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Age-Related Differences in Motor Learning and Brain Function

By

JESSICA ANNE KORTE

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

BIOMEDICAL ENGINEERING

in the

OFFICE OF GRADUATE STUDIES

of the

UNIVERSITY OF CALIFORNIA

DAVIS

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Abstract

As the number of people aged 65 and older continues to grow, distinguishing typical aging from neurodegenerative disease has become increasingly important. Motor learning refers to the internal processes associated with practice or experience leading to relatively permanent changes in the capability for responding. Understanding the impact of age on motor learning is important for developing rehabilitation strategies, maintaining functional independence, and understanding how aging affects cognition. In this dissertation, I characterize motor learning and its functional neural correlates in younger (18-35 y.o.) and older adults (60-90 y.o.). I first characterized semi-quantitative resting state functional MRI metrics in brain regions relevant to motor learning, namely the cerebellum, in 120 people using a large existing data repository (Human Connectome Project). I then quantified age differences in motor learning between younger versus older participants by administering a motor learning task where I measured the difference across aging in explicit (conscious) and implicit (subconscious) learning mechanisms. I then assessed memory of this task following multiple days and given an opposite visual perturbation. In these same participants, I collected rsfMRI data to measure how the inherent network differences are associated with behavioral changes and aging. Collectively, these studies demonstrate how individual differences in brain function relate to consolidation and retention of motor memories and investigate the components of learning that are vulnerable to aging and disease.

Acknowledgements

This work is a reflection of everyone that has supported me throughout my graduate school career, and would not have been possible without the people that have encouraged and supported me over the years. Of course, Drs. Audrey Fan and Wilsaan Joiner: thank you for being such kind mentors, for being willing to listen, for being my advocate inside and outside of research, and for letting me explore and develop the scientific curiosity I have today. I'd also like to thank Dr. Alyssa Weakley and Dr. Rachael Seidler for serving on my committee and providing feedback on all things related to and outside of my project: you've helped me become a more well-rounded scientist.

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To my parents, Beth, Ben– thank you for supporting me while I was so far from you. I wouldn't be the person I am today without your love and encouragement. To Jacob: thank you for absolutely everything, and I'm looking forward to the chapters that come after this dissertation.

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Introduction, Motivation, and Overview

There is a growing need to characterize typical aging. The number of people aged 80 and older globally is projected to grow exponentially (United Nations, n.d.) with the number of people aged 65 and older in the United States alone projected to grow 30% in the next 20 years (*2023 National Population Projections Tables*, 2025). A growing aging population will bring increased incidence of functional decline (i.e., decreased activities of daily living, greater hospitalization, loss of independence, and increased nursing home admittance) (V. Lee et al., 2001), increased risk of developing neurodegenerative diseases such as Alzheimer's Disease (AD) or Parkinson Disease (PD) (Niccoli & Partridge, 2012), as well as an increased demand and burden on their caretakers and the resulting economy (Cristea et al., 2020).

Cognitive change in typical aging is highly heterogeneous, making it difficult to identify a specific cognitive change that coincides with functional decline or disease development (Mungas et al., 2010; Salthouse, 2019; Salthouse & Ferrer-Caja, 2003). Cognitive aging also affects motor learning efficiency and performance (Ren et al., 2013). Motor learning refers to the set of processes associated with practice that lead to persistent changes in physical actions and movements (i.e., **behavioral responses**) (Schmidt, 1991), with motor adaptation referring to a type of motor learning that involves modifying an existing behavior to an environmental change. Adaptation is not purely procedural, but also requires contributions from other cognitive processes such as attention, memory, and processing speed (Krakauer et al., 2019; Krakauer & Mazzoni, 2011; Seidler et al., 2012; Tsay et al., 2024). Adaptation paradigms have also been used to probe phenomena related to the memory of a learned motor task, including 'savings'

(faster relearning), generalization (transfer of learned mapping across contexts), or interference (interaction between learned mappings) (Krakauer et al., 2019). Previous work investigating aging differences in motor adaptation have focused on differences in acquisition of the task (see (Cisneros et al., 2026) for a review of relevant literature), and a handful of studies have investigated how age affects the memory and generalization of adaptation tasks (Clayton et al., 2024; Mariscal et al., 2025; Seidler, 2007). However, how aging affects the ability to acquire new, competing sensorimotor mappings has not been well characterized, providing limited insight into the flexibility of motor memories in aging. Moreover, by observing how performance changes over longer timescales (i.e., several days), the persistence of learned adaptations can be investigated. When coupled with neuroimaging such as functional MRI, the neural systems involved in motor adaptation learning and memory can be characterized *in vivo* and used to identify neural differences that may accompany aging-related behavioral differences.

