista-García-Ramó & Fernández-Verdecia, 2018). Especially in healthy older adults, the study of the relationship between structure and function is relevant as it appears that the structure-function correspondence changes across the lifespan (Esfahlani et al., 2022). In this thesis, we report that stronger baseline structure-function correspondence was related to superior motor learning ability in older adults. Greater structure-function correspondence in the dorsal attention, ventral attention, and frontoparietal networks as well as the whole-brain network before motor learning was predictive of motor learning ability. By considering the absence of changes in functional topology in the whole-brain and attentional networks in relation to motor learning ability, this result could mean that the integrity of these networks predicts motor learning ability. Furthermore, reduced structure-function correspondence post learning in the visual, ventral attention, and frontoparietal networks as well as the whole-brain network was related to motor learning ability (Figure 24).

Few studies have investigated the structure-function correspondence relevance for cognitive abilities and to our knowledge, there are no studies that have addressed it in the view of motor abilities and motor learning. Among the available reports, Wang and colleagues demonstrated that higher structure-function correspondence was associated with poorer visual memory performance, and executive and visuoconstruction performance (Wang et al., 2018). In a similar direction, a recent study found that high structure-function correspondence in preschool children was associated with poor executive functioning performance in later childhood (Chan et al., 2022). Our prediction result is in the opposite direction, that is higher structure-function correspondence at baseline predicted higher motor learning ability. Several interpretations could be given for this discrepancy. First, the results of the cited studies were the association with a score acquired at one time point while we are looking at the association with a change in motor learning performance. Actually, an explanation could be that the subjects who have higher structure-function correspondence at baseline are the ones performing the worse at the beginning of the learning session. If they are showing low performance at baseline, they would have more room to improve on the motor learning ability. Another interpretation might be related to the fact that the structure-function coupling is decreasing with age (Esfahlani et al., 2022). Considering this, it might be that the structure-function correspondence at baseline is a measure of the integrity of the networks in older age. If the structure-function correspondence is high, the brain of the subjects in some ways resembles younger brains and is behaving like a younger brain when looking at the process of motor skill acquisition. This interpretation is to be taken with caution as we do not have a young group to compare with. Especially, the frontoparietal network was proposed as a network including information for individual fingerprinting in terms of brain structure-function correspondence (Petrovic, Liegeois et al. 2020). Last but not least, a concern mentioned by Esfahlani and colleagues is that the decreasing correspondence with age might present a floor effect (Esfahlani et al., 2022). In other words, the subjects who have low structure-function correspondence do not have the room to further decrease the correspondence and do not increase substantially on the motor learning ability, this interpretation is speculative and to be taken with caution.

As mentioned earlier, reduced correspondence from pre to post-learning was associated with higher motor learning ability in the whole brain as well as in visual and cognitive systems comprising ventral attention and frontoparietal network. It was posited that low structure-function correspondence could promote flexibility in

the brain (Baum et al., 2020) while a high degree of correspondence is interpreted as a high degree of specialization (Chan et al., 2022). This interpretation is relevant when we consider that high baseline structure-function correspondence is related to high motor learning ability, and parallelly, that visual-sensorimotor autonomy at baseline predicts higher motor learning (Mattar et al., 2018), although this last point was not tested in our studies. Following this view, the network topology measure of modularity has been employed to shed light on associations between functional and structural subnetworks (Hagmann et al., 2008; Sami & Miall, 2013). In our study, decreased correspondence after the acquisition of motor learning could reflect enhanced flexibility in the functional systems that supported motor learning. This highlights the importance of brain flexibility as the potential main characteristic to achieve motor learning (Bassett et al., 2011; Reddy et al., 2018). Especially, the importance of a low structure-function correspondence in the frontoparietal network may support functional flexibility and dynamic recruitment for diverse task demands (Baum et al., 2020) such as the development of spatial coordinates and correct dynamic selection of actions throughout the learning process (Hikosaka et al., 2002; Hardwick et al., 2013).

We expected to observe that changes in structure-function correspondence would occur in the same networks that showed changes in network topology. However, the common networks in both types of changes were only seeable for the visual and frontoparietal networks. Several explanations can be posited for this discrepancy. First, global efficiency and modularity are good representatives of integration and segregation of information transfer in the brain connectome, however, there do not exhaustively represent the characteristics of the functional connectome. Indeed many other measures have been used with some representing more local characteristics such as node degree, clustering coefficient, node centrality, and other more global measures such as connection density, small worldness, and others (Bullmore & Sporns, 2009). Other measures of topology might have changed in the whole brain and ventral attention networks and inducing a change in structure-function correspondence. An alternative hypothesis could be that our assumption of a static brain structural connectome is wrong. It is well known that learning induces changes in the structure of the brain by the means of experience-dependent plasticity (Poldrack, 2000; Sagi et al., 2012; Tavor et al., 2013; Sampaio-Baptista et al., 2013, 2018). While it was initially seen as a slow process occurring at least over days, evidence for more rapid structural changes was reported (for review, see Stee & Peigneux, 2021). The work of Tavor and colleagues for example revealed changes in mean diffusivity, a structural measure derived from DWI, following the practice of visuomotor learning in 1-2 hours. More recently, a study detected learning-specific neocortical plasticity after only one hour (Brodt et al., 2018). To our knowledge, minutes-dependent structural plasticity has not been reported.

5.1.5 The relevance of multimodal studies

The brain is a complex system that follows Gestalt phenomena meaning that its properties cannot be derived from the sum of its parts (Tononi et al., 1994; Telesford et al., 2011; Bassett & Gazzaniga, 2011). Therefore, multimodal studies in the sense of using different types of brain imaging and analyses can help to understand holistically different aspects of brain network organization. Especially in the motor learning process, we have seen throughout this thesis that many interacting processes are at play, and already as early as during the acquisition phase of motor learning. Indeed, we were able to demonstrate that during this phase, multiple brain regions were involved differentially over time and in function of several aspects of performance (Chapter 3) while the interaction between these brain regions, as well as their relationship to the brain structure, were differently related to the behavioral change (Chapter 4). Multivariate methodologies and multimodal neuroimaging methods are thus necessary to explore activation patterns displaying integrative processes and dynamic, complex interactions across distributed brain regions.

As one compelling example, in the second study, we could highlight the additive value of the brain structure-function correspondence on top of the sourced brain structural and functional connectomes to predict motor

learning ability. Indeed, structure-function correspondence only, but not structural and functional topology, predicted motor learning ability. This suggests the usefulness of relationships between structure and function in explaining individual differences (Griffa et al., 2022) in motor learning ability.

5.2 Future developments

This thesis work adds to the knowledge of the motor learning process in aging by focusing on the acquisition phase of motor learning. To probe motor learning, we employed a relatively novel motor learning task that was not yet performed in the MRI before. The analysis and interpretation of this task showed that the task seems to relate differently to the pathway from goals to action (Figure 1) compared to a motor sequence learning task. In particular, being skilled in this task seems to entail effective goal and action selection and accurate and fast action execution. Therefore, it seems to relate to all aspects of the pathway from goals to action. Accordingly, the grip force modulation task, feasible in the MRI environment, could be utilized and manipulated to investigate the different steps of the motor planning and execution pathway.