Ultimately, understanding motor adaptation retention in older adults may inform rehabilitation strategies by clarifying how older adults acquire and retain new behaviors. Older adults require physical therapy to address age-related declines in mobility, balance, and motor function (de Vries et al., 2012; Karinkanta et al., 2010), processes that rely on motor adaptation ability (Kafri & Atun-Einy, 2019; Winstein et al., 2014). As a result, understanding motor learning provides insight into processes that underpin the acquisition and retention of new motor behaviors, with implications for both optimizing rehabilitation and understanding changes in brain function across aging. This is particularly relevant to healthy aging as well as rehabilitation for brain injury, where

substantial individual variability in cognition and behavior can make it difficult to distinguish normal variation from changes associated with pathology.

Characterizing how older adults acquire, retain, and express motor memories, and the neural systems supporting those processes, can establish typical patterns of aging that in turn, can be used to identify pathological change. In this dissertation, we examined how aging affects retention of sensorimotor mappings, age-related neural differences in adaptation-relevant regions, and identified networks relevant to implicit and explicit memory of competing sensorimotor mappings.

This dissertation is organized into 6 chapters:

Chapter 1 serves as the first primer for this dissertation. This chapter discusses motor learning, relevant brain circuits involved in motor adaptation tasks, and the different ways in which aging may affect motor learning tasks.

Chapter 2 is the second primer chapter that provides background information on resting state functional Magnetic Resonance Imaging (rsfMRI), the neuroimaging method of focus in this dissertation and its application in studying motor learning-related brain regions.

Chapter 3 serves both as an overview of motor learning and a systematic review of existing literature regarding motor learning-neuroimaging studies applied to AD populations. This chapter also identifies the cerebellum as a potential brain region of interest (ROI) in differentiating healthy aging from neurodegenerative disease.

Chapter 4 compares rsfMRI of the cerebellum in typical older adult (OA) versus typical younger adult (YA) populations.

Chapter 5 identifies age group differences in long-term retention of a motor adaptation task and how rsfMRI measures may be reflective of performance changes.

Chapter 6 highlights the major contributions of this work, demonstrates application of the above studies in cognitively impaired populations and provides future steps of study.

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Title: Neural underpinnings of learning in dementia populations: a review of motor learning studies combined with neuroimaging

Authors: Jessica A. Korte, Alyssa Weakley, Kareelynn Donjuan Fernandez, Wilsaan M. Joiner, and Audrey P. Fan

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Title: Age-Related Low Frequency Amplitude Differences in Resting-State Blood Oxygenation Level-Dependent Signal in the Cerebellum

Authors: Jessica A. Korte, Christopher J. Steele, Wilsaan M. Joiner, Audrey P. Fan

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Chapter 1 - Motor control & motor learning

Our ability to make volitional movements and refine them over time is an impressive feat that we demonstrate in our everyday lives. This skill enables the refinement of reaching and grasping movements during childhood, ultimately supporting complex motor behaviors that require the coordination of multiple limbs in diverse environments, such as riding a bicycle or swimming. Understanding motor control and motor learning helps explain how individuals can grow from novices in an activity to professionals. Moreover, when neurological disorders or injury occur, our knowledge of motor skill acquisition and retention helps inform performance and rehabilitation of these skills. This chapter will define the typical terminology used in motor learning studies, discuss methods for capturing motor adaptation, review the neural correlates of these processes, and summarize literature on how aging affects these processes.

1.1. Definitions & motor learning concepts

Motor skills refer to goal-oriented actions or behavior. **Motor control**, on the other hand, refers to how the neuromuscular system coordinates muscles and limbs when performing a motor skill. Finally, **motor learning** refers to the internal processes that with practice, lead to changes in the capability for responding (Schmidt, 1991). This type of learning is used to describe 1) the acquisition of a novel motor skill, or 2) motor adaptation: modifying an existing behavior to maintain performance in response to a changing environment, whether external (e.g., swimming in a pool versus an open lake) or internal (e.g., injury or disease) (Krakauer et al., 2019; Wolpert et al., 2011).

A central focus of motor control and the study of motor adaptation is the contribution of internal models to smooth movements. **Internal models** are neural representations acquired through learning that can simulate body movements (Ramnani, 2006). There are two types of suggested internal models: a **forward model**, in which a copy of the motor command is used to generate a prediction of the motor outcome (Frens & Donchin, 2009; Wagner & Smith, 2008; Wolpert & Miall, 1996), and an **inverse model**, where true sensory information is acquired and used to estimate the required motor command to achieve the desired goal (Frens & Donchin, 2009; Wei & Koerding, 2010). When the difference between the sensory prediction and sensory outcomes are unexpected, they result in **sensory prediction errors (SPEs).** Motor adaptation is a form of short-term motor learning that is highly dependent on SPE reduction. This is generally thought to be an **implicit learning** mechanism, as motor adaption often occurs without conscious awareness. In contrast, **explicit learning** is a general term for cognitive strategy and declarative processes that contribute to motor learning. In other terms, these are processes where movement patterns are encoded consciously (Sosnik et al., 2009), and can be disengaged when desired (Benson et al., 2011; McDougle et al., 2015; Taylor et al., 2014a). In addition to error-based and strategy-based learning, there are other proposed frameworks that contribute to motor learning, such as **reinforcement learning**, which is a model-free form of learning (Galea et al., 2011; V. S. Huang et al., 2011), and **use-dependent learning** (Verstynen & Sabes, 2011). All of these types of learning contribute to successful adaptation, but their relative contributions during different phases of learning are still not completely understood, both in healthy conditions and neurological disorders (‘t Hart et al., 2024; Therrien & Wong, 2022; Todorov et al., 2019).