One of the main novelties of this thesis is the application in Study 2 of graph network and structure-function analyses for studying motor skill acquisition in older adults. In this report, we investigated resting-state networks' topology changes in association with motor learning ability. The validity of this analysis stems from the observation that motor learning-related functional changes during the task are impacting the following resting-state networks (Albert et al., 2009; Sami & Miall, 2013). However, task-based functional connectivity can give us additional insight into the connectivity of the brain while executing the task (Braun et al., 2015; Elton & Gao, 2015). Especially, this aspect is particularly relevant for healthy older adults who show differential patterns of task-based connectivity according to the task tested (Varangis et al., 2021). Furthermore, we interpreted the positive associations of different network measures changes with motor learning ability as a need for flexibility of the brain for motor learning. This notion of brain flexibility could be assessed in terms of the temporal changes using dynamic functional connectivity as in the studies of Bassett and colleagues (Bassett et al., 2011, 2015; Betzel et al., 2022). Besides, concerning flexibility, the literature stresses the importance of the modular architecture of the brain (Mattar et al., 2016). The modular architecture is relying on the presence of highly connected nodes called connector hubs (Bullmore & Sporns, 2009). It was shown previously that in older adults, the number of connector nodes over different modules of the brain changed compared with young adults (Meunier et al., 2009). An interesting point of further development would be to assess how the modules and the connector nodes are reorganized following learning in our cohort. Finally, while we assessed the contribution of changes in functional subnetworks to motor learning ability, the relationship between the specific networks was not assessed in this thesis. Previous research suggests that a need for integration between different functional systems may arise as motor learning progresses (Coynel et al., 2010). The investigation of internetwork connectivity changes would thus increase our understanding of the interaction between functional systems during motor learning. Related to this, the integrity of the highly interconnected hubs that are forming the "rich club" (van den Heuvel & Sporns, 2011) might have a relevant role in motor learning ability as it is for cognitive processes (Baggio et al., 2015). Last but not least, we could further assess internetwork connectivity at baseline as it seems to be a good predictor of learning in young (Wu et al., 2014; Mattar et al., 2018) and older adults (Mary et al., 2016; King et al., 2018).

As for structure-function correspondence, we assessed the short-term changes in the correspondence related to learning in older adults. It should be mentioned that the relationship between structure and function can be measured with several methods (Preti & Van De Ville, 2019; Vázquez-Rodríguez et al., 2019), so it would be worth investigating whether the different methods provide similar findings. Also, as we only tested older adults, future investigations are warranted to check whether similar dynamics are observable in young adults.

Furthermore, we could also examine the contribution of changes in brain structure-function correspondence for motor learning on a longer timescale, keeping in mind that the structural connectome would probably change. One interpretation mentioned in the discussion was that a high degree of structure-function correspondence is related to a high degree of specialization (Chan et al., 2022). Our design would allow us to test this interpretation by checking whether visual-sensorimotor autonomy at baseline predicts higher motor learning following the analysis of Mattar and colleagues (Mattar et al., 2018) and correlates the visual-sensorimotor autonomy with the structure-function correspondence of these regions.

Last but not least, while the main goal of this thesis was to characterize the brain dynamics in the acquisition of motor learning in older adults, a similar analysis would give us great insight into the processes at play in the motor learning process during recovery in stroke patients. Multimodal studies are beneficial for understanding and characterizing diseases such as stroke and its recovery (Di Pino et al., 2014; Fleury et al., 2022). Especially, it was shown before that we can substantially benefit from connectome analysis to understand recovery after stroke (P. J. Koch et al., 2021; Egger et al., 2021; Evangelista et al., 2022). As motor learning is crucial for stroke recovery and rehabilitation (Krakauer, 2006), applying the analyses of this thesis in stroke patients will further add knowledge to the understanding of stroke recovery and help the development of new rehabilitation strategies for better recovery.

5.3 Conclusion

This thesis project aimed at characterizing in detail the dynamic changes occurring in the brain of older adults during the acquisition phase of a motor learning task. To do such, we employed multimodal techniques that allowed us to associate motor performance changes with brain activation during the acquisition of a novel motor skill and with resting-state functional topology and structure-function correspondence changes. In the first study, we wondered which brain regions showed activation changes throughout the training and if these same brain regions were associated with the improvement in motor skill (Chapter 3). We could demonstrate that better performance was achieved by the contribution of frontoparietal regions responsible for efficient visuomotor processing and cortical motor regions involved in the correct selection of action. In the second study, by implementing a design with baseline and immediate post resting-state sessions, we were able to quantify the changes in functional topology and structure-function correspondence following the acquisition of the motor skill (Chapter 4). The structure-function uncoupling was accompanied by the enhanced segregation into modular structures over the core functional networks involved in the learning process. These results highlight in a multimodal way that successful acquisition of the motor skill depends on brain flexibility.

The acquired knowledge presented in this thesis adds to the existing corpus of literature on motor learning in aging, and could hopefully be used as a point of comparison for studies in older adults with motor deficits and as a basis of knowledge to adapt motor training strategies for healthy aging and rehabilitation in clinical settings. Finally, one of the focus was to characterize the brain regions responsible for the acquisition of motor learning, it might help to define novel targets for interventional approaches such as brain stimulation.

A. Supplementary Material for Chapter 3

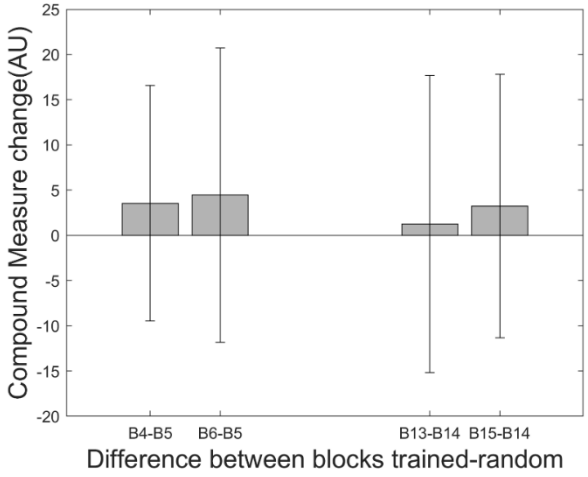
Supplementary Information

Investigation of the difference between trained sequence versus random sequence

Behavior: The random blocks (B5 and B14) did not significantly differ from the neighboring blocks, B4 vs. B5 $t(40) = 1.75$, $p = 0.088$, Cohen's $d = 0.27$, B6 vs. B5 $t(40) = 1.75$, $p = 0.088$, $d = 0.27$, B13 vs. B14 $t(40) = 0.49$, $p = 0.627$, Cohen's $d = 0.076$, B15 vs. B14 $t(40) = 1.42$, $p = 0.163$, $d = 0.22$, although a trend is present for the first random block. This implies that sequence-independent learning was present.

BOLD activation: Although the behavioral results did not show any significant difference between random blocks and neighboring blocks, we checked as a control analysis whether BOLD activity would be different between these blocks to make clear whether there was brain activation specific to the learned sequence. To do so, we implemented a new GLM design at the subject level, creating new regressors for the neighboring blocks. We then computed the contrasts preblock-randomblock, postblock-randomblock for session 1 and 2, with the preblock being B4 or B13 and postblock being B6 or B15. Additionally, we computed the contrast postblock-preblock as a control analysis to see if there was a difference between the neighboring blocks of the random. We can see the results in the Supplementary Table 1 and the Supplementary Figure 1. As the random block occurs only once within each session, the statistical power is low and we should thus interpret these results with caution. We would expect to see the most differences in the contrast preblock-randomblock in session 2 as the sequence has been learned already for 11 previous blocks. The postblock-randomblock contrast is less of interest as the activity of the random block might have aftereffects. As expected we observed significant differences in the contrast preblock-randomblock in session 2 with more activity during the learned sequence in middle cingulate area, supplementary motor area, frontal opercular areas, cerebellar areas and right primary motor area. Inversely, we observe more activity during the random block in left visual and superior parietal areas. This analysis points toward the fact that although we do not observe a significant difference behaviorally, there is a sequence-specific learning component occurring in the first acquisition phase.

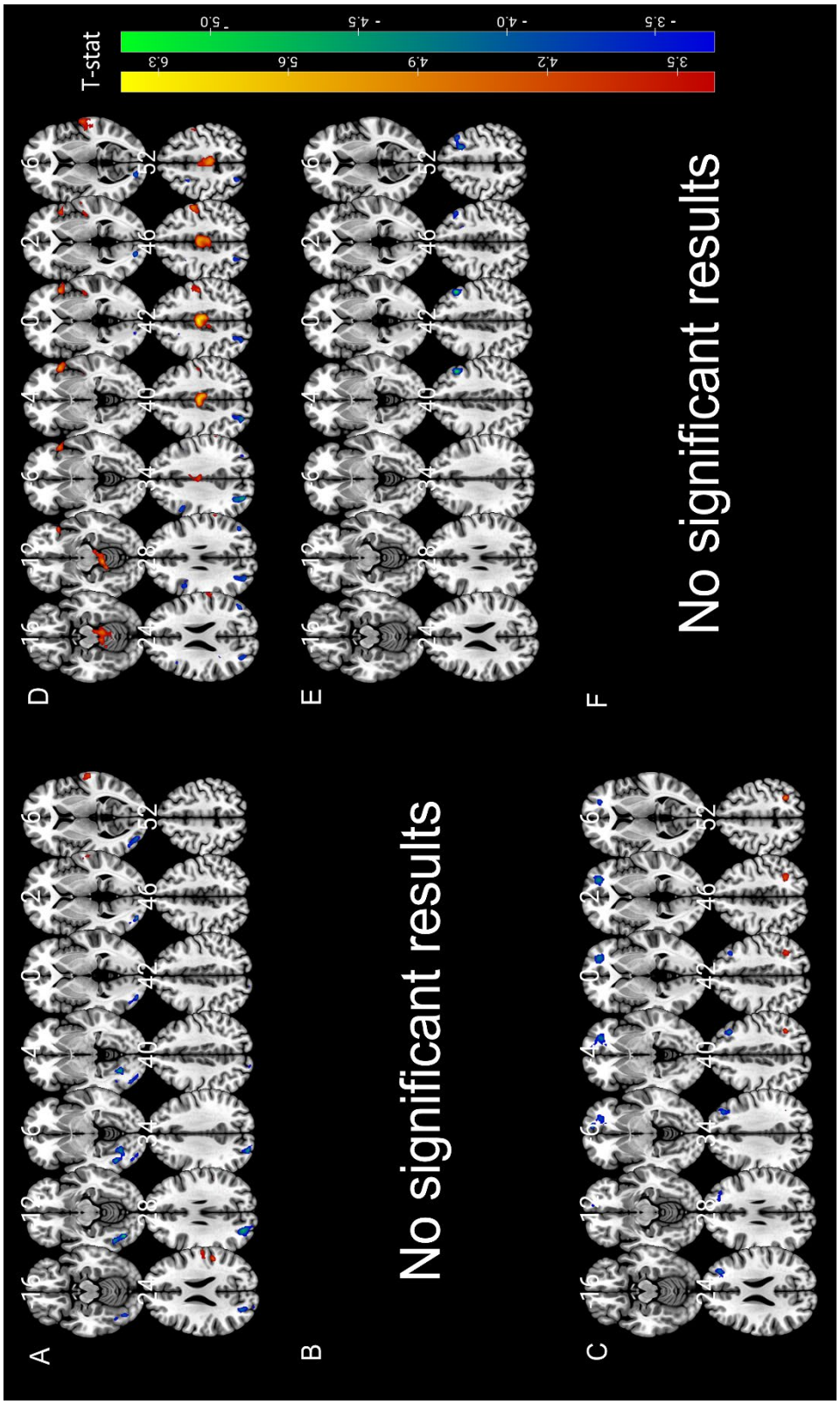
Supplementary Figures and Tables



Supplementary Figure 1. Differences between the compound behavioral measure of the random blocks (B5 and B14) compared to the neighboring blocks (B4, B6, B13, B15). The error bars are standard deviation from the mean. No differences were significant.

		Session 1							Session 2						
A		preblock-randblock							preblock-randblock						
Sign	Region Label	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates			cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates		
						x	y	z					x	y	z
Positive	Cingulate_Mid_L	-	-	-	-	-	-	-	<0.001	888	0.004	6.54	0	-12	42
	Cingulate_Mid_R	-	-	-	-	-	-	-	<0.001	888	0.044	5.66	2	-26	48
	Frontal_Inf_Oper_R	-	-	-	-	-	-	-	0.015	206	0.042	5.68	48	20	-2
	Frontal_Inf_Orb_2_R	-	-	-	-	-	-	-	0.015	206	0.154	5.18	46	22	-
	Cerebelum_4_5_L	-	-	-	-	-	-	-	0.002	308	0.052	5.60	-6	-42	-
	Vermis_3	-	-	-	-	-	-	-	0.005	261	0.242	4.98	6	-42	-
	Precentral_R	-	-	-	-	-	-	-	0.044	158	0.186	5.10	54	-4	46
	Temporal_Sup_R	0.001	322	0.117	5.30	54	-30	20	0.005	261	0.704	4.40	64	-14	8
	SupraMarginal_R	0.001	322	0.987	3.88	60	-18	24	0.005	261	0.973	3.94	68	-24	22
Negative	Occipital_Inf_L	<0.001	334	0.111	5.32	-36	-74	-	-	-	-	-	-	-	-
	Occipital_Mid_L	0.001	326	0.418	4.74	-28	-78	28	<0.001	481	0.385	4.77	-30	-76	38
	Occipital_Sup_L	0.001	326	0.999	3.68	-18	-86	40	-	-	-	-	-	-	-
	Parietal_Sup_L	-	-	-	-	-	-	-	<0.001	481	0.979	3.91	-26	-68	52
B		postblock-randblock							postblock-randblock						
Sign	Region Label	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates			cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates		
						x	y	z					x	y	z
Positive	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Negative	Frontal_Mid_2_R	-	-	-	-	-	-	-	<0.001	363	0.129	5.27	46	20	42
	Frontal_Sup_2_R	-	-	-	-	-	-	-	<0.001	363	0.556	4.58	26	16	54
C		postblock-preblock							postblock-preblock						
Sign	Region Label	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates			cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates		
						x	y	z					x	y	z
Positive	Parietal_Inf_R	0.026	174	0.204	5.08	32	-54	52	-	-	-	-	-	-	-
Negative	Frontal_Mid_2_R	0.001	306	0.557	4.58	34	34	38	-	-	-	-	-	-	-
	Frontal_Sup_2_R	0.001	306	0.998	3.70	20	44	28	-	-	-	-	-	-	-
	Frontal_Mid_2_R	<0.001	328	0.642	4.49	26	48	2	-	-	-	-	-	-	-
	Frontal_Med_Orb_R	<0.001	328	0.701	4.42	10	58	-6	-	-	-	-	-	-	-

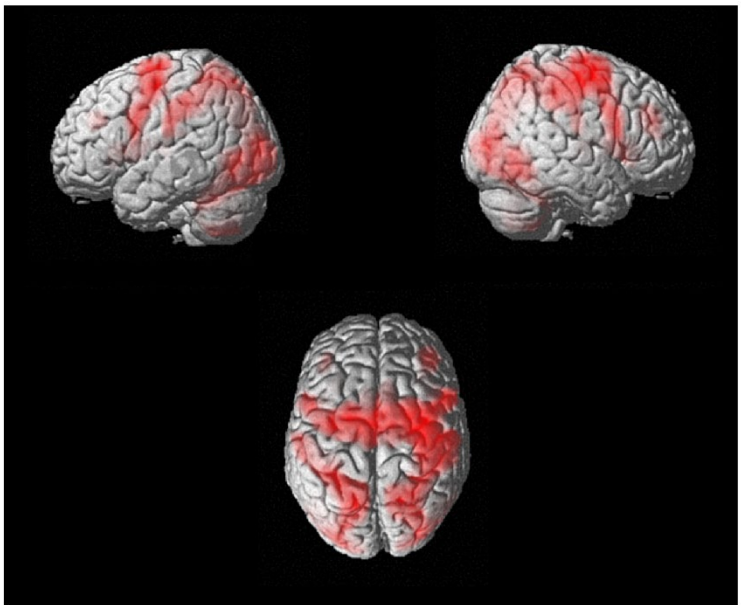
Supplementary Table 1. BOLD activation results for the contrasts between the learned sequence blocks versus the random sequence blocks. Results are reported at uncorrected p<0.001 at the voxel level, cluster level p-FWE<0.05.