1.2. Motor adaptation tasks

To study how movements are modified in response to the environment, fatigue, or injury, laboratory studies will typically employ either visuomotor distortions through prisms or a virtual environment, or mechanical perturbations through a robotic manipulandum. During a goal-directed movement, a perturbation will occur, resulting in unexpected sensory feedback. This generates a large SPE from the intended movement. Participants then learn, trial-by-trial, how to minimize this error using feedforward mechanisms (M. Ito, 2008; B. R. King et al., 2013; Tanaka et al., 2020).

Using these paradigms, there are several other mechanisms relating to memory that can be examined. **Savings** refers to the short-term retention of a motor adaptation recalibration. It reflects how quickly an internal model can be re-engaged (V. S. Huang et al., 2011; Krakauer et al., 2019; M. A. Smith et al., 2006a), and is typically assessed by first having a participant learn to adjust to a perturbation, then inducing a washout block where the perturbation is removed, and then re-introducing the same perturbation, all within the same session. **Interference** is the disruption of retaining existing task performance, and can either be **retrograde**, where a new version of the task (i.e., a countering perturbation, Task B) results in lower performance of an already experienced perturbation (Task A), or **anterograde**, where the learned task (Task A) results in slower learning of a new perturbation (Task B) (Krakauer et al., 2005; Krakauer & Shadmehr, 2006).

1.3. Neural correlates of motor adaptation measures

Adaptation in response to sensorimotor perturbations is attributed to cerebellar function (Imamizu et al., 2000; Ramnani, 2006), largely due to experiments that

observed reduced adaptation in cerebellar lesion patients, as well as task-based functional studies (Burciu et al., 2014; Donchin et al., 2012; Taylor et al., 2010; Tseng et al., 2007). Adaptation tasks that parsed between implicit and explicit contributions noted that the implicit component is impaired in cerebellar lesion patient populations when behavioral performance is compared to healthy counterparts (Taylor et al., 2010; Tzvi et al., 2022). While there is some heterogeneity across studies as to which regions of the cerebellum are considered key players in adaptation, lobules V and VI within the cerebellum are often considered responsible for internal models (Schlerf et al., 2012). On the other hand, explicit components are attributed to working memory (Anguera et al., 2010; A. I. Christou et al., 2016; McDougle & Taylor, 2019a), and/or discrete response caching (i.e., generation of a look-up table for appropriate movement execution) (McDougle & Taylor, 2019a; Trewartha et al., 2014). The main cortical regions associated with these functions and implicated in explicit mechanisms are the dorsolateral prefrontal cortex (DLPFC) (Anguera et al., 2010, 2011; Floyer-Lea & Matthews, 2004; M.-F. Ghilardi et al., 2000) and medial temporal regions (Cisneros et al., 2026; Wolpe et al., 2020), respectively. Studies have also identified that within the cerebellum, lobule VI is engaged in early phases of adaptation and associated with explicit processes (Bernard & Seidler, 2013; Debas et al., 2010).

From a controls perspective, a simplified motor control system might look like the following: first, the motor command is initiated with prefrontal and parietal cortices (Beurze et al., 2010; Cisek & Kalaska, 2005; Y.-Y. Lee et al., 2016). The motor command is sent to the primary motor cortex (Casellato et al., 2012; D'Angelo et al., 2013), and an efferent copy is sent to the cerebellum. Here, the cerebellum integrates the motor

command, the predicted outcome of this command, and the incoming sensory information, resulting in SPE and requiring the internal model and consequent motor output to be updated accordingly (Boisgontier & Nougier, 2013; Koziol et al., 2014), until the final output is achieved. A simplified schematic can be found in Figure 1.1; however, if readers are interested in a more complete interpretation of the motor control system, (D'Angelo et al., 2013) and (Popa & Ebner, 2019) have diagrams that capture the contribution of relevant brain regions in greater detail.