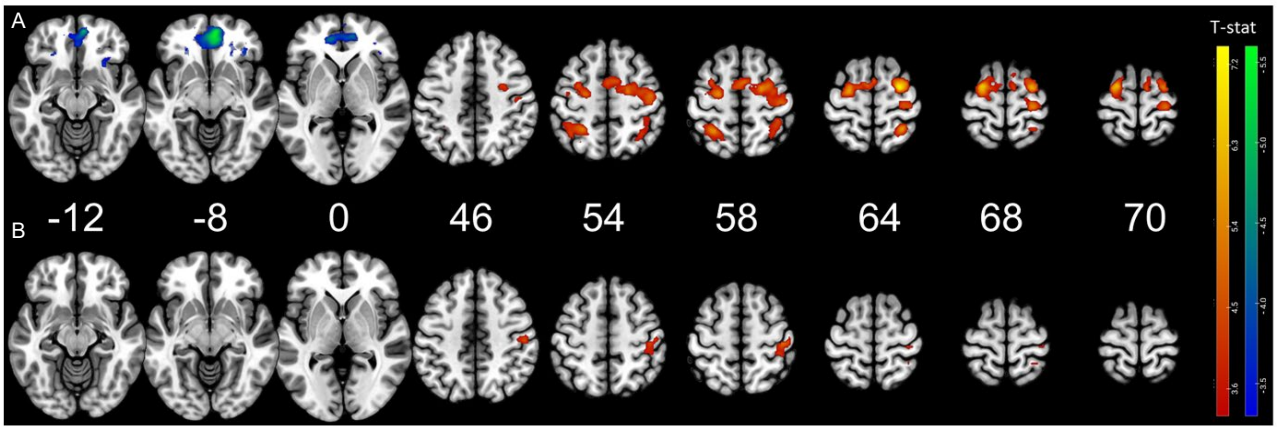
Supplementary Figure 2. BOLD activation results for the contrasts between the learned sequence blocks versus the random sequence blocks. The organization of the figure is similar to supplementary Table 1. (A) Contrast preblock-randblock of Session 1. (B) Contrast postblock-randblock of Session 1. (C) Contrast postblock-preblock of Session 1. (D) Contrast preblock-randblock of Session 2. (E) Contrast postblock-randblock of Session 2. (F) Contrast postblock-preblock of Session 2. Results are reported at uncorrected $p<0.001$ at the voxel level, cluster level p-FWE<0.05.

Region Label	cluster level p(FWE-corr)	cluster size (number of voxels)	peak-level p(FWE-corr)	peak (T-value)	MNI Coordinates x	y	z
Main effect of training							
Frontal_Mid_2_R	<0.001	47720	<0.001	19.73	36	-8	52
Vermis_8			<0.001	18.28	-2	-62	-30
Precentral_R			<0.001	16.67	32	-20	48
Cerebelum_8_R			<0.001	16.51	10	-70	-44
Frontal_Sup_2_L			<0.001	16.45	-24	-6	56
Supp_Motor_Area_L			<0.001	16.33	-10	-12	70
Precentral_R			<0.001	16.27	36	-16	52
Occipital_Mid_R			<0.001	16.11	32	-86	10
Frontal_Sup_2_R			<0.001	15.93	22	-4	60
Parietal_Sup_L			<0.001	15.77	-20	-66	58
Cerebelum_6_L			<0.001	15.69	-26	-56	-22
SupraMarginal_R			<0.001	15.51	46	-34	44
Precentral_R			<0.001	15.50	28	-2	50
Occipital_Mid_L			<0.001	15.36	-28	-88	12
Occipital_Mid_R			<0.001	15.28	28	-72	30
Putamen_L	<0.001	548	<0.001	11.86	-24	-14	8
Thalamus_L			<0.001	9.27	-16	-16	10
Frontal_Mid_2_L	0.02	263	0.002	6.56	-40	34	30

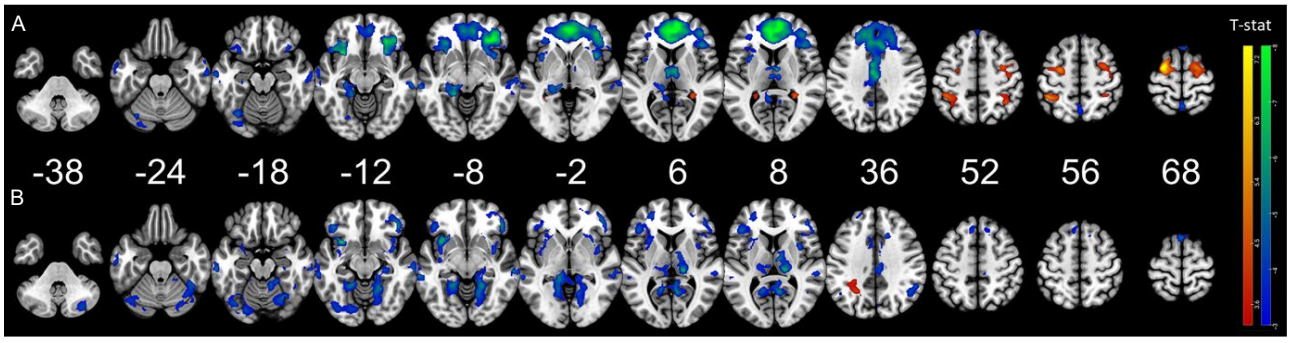
Supplementary Table 2. BOLD activation result for the contrast Average of both training sessions. The main areas are listed. The threshold was at the cluster-level p<0.05 FWE-corrected.



Supplementary Figure 3. Rendered figure of the average BOLD activation during the training blocks.

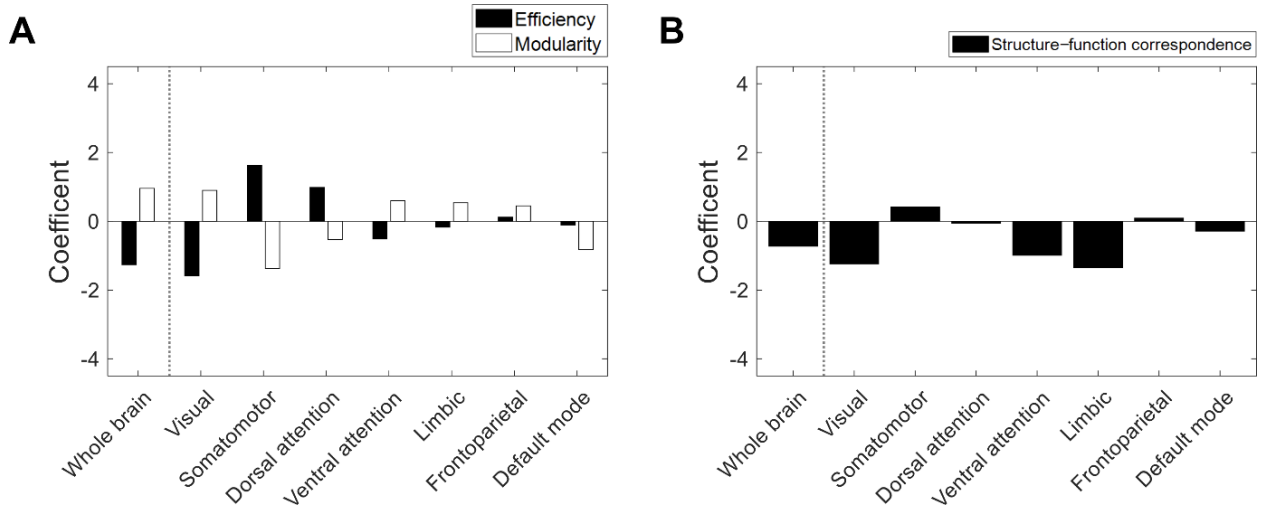


Supplementary Figure 4. Performance-modulated brain activation masked by the time-modulated activation. (A) Performance-modulated activation that also showed time-modulation. The results were computed within an inclusive mask of time-modulated activation. (B) Regions showing performance-related activation which do not show a linear increase (exclusive mask of time-modulated activation).

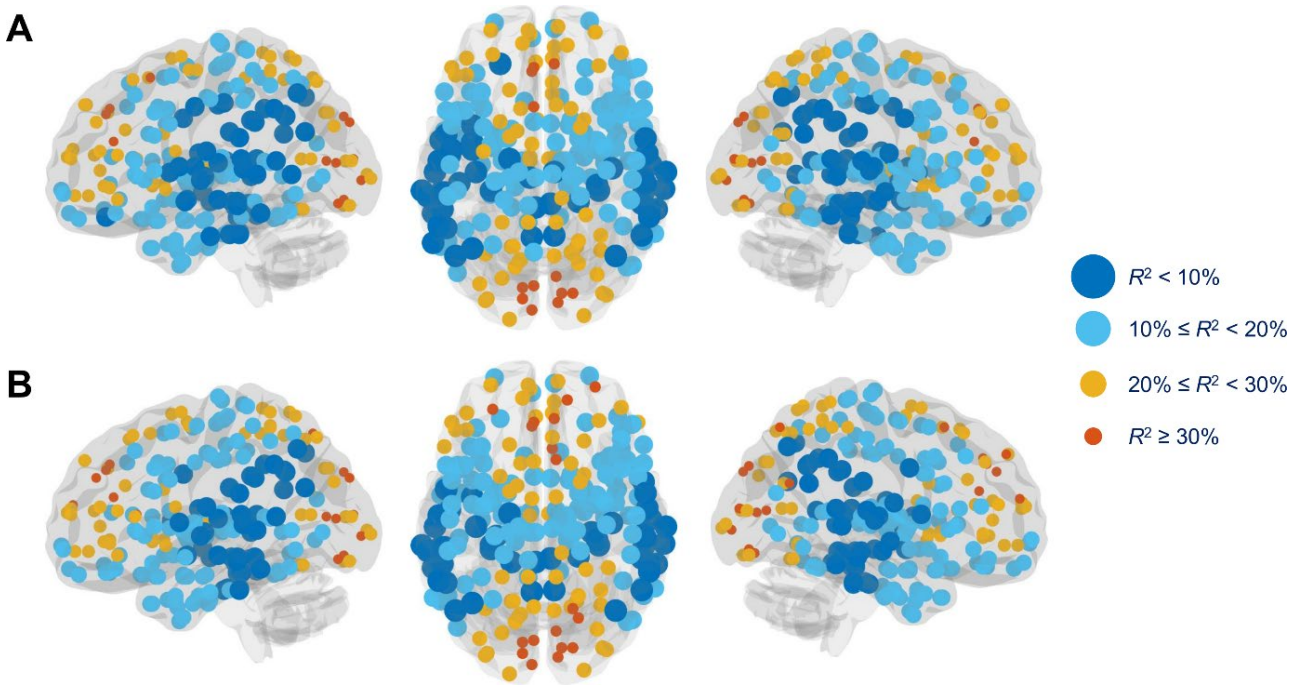


Supplementary Figure 5. Time-modulated brain activation masked by the performance-modulated activation. (A) Time-modulated activation that also showed performance-modulation. The results were computed within an inclusive mask of performance-modulated activation. (B) Regions showing time-related activation which do not show an association with behavior.

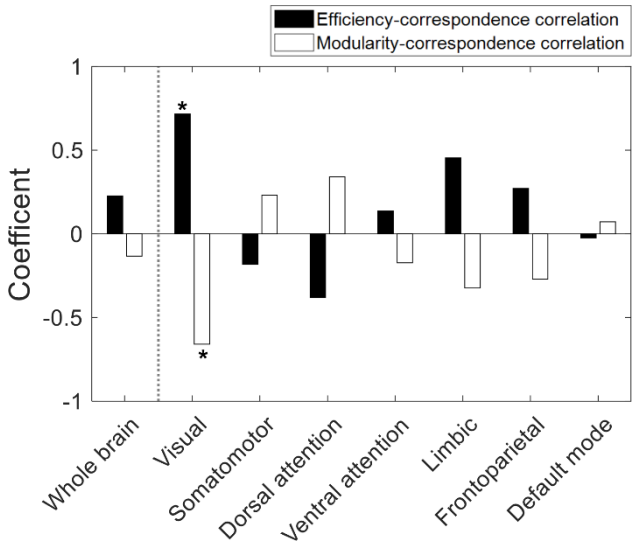
B. Supplementary Material for Chapter 4



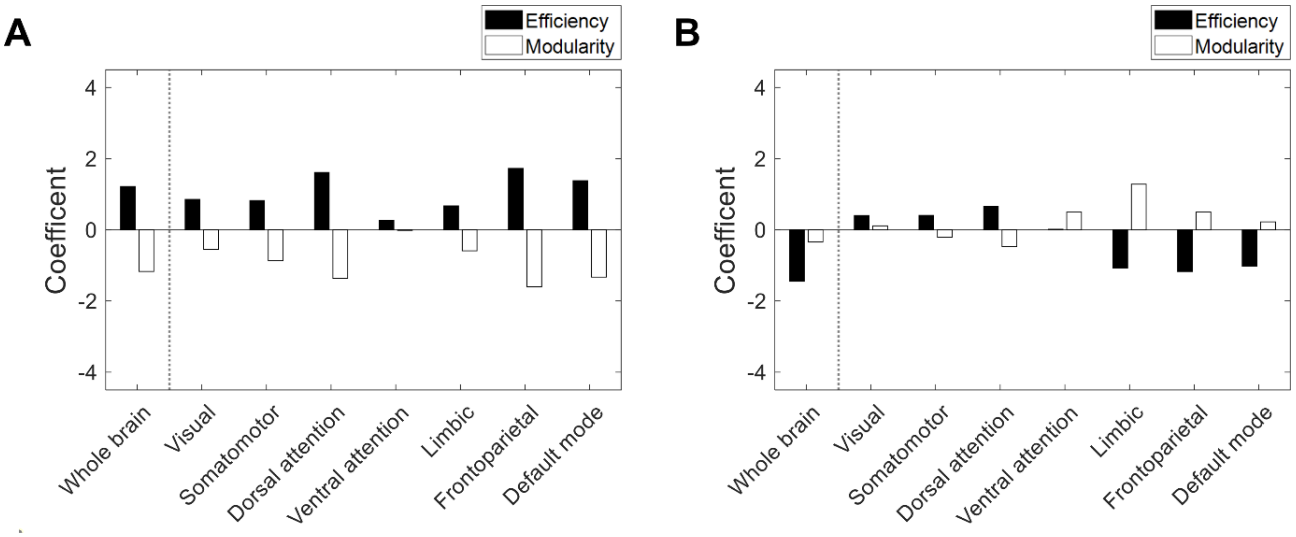
Supplementary Figure 6. Brain connectome changes. Changes in network topology of the brain functional connectome (A) and changes in brain structure-function correspondence (B) between before and after motor learning were measured for the whole brain and seven cerebral networks.



Supplementary Figure 7. Changes in brain structure-function correspondence. Node-wise structure-function correspondence was measured before (A) and after motor learning (B) in terms of the coefficient of determination (R^2 value). Circles with different sizes indicate R^2 values at corresponding nodes.