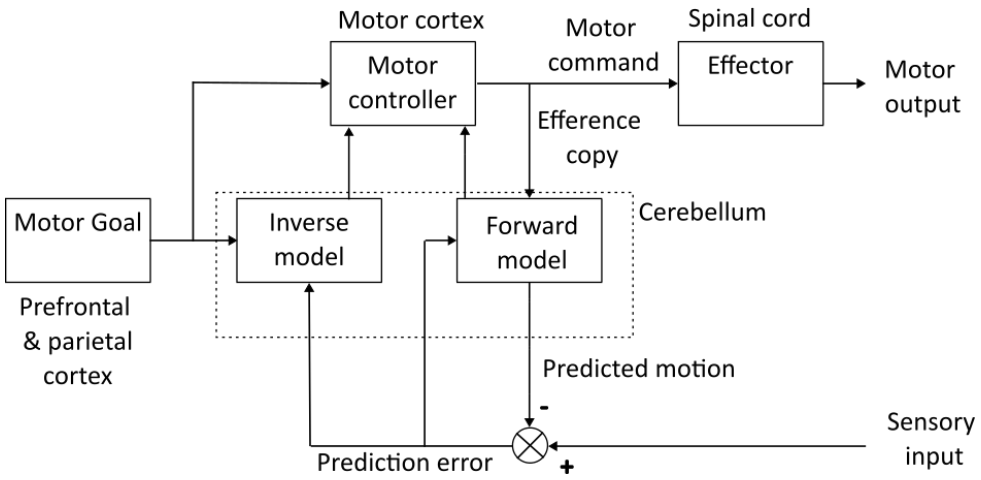


Figure 1.1 *A simplified controls diagram demonstrating the processes and associated brain regions for motor adaptation learning*

3.1 Long-term memory of motor adaptation

When a motor task becomes learned, there are three generally agreed-upon stages that the memory undergoes: the learning stage, the consolidation stage, followed by the retention phase (Dahms et al., 2020). Consolidation is considered the stage after initial learning of a task, referred to as 'offline learning', where the internal model becomes resistant to retrograde interference (Byczynski et al., 2025; Shadmehr & Brashers-Krug, 1997). Retention describes the point at which the performance of the task becomes 'automatic'. Existing theories of motor learning suggest that as a task becomes learned,

the implicit component of the task dominates the performance as the adaptation is repeated (Dahms et al., 2020). In adaptation studies, this is posited to be reflected by brain activity that shifts from prefrontal to motor, parietal, and cerebellar regions over the course of multiple sessions (Byczynski et al., 2025; Muellbacher et al., 2002). Studies that have investigated the neural underpinnings of motor adaptation memory align with this theory and have demonstrated that better performance in a follow-up session (i.e., faster re-learning compared to baseline) is associated with similar regions that are active during late trials of the learning stage (Bursztyn et al., 2006; Cassady et al., 2018; Debas et al., 2010; Ruitenberg et al., 2018; Wali, 2020). These studies implicate regions including cerebellar lobule VI, the striatum, the caudate nucleus, and the somatosensory cortex. On the other hand, behavioral-only studies have found that savings is strongly associated with mechanisms recruited during early learning: mainly cognitive or strategic processes (Cassady et al., 2018; Morehead et al., 2015; Seidler et al., 2017). In other words, better memory of an adaptation task is associated with greater explicit contributions, a finding that implicates more 'early phase' or cognitive brain regions within the prefrontal and parietal cortices. Taken together, these neural and behavioral findings highlight ongoing debate regarding the mechanisms that underlie long-term adaptation memory.

1.4. Aging effects on motor learning and performance

While older adults (60 years and older) maintain the ability to learn new skills, the rate of learning and performance in motor tasks compared to younger adults (18 – 30 years old) is heterogeneous and varies greatly between tasks and even across older adults (E. A. Christou, 2011; Fernández-Ruiz et al., 2000; Vachon et al., 2020; Zvornik et al., 2024). Some of these differences can be attributed to changes in the peripheral nervous

system – structures such as sensory receptors, muscles, and joints are impaired with age (Verdú et al., 2000; L. Xing et al., 2023). This results in impaired processing of sensory information and output of desired motor response. As a result, older adults typically demonstrate declines in coordination (Contreras-Vidal et al., 1998; Serrien et al., 2000), balance and gait (Osoba et al., 2019; Viswanathan & Sudarsky, 2012; L. Xing et al., 2023); generalized slowing (Ketcham & Stelmach, 2004); or increased variability of movement (Newell et al., 2009; Stergiou et al., 2016).

Additionally, the central nervous system is impaired with age. Cortical gray matter shrinks (Christova & Georgopoulos, 2023; Sowell et al., 2004), white matter tracts degrade (Davis et al., 2009; Groh & Simons, 2025), and functionally distinct regions become less segregated (Cabeza, 2002a; Davis et al., 2008; Park & Reuter-Lorenz, 2009; Reuter-Lorenz et al., 1999). These changes affect the processing of information involved in motor learning. In motor adaptation, these neural changes are associated with subsequent behavioral shifts, where learning is slower compared to younger adults (Bernard & Seidler, 2014; B. R. King et al., 2013). There are generally four different hypotheses as to how motor learning and its control system is affected by aging (Vandevoorde & Orban de Xivry, 2019), which will be explained below. A visual summary of the different hypotheses can be found in Figure 1.2.