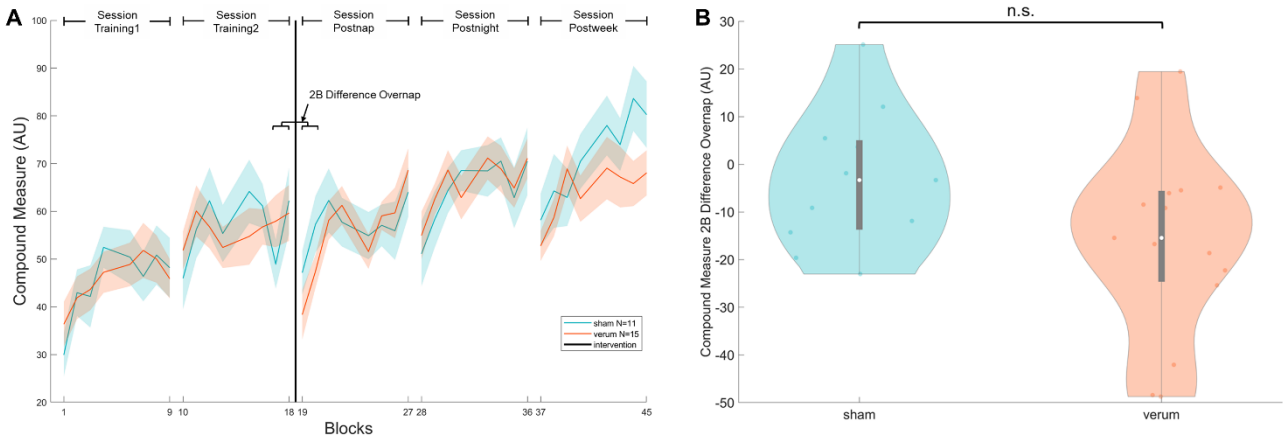
Supplementary Figure 8. Correlation of brain connectome changes between measures. Changes in network topology of the brain functional connectome and changes in brain structure-function correspondence between before and after motor learning were measured for the whole brain and seven cerebral networks. *, statistical significance.



Supplementary Figure 9**.** Brain connectome bases of motor learning ability. Network topology of the brain (A) structural and (B) functional connectomes before motor learning was measured for the whole brain and seven cerebral networks.

C. Appendix 1: Effects of spindle-like tACS on task-related activation

As introduced in Chapter 2 Section 2.1, the EconS project aimed at answering different research questions. One of them was to assess whether a non-invasive brain stimulation protocol mimicking the natural sleep spindles of young adults applied during a daytime nap would be beneficial for motor memory sleep-dependent consolidation in older adults. This research question was investigated extensively in another thesis (Maëva Moyne's work) and thus is succinctly presented here. To answer this question, a placebo-controlled spindle-like tACS stimulation protocol was applied during the afternoon after the initial acquisition phase of the motor skill while subjects were asleep. Within our pool of subjects, 15 received a real stimulation (also called the "verum group") and 11 received a placebo stimulation (called the "sham group"). We assessed whether we could see a difference between groups in the overnap memory consolidation by comparing the difference of the average of the two first blocks of the compound measure postnap versus the two last blocks of training (prenap) (Supplementary Figure 10A). We computed the difference as mean(compound_post(2blocks)) - mean(compound_pre(2blocks)) in the 26 subjects that received either sham or verum stimulation and then tested the differences with a two-sample t-test (Supplementary Figure 10B).



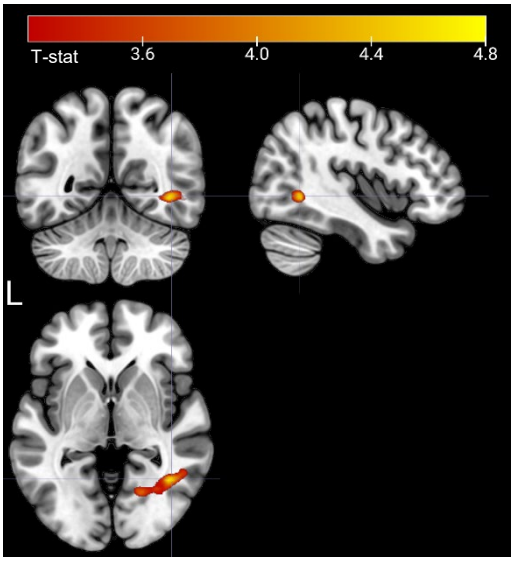
Supplementary Figure 10. Depiction of the compound measure for sham and verum groups. (A) Evolution of the compound measure per block over the entire experiment for the sham and verum groups. (B) Violinplots of the two-block averaged difference of compound measure for sham and verum groups. n.s. represents non-significance on the two-sample t-test.

No significant differences in the offline change overnap were found between the sham and verum groups $t(24)=1.78$, $p=0.088$. A trend was visible towards more decrease in performance in the verum group compared with the sham group. Therefore, the stimulation might rather have a detrimental than beneficial effect on performance, although the difference was not significant.

Although we did not see a significant difference in behavior, we were wondering if we could observe relevant differences in brain activation. Our research question was formulated as "Do we observe a difference from pre to post intervention in the execution-related brain activation in sham and verum groups?" A follow-up question was "Is the difference we observe related to the offline change of behavior?". Our hypothesis here is that although we could not observe significant differences in behavior, the neural processes during task execution might have been impacted by the stimulation and might be seeable with fMRI after intervention.

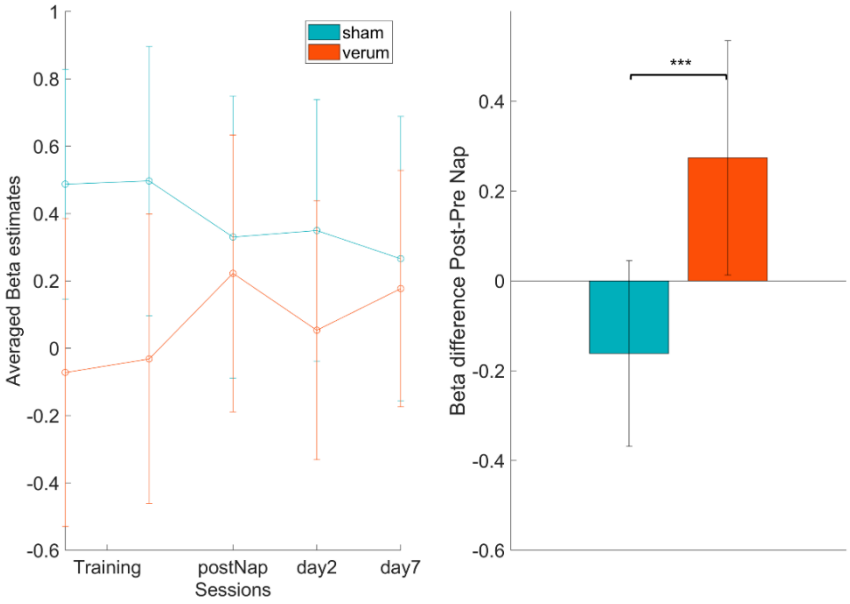
To answer this question, we used the fMRI data of session 1, session 2 and post nap session preprocessed as in Chapter 3 and performed linear contrasts testing the main effect of practice for each session (model 1 Chapter 3). These contrasts were then entered in a second level model consisting of a mixed ANOVA with factors group and prepost. To clarify, session 1 and session 2 (acquisition phase) were labeled as pre and the postnap session was labeled as post. Our interest was to test whether an area would show a group × prepost interaction

effect. The results showed one significant cluster of 219 voxels comprising part of the right (contralateral) lingual gyrus and part of the right middle temporal area (Supplementary Figure 11).