Strategy hypothesis

This theory suggests that the largest contributor to decreased performance in older adults is the decline of explicit processes related to mental rotation. This functioning helps participants compute a spatial transform to generate an appropriate re-aiming response (Anguera et al., 2010, 2011; Vandevoorde & Orban de Xivry, 2019, 2020). In contrast,

cerebellar function is posited to be robust to aging. There have been suggestions of 'cerebellar reserve', in which the resiliency and plasticity of the cerebellum allows older adults to maintain performance in cerebellar-dependent processes, such as SPE reduction (Arleo et al., 2024; Mitoma et al., 2021, 2023).

Retention hypothesis

The retention hypothesis also attributes slower adaptation learning to explicit contributions, and stems from the reduced short-term retention of new information in older adults (Bindra et al., 2021a; Trewartha et al., 2014). This hypothesis suggests that working memory contributes mainly to response caching (generating a look-up table) of appropriate explicit strategies as opposed to spatial transformations. The decreased working memory capacity in older adults affects appropriate response selection, resulting in decreased explicit contribution (Cisneros et al., 2026).

Internal model hypothesis

Aging results in significant volume loss in the cerebellar vermis regions associated with posture and locomotion (McElroy et al., 2024; Romero et al., 2021a). Changes in volume have been associated with decreased performance in tasks that recruit internal model processing (Bernard, 2022; Cui et al., 2020; Hicks et al., 2024). As a result, it is hypothesized that structural degradation of the cerebellum results in altered processing of the internal models, resulting in inaccurate generation of forward models and poorer adaptation in motor learning tasks.

Variability hypothesis

As aging results in degradation of the peripheral nervous system, older adults tend to make more variable movements (Lei & Wang, 2018; Risso et al., 2025; Saenen et al., 2023), and interpret incoming sensory information with greater variability (Cisneros et al., 2026). Proprioception and visual cues are noisier, and as a result, weighted improperly and result in greater implicit contributions to the motor output (Z. Zhang et al., 2024).

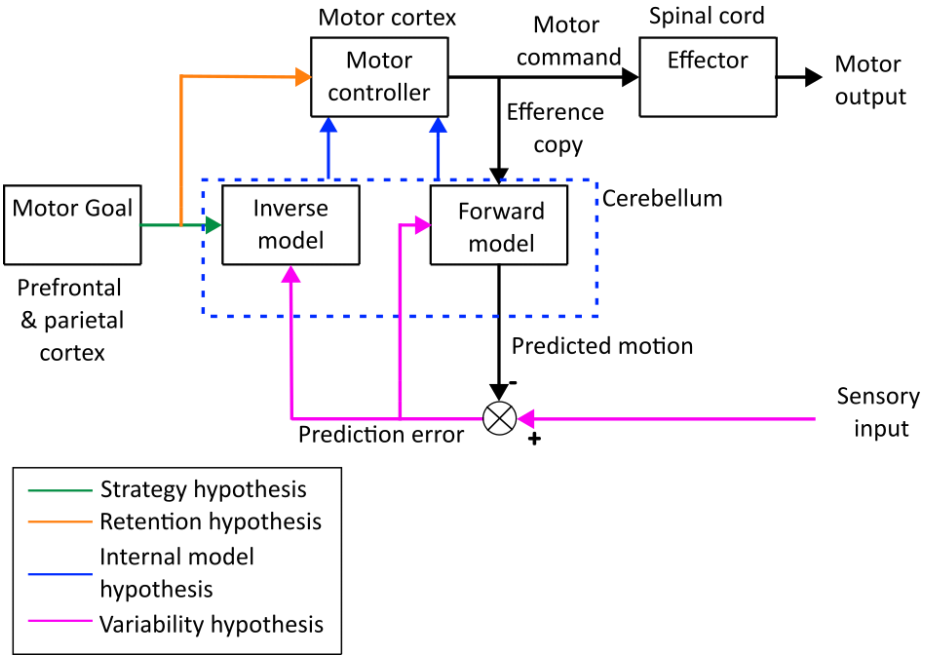


Figure 1.2 A general schematic of the motor adaptation control framework highlighting brain regions implicated in age-related differences in motor adaptation. *Colors denote the corresponding hypothesis.*

1.5. Aging and long-term motor memory

There are limited studies that have investigated how consolidation and retention of motor adaptation are impacted by aging. Several studies have investigated other types of motor learning, such as sequence learning or *de novo* learning and aging impacts, and found that older adults demonstrate impairment in offline learning (Brown et al., 2009; Murray & Prashad, 2025; Nemeth & Janacsek, 2011; Roig et al., 2014). A review of offline

implicit motor sequence learning found that age, time between tasks, and task exposure all impact performance in older adults. The mechanisms underlying these age-related deficits remain unclear. However, these studies all suggest that older adults do not demonstrate offline gains in between learning sessions such that performance during a delayed retention test (~24 hours apart) is no different than the initial learning of the task, while younger adults demonstrate substantial improvement.

Two interpretations emerge from the literature summarized above. One interpretation is that the neural correlates of savings and longer-term memories of motor learning are dependent on implicit-relevant structures, suggesting that older adults demonstrate impairment in consolidating motor tasks due to changes in consolidating internal models. Another interpretation comes from behavioral assessments and suggests that if performance of savings and longer-term motor memories are more dependent on explicit processing, deficits in older adults are a result of poorer consolidation of explicit strategies. Distinguishing between these competing mechanisms is essential for understanding why and how memory in motor adaptation tasks changes with age and represent an important gap in the current literature.

1.6. Conclusions

This chapter lays the foundational anatomy, terminology, and controls theory perspectives necessary to understand the behavioral studies described later in this dissertation. The gaps in literature related to relevant neural mechanisms for offline learning of motor memory, how multiple days affects this memory, and the impact of age, will be investigated as a part of this work.

Chapter 2 – Resting state functional MRI

Resting state functional MRI (rsfMRI) is a popular *in vivo* method of assessing brain function. This section will discuss the basic MR physics underlying rsfMRI, the physiology underlying rsfMRI signal, its relation to brain function, and how aging affects this signal and its associated physiology.

2.1 Functional Magnetic Resonance Imaging

Nuclear Magnetic Resonance (NMR) is the central principle of MRI. NMR describes the ability of certain atomic nuclei's ability to absorb and reemit radiofrequency (RF) energy when placed in a strong magnetic field. In most MRI studies, the atom of interest is hydrogen due to its abundance in water and fat, as well as its sensitivity to magnetic fields. When a participant is placed in an MRI scanner, the main magnetic field (B_0), aligns the hydrogen atoms parallel to the field. When a transient RF pulse is administered, the nuclei are no longer parallel with the B_0 field and emit a detectable RF signal. As the nuclei relax, there are two simultaneous processes: **T2 relaxation**, which refers to the loss of phase coherence among the precessing nuclei in the transverse plane, and **T1 relaxation**, which describes the recovery of signal in the longitudinal plane (i.e., the B_0 axis). Different brain tissues exhibit distinct T_1 and T_2 relaxation properties, resulting in high-contrast visualization of structure.

Functional MRI (fMRI) exploits an additional source of contrast from local magnetic field inhomogeneities that change during neural activity. In the brain, these inhomogeneities are influenced by deoxyhemoglobin (**dHb**), a paramagnetic molecule, which accelerates signal dephasing and shortens the transverse relaxation time (**T_2^***).

Local brain activity drives changes in local metabolic activity, which in turn drives local hemodynamics, affecting the presence of dHb. To supply oxygen for metabolism, oxygenated blood (**HbO**) flow increases regionally, reducing the concentration of dHb and increasing the T2*-weighted signal. The **Blood Oxygenation Level-Dependent (BOLD)** signal, the signal of interest in fMRI scans, is driven by the regional proportion of HbO and dHB, where increases in HbO produces greater detected BOLD signal.

Early fMRI studies mapped increased BOLD signal in specific regions associated with a functional task – such as the visual cortex in response to a flashing checkerboard (Kwong et al., 1992), or signal in the motor cortex in response to finger presses (Porro et al., 1996), demonstrating how fMRI can be used for mapping functional brain regions. However, it is important to note that because the BOLD signal reflects blood oxygenation, it lags neuronal activity by 10-20 seconds, typically modelled using the **hemodynamic response function (HRF)**. The HRF is a mathematical and graphical method that captures the temporal pattern of the BOLD signal: a brief dip in signal driven by Oxygen consumption, followed by a peak in the BOLD signal around 6 seconds after stimulus presentation driven by vasodilation, then an undershoot over the course of 20-30 seconds (Logothetis et al., 2001) (Figure 2.1). The relationship between brain activity and the hemodynamic response underlying the BOLD signal is referred to as **neurovascular coupling** and can be influenced by other physiological factors including cerebral blood flow (CBF), cerebral blood volume (CBV), and cerebral metabolic rate of oxygen consumption (CMRO2) (Q. Shen et al., 2008). Head movement, cardiac, and respiratory effects also contribute to noise in the BOLD signal (Power et al., 2012, 2017), requiring

careful signal processing to remove unwanted noise while maintaining relevant biological information.