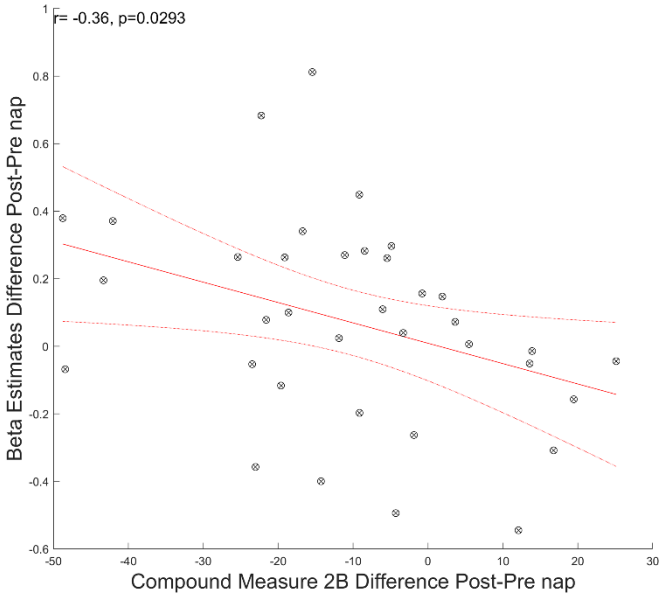
Supplementary Figure 11. Brain activation showing an interaction group x prepost. The cluster of 219 voxels comprises part of the right lingual area and the right middle temporal area.

We then created a ROI from this cluster to extract the β estimates of this region for each session using MarsBaR toolbox in SPM12 (Brett et al., 2002). The investigation of the evolution of the β estimates permitted us to observe that this region showed decreasing activation in the sham group from pre to post nap whereas this region increased in the verum group (Supplementary Figure 12). A two-sample t-test revealed as expected a significant difference between the two groups $t(24) = 4.57$, $p<0.001$.



Supplementary Figure 12. Evolution of Beta estimates in the cluster showing an interaction between group and prepost. The sham group show a decrease of activation while the verum group show an increase. *** refers to statistical significance with p-value inferior to 0.001.

Activation change of this area was not differentially related to behavior however when pooling all subjects together (and including the wake subjects), we found a negative association between the change of activation and the offline improvement during the nap r(34) = -0.36, p = 0.029 (Supplementary Figure 13).



Supplementary Figure 13. Correlation between beta estimates change from postnap to prenap and behavioral change from postnap to prenap.

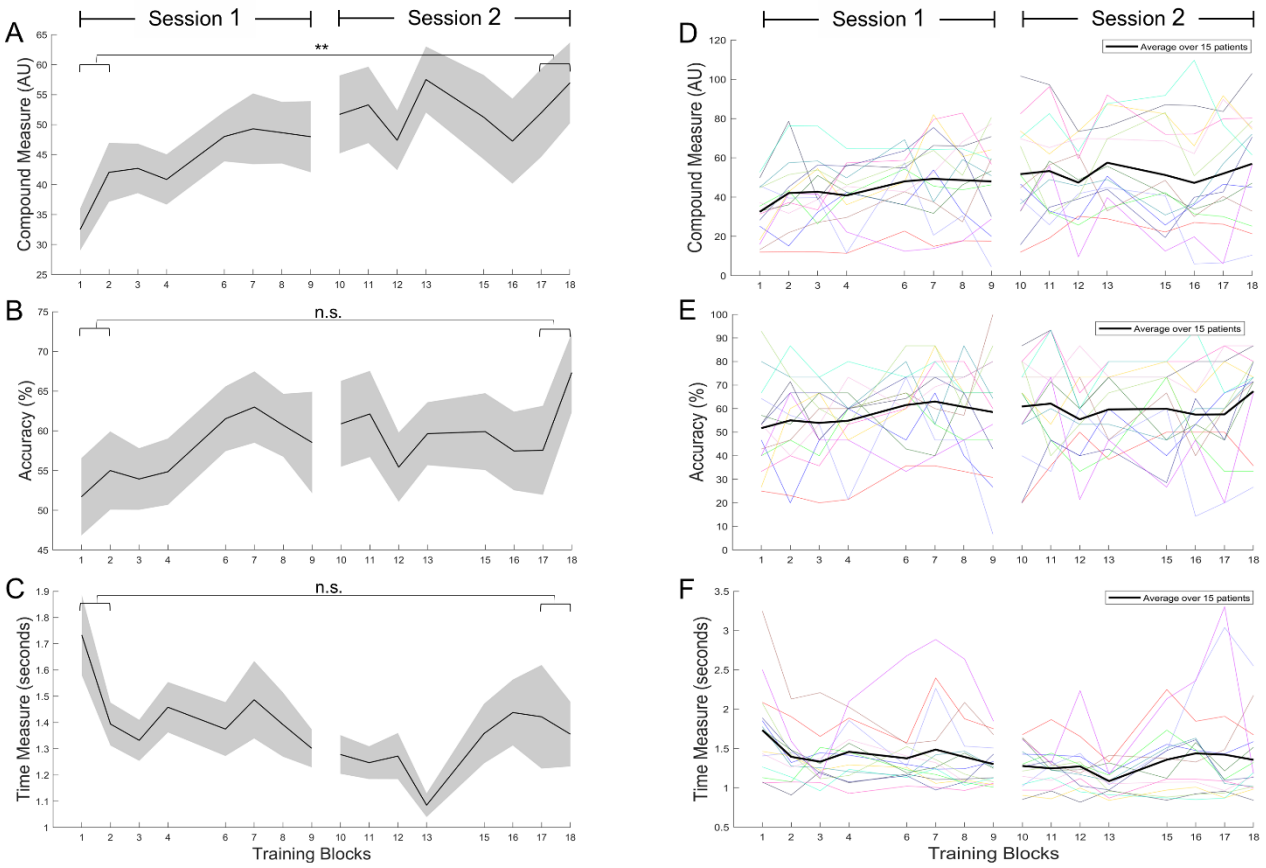
Therefore, regardless of the group, the change of activation in this area was negatively associated with better behavior, i.e. less activation in this area after the nap was associated with better performance. The right lingual gyrus (BA19) is a region involved in object and color recognition (Brewer et al., 2005) and the right middle temporal area (BA37) is thought to be involved in the ventral visual pathway (the what) and especially in complex visual perception (Gross, 1994). Moreover, the right middle temporal area has been shown to be more activated in visually-guided movement of joystick compared with proprioceptively guided movement (Grefkes et al., 2004).

To summarize, the subjects who got better post-nap compared with pre-nap showed a decrease in activation in this area. It might be interpreted as a compensatory mechanism for those who lost substantially on the performance of the task from pre to post nap and thus need to rely more on visual processing to perform the task after the nap.

D. Appendix 2: Behavioral change during acquisition in stroke patients

One goal of the EconS project was to conduct the same experimental paradigm in a population of stroke patients as a proof of concept to investigate underlying mechanisms of motor learning in stroke and whether spindle-like tACS during a nap can enhance consolidation of an acquired motor skill. Stroke can lead to significant impairment in several domains ranging from cognitive (Tatemichi et al., 1994) to motor execution and learning (Raghavan, 2007). Of particular interest in our context, a recent review of the literature reports that stroke patients with motor impairments show impairment in the early learning phase of motor sequence learning, indicated by deficits in integration of information (Dahms et al., 2019). Furthermore, it is well-accepted that motor recovery beneficiates from motor learning principles as stated by several research groups (Carr & Shepherd, 1989; Krakauer, 2006; Muratori et al., 2013; Dahms et al., 2019). Considering those facts, investigating the early learning phase and its neural correlates in stroke patients is of paramount importance. The analyses of the stroke data are still ongoing and will be presented later in further publications. In this appendix, the behavioral results of the training phase of motor learning in fifteen stroke patients are presented.