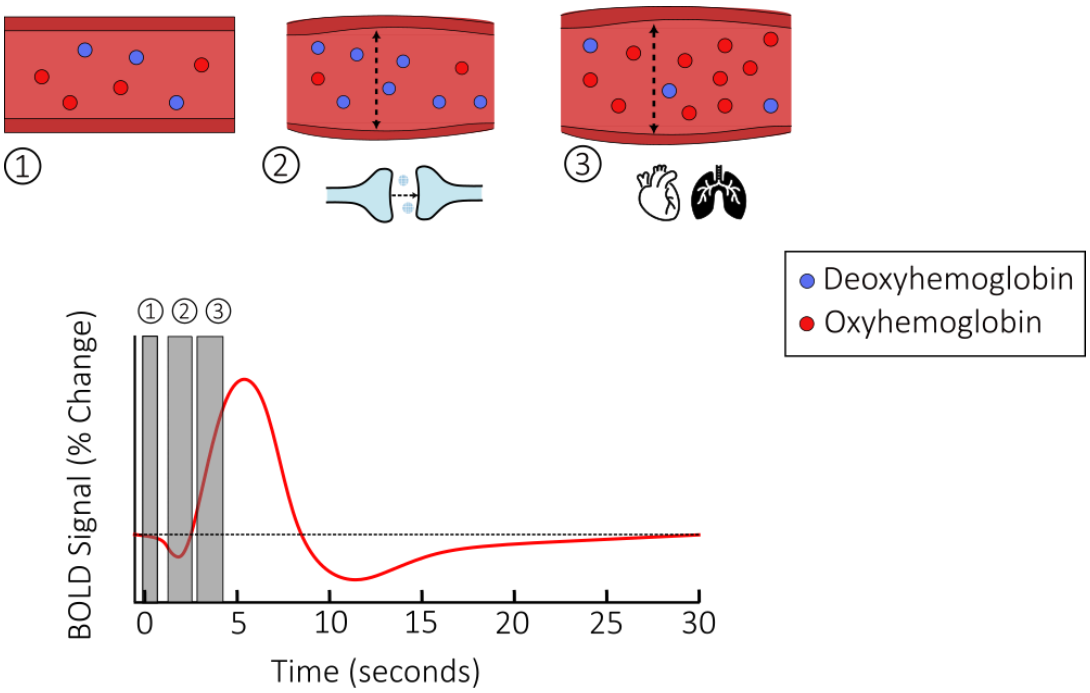


Figure 2.1 The hemodynamic response function. *The HRF captures the temporal response of the BOLD signal to neuronal signaling. The first stage reflects the baseline ratio of dHb/HbO. When neuronal activity occurs, there is a brief dip in in HbO, resulting in decreased BOLD signal. Then, vasodilation results in greater HbO presence in the region, resulting in greater BOLD signal 4-6 seconds after stimulus presentation. The increase in BOLD signal can be driven by other physiological factors that increase blood flow, including changes in heart rate and respiration.*

2.2 fMRI acquisition parameters

BOLD fMRI is commonly acquired using gradient echo echo-planar imaging (GE EPI) or spin-echo echo-planar imaging (SE EPI) BOLD sequences. GE sequences are T2* relaxation weighted and have inherent refocusing at the **echo time (TE)** due to the readout gradients, while SE sequences are T2-relaxation weighted, and apply an additional RF pulse (e.g., a 180° pulse) for refocusing. GE sequences are much more common than SE sequences. These sequences allow 2D brain slices to be acquired in fractions of a second, enabling whole-brain coverage in the span of 2-3 seconds. The

amount of time it takes to obtain a whole-brain image is referred to as the **Repetition Time (TR).** TE determines the sensitivity to the T2* contrast. TE is typically selected to be the T2* relaxation time of brain tissue, around 35 ms.

There are several factors to consider when implementing an EPIBOLD scan. Of course, the initial acquisition parameter to consider is the TR/TE. The TR determines the temporal resolution at which the BOLD signal is sampled. As the HRF occurs over the course of seconds, TRs of 1-3 seconds adequately capture the change in dHb/HbO. However, shorter TRs (<1s) provide improved characterization of physiological noise, including respiratory and cardiac effects (i.e., ~0.3 Hz and 1 Hz, respectively), reducing frequency aliasing. Many EPI BOLD scans, such as standard protocols utilized by the Human Connectome Project (a large repository of rsfMRI data) obtain whole-brain images at TRs of 0.7-0.8 seconds (Glasser et al., 2016; Van Essen et al., 2012). This faster acquisition can achieved by designing protocols that use parallel imaging techniques such as SENSE or GRAPPA, simultaneous multi-slice (SMS) acquisition (acquiring separate slices at the same time), or some combination of the two acceleration techniques (Preibisch et al., 2008). Higher temporal resolution requires compromises in spatial resolution, resulting in lower signal-to-noise ratio (SNR) and partial volume effects. Typical image resolution of rsfMRI images at 0.7s TR is around 2 – 2.5mm isotropic. While this is sufficient to visualize large structures, this still results in partial volume effects, making it difficult to localize BOLD signal in smaller brain structures (Goense et al., 2016).