For methods, please refer to Chapter 2 as well as Chapter 3. The analysis pipeline is the same as for healthy older subjects. To test whether the initial scores and end-of-training scores of the compound measure were different, we performed a paired sample t-test on the average of the first (mean ± std = 37.3 ± 15.3) and last (mean ± std = 54.5 ± 25.7) two blocks of the compound measure (Supplementary Figure 14). This analysis showed a significant difference with $t(14) = -2.92$, $p < .01$. Cohen's *d* was estimated at -0.75, which is a medium effect based on Cohen's guidelines (J. Cohen, 1992). When conducting secondary analyses testing



Supplementary Figure 14. Evolution of performance measures in stroke patients depicted in the form of (A and D) a compound measure of (B and E) accuracy and (C and F) time. The left panel is the average over 15 patients with shaded areas being the standard error of the mean (SEM). The right panel depicts the average and the individual data. ** refers to statistical significance with $p < 0.01$.

the difference in speed and accuracy, we did not find significant improvements between initial and end-of-training scores of accuracy $t(14) = -1.47$ $p < .165$ and average time to complete trials $t(14) = 1.29$, $p < .217$.

In conclusion, when considering a compound measure containing information on both speed and accuracy, we could observe a significant improvement in performance during the acquisition phase of motor learning in our dataset of fifteen stroke patients. However, probably due to the low sample size and a large but expected variability in performance across our patients, the changes in performance were not significant for accuracy or time to complete trials.

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04/2018 – Present	**Doctoral Student** in Neuroscience program (EDNE), Ecole Polytechnique Fédérale de Lausanne (EPFL).
09/2014 – 03/2017	**Master of Science** in Life Sciences and Technologies at EPFL, Lausanne, Specialization in Neuroscience.
09/2011 – 06/2014	**Bachelor of Science** in Physics, University Pierre et Marie Curie (UPMC), Paris VI, Specialization in fundamental physics (quantum physics, thermodynamics, electromagnetism). Obtained with distinction.
09/2008 – 06/2011	**High School** in Jean-Baptiste Say, Paris XVI^{e}. Scientific Baccalauréat with specialization in Physics, and option History of Arts. Obtained with high distinction.

EMPLOYMENT HISTORY

09/2017 – 02/2018	**Assistant** for Education Programs and International Relations in the Institut du Cerveau et de la Moëlle Epinière (ICM), Salpétrière Hospital, Paris. Developing a new international master in neurodegenerative diseases (iMind) in collaboration with UPMC and international partners.
09/2016 – 03/2017	**Research Intern** in PEAK, Brainbow Ltd and University College London (UCL), London. Performing the master thesis supervised by Dr. Misirlisoy (PEAK) and Prof. Walsh (UCL), and under the direction of Prof. Sandi (EPFL). Thesis title: "*Validation of a mobile meditation application and its possible benefits*".
03/2016 – 06/2016	**Research Intern** in the Laboratory of Cognitive Sciences, Lausanne University Hospital (CHUV). Studying the effect of prismatic adaptation on resting-state functional connectivity in healthy subjects, mainly analyzing the data.
09/2015 – 12/2015	**Research Intern** in the Laboratory of Neuroenergetics and Cellular Dynamics (LNDC), Dr. Marquet team, EPFL. Employing a digital holographic microscopy technique to study neuron physiology.
02/2015 – 07/2015	**Research Intern** in the Laboratory of Behavioral Genetics (LGC), EPFL, in collaboration with the Laboratory of Cognitive Neuroscience, EPFL under the supervision of Prof. Andrea Serino. Conducting a behavioural experiment studying the effect of stress on peripersonal space.
06/2014 – 07/2014	**Research Intern** in the Neural Circuits and Behaviour lab, Max Delbrück Center (MDC), Berlin. Building a new experimental setup and designing a protocol to study the paw movement of the mice and the process of decision.
06/2013 – 07/2013	**Research Intern** in Team Memory, Oscillations and Brain States (MOBs), Brain Plasticity Unit, CNRS UMR 8249, Paris. Participating in the study of the mouse's auditory memory by electrophysiology.
2011 – 2012	**Summer Intern** in a recruitment company (Staff Consultants) and in a business incubator (Quattrocento).

TEACHING EXPERIENCE

01/2021 – 08/2021	**Master project supervision** of Mihaly Gayer in UPHUMMEL Lab. Investigating motor learning in older adults by dynamic functional connectivity.
09/2020 – 02/2021	**Master thesis supervision** of Julie Brancato in UPHUMMEL Lab. Thesis title: "*Investigation of resting-state fMRI networks involved in motor learning in healthy older adults*."
2019 – 2020	**Teaching Assistant** at EPFL for BA3: *Neuroscience for Engineers,* BA2: *General Physics: Quanta*, BA2: *Probabilité et Statistiques II*.

CONFERENCES

09/2022	**Poster presentation** at the 32nd International Congress of Clinical Neurophysiology (ICCN), Geneva. Poster title: "*Neural correlates of acquiring a novel motor skill in healthy older adults: a fMRI study*".
10/2020	**Poster presentation** at the 11th World Congress for Neurorehabilitation (WCNR), Lyon (online). Poster title: "*Cortical correlates of acquiring a novel motor skill: a fMRI study in healthy older adults*".

PUBLICATIONS

2022	**Durand-Ruel M**, Park C-H, Moyne M, Maceira-Elvira P, Morishita T, Hummel FC. (submitted). Early motor skill acquisition in healthy older adults: brain correlates of the learning process.
2022	Park C-H*, **Durand-Ruel M***, Moyne M, Morishita T, Hummel FC. (submitted). Brain Connectome Correlates of Short-Term Motor Learning in healthy older.
2022	Moyne M, **Durand-Ruel M**, Salamanca-Giron RF, Park C-H, Sterpenich V, Morishita T, Hummel FC. (in preparation). Impact of transcranial alternating current stimulation during a nap on sleep-dependent motor memory consolidation: a behavioural and electrophysiological study in healthy older adults.
2022	Wessel MJ*, Draaisma LR*, **Durand-Ruel M**, Maceira-Elvira P, Moyne M, Turlan J-L, Mühl, A, Léger B, Chauvigné L, Park C-H, Koch PJ, Morishita T, Guggisberg AG & Hummel FC (in preparation). Multi-focal stimulation of the cortico-cerebellar loop during the acquisition of a novel hand motor skill in chronic stroke patients.
2022	Ellena G, Bertoni T, **Durand-Ruel M**, Thoresen J, Sandi C, Serino A. 2022. Acute stress affects peripersonal space representation in cortisol stress responders. Psychoneuroendocrinology. 142:105790. https://doi.org/10.1016/j.psyneuen.2022.105790
2020	Wessel MJ*, Draaisma LR*, de Boer AFW, Park C, Maceira-Elvira P, **Durand-Ruel M**, Koch PJ, Morishita T, Hummel FC. 2020. Cerebellar transcranial alternating current stimulation in the gamma range applied during the acquisition of a novel motor skill. Sci Rep. 10(1):11217. https://doi.org/10.1038/s41598-020-68028-9

SKILLS

Trainings and certifications	Certified MRI Operator (Siemens 3T), Training in Good Clinical Practice, and Research ethics evaluation.
Computer Softwares and Languages	Matlab (extensive), C++ (basic), Python (basic), R (basic), Microsoft Office (extensive), LabView (basic).

LANGUAGES

French (native), English (fluent), Spanish (good command).

VOLUNTEERING

2014-2018	**Treasurer** (2015-2016) and otherwise **volunteer** at Satellite (EPFL). Student association managing the bar of the campus, organising weekly cultural events and having over 30 active volunteers and more than 10 employees.
2011-2014	**Volunteer** in TV Jussieu (UPMC). Student association producing weekly news broadcast focused on students and campus life.

INTERESTS

Contemporary art. Science vulgarization for children, in the context of environmental change. Sports (Paragliding, Hiking, Snowskiing, Dancing: 8 years of ballet and modern dance), Music (Singing, Volunteering as technician for concerts, 4 years of piano).