Flip angle is another parameter that affects image quality, and is the parameter that determines how far into the transverse plane nuclei are tipped. Low flip angles are

selected to minimize saturation effects while maintaining adequate BOLD sensitivity (Gonzalez-Castillo et al., 2011; Song et al., 1997). Low flip angles also reduce inflow effects, where unexcited "fresh" spins move into the acquisition plane, changing the overall detected signal particularly near large blood vessels (J.-H. Gao et al., 1996; J.-H. Gao & Liu, 2012).

The fast acquisition of whole-brain images can also result in geometric or intensity distortions from larger inhomogeneities in the magnetic field. These can be a result of the fast-switching gradient during the EPI readout (caused by **eddy current** effects, which can also cause **Nyquist ghosting** or "extra brains" in the image), air-tissue interactions (resulting in signal dropout in tissue proximal to ear and sinus canals), or general magnetic field inhomogeneities. This can result in poor localization of the fMRI signal, resulting in inaccurate findings. While signal loss cannot be recovered, shifts in the signal can be mitigated during the acquisition by optimizing the shimming or minimizing the readout time. Additional scans can also be acquired to map the inhomogeneities for post-processing correction, such as a gradient echo field map that records the phase and magnitude of the magnetic field, or a separate blip-up/blip-down phase-encoding scan (Giannelli et al., 2010; Jezzard & Balaban, 1995; Yu et al., 2023).

2.3 Resting state fMRI

rsfMRI utilizes the same principles as fMRI; however, there is no external stimulus provided. Instead, participants are instructed to lie in a scanner and not to think about anything. While fMRI identifies relevant brain networks based on regional BOLD signal after stimulus presentation, rsfMRI identifies brain regions that are temporally correlated at low frequencies [0.01 and 0.1 Hz] during rest, referred to **functional connectivity**

(FC). The collection of brain regions that share similar FC (determined by a statistical significance threshold, e.g. $p < 0.05$ corrected for multiple comparisons) build up **resting-state networks.** Whole-brain networks have demonstrated high similarity between task and resting state scans (Cole et al., 2014). Although task-based fMRI maximizes brain-behavior prediction accuracy (Greene et al., 2018) and may generalize to related processes, rsfMRI has greater utility for identifying brain-behavior associations across a large range of observable characteristics (Uddin & Garavan, 2026) and is considered relatively straightforward, enabling accessible data collection across pediatric, clinical, and geriatric populations that can be otherwise difficult to study (B. B. Biswal & Uddin, 2025; H. H. Shen, 2015).

The Amplitude of Low Frequency Fluctuations (**ALFF**) and fractional ALFF (**fALFF**) are semi-quantitative metrics derived from the BOLD signal that are reflective of spontaneous neuronal fluctuations (Yu-Feng et al., 2007; Q.-H. Zou et al., 2008). ALFF is a voxel-wise metric that reflects the square root of the power within a neuronally-relevant frequency band (typically [0.01-0.1 Hz]). fALFF is calculated similarly to ALFF but is normalized by the square root of the average power over the full spectrum [0.01 – 0.25 Hz], with the upper frequency cut-off being dependent on the TR (i.e., must be below the Nyquist sampling frequency: $1/(2*TR)$), and the lower frequency cut-off requiring enough samples (i.e., long enough scan time) to detect the slow oscillations. These metrics have been demonstrated to be highly repeatable across sessions (Golestani et al., 2017), and fALFF has demonstrated robustness to physiological effects as well as greater T2* effects near draining veins (Huck et al., 2023). Both ALFF and fALFF have been proposed to be driven by FC within networks (X.-N. Zuo et al., 2010), but are also confounded by

slow oscillations driven by heart rate variability and respiratory volume (Q. N. Lee et al., 2023), even after normalization.

2.4 Aging effect on BOLD signal

The BOLD signal reflects both brain vasculature and neuronal activity, making it difficult to parse between the two effects as drivers for differences between older and younger adults. Regarding vasculature influences, older adults demonstrate decreases in global CBF, potentially driven by impairment in vasoactivity or cardiovascular regulation (Flück et al., 2014; Tarumi & Zhang, 2018), which may affect the sign and magnitude of the BOLD signal independently of underlying neural drivers. Cerebrovascular reactivity (**CVR**) is a measure of CBF in response to arterial CO_2, where hypercapnic environments result in greater BOLD signal. CVR reflects the response of vascular endothelium and smooth muscle responses, which is delayed and stiffer in aging (H. Ito et al., 2002; Yamaguchi et al., 1979), resulting in a reduced dynamic range of the BOLD signal. The stiffened arterial walls in brain aging also increase pulsatility (Nichols et al., 2011), resulting in large fluctuations in BOLD intensity. Studies suggest that these age-related vascular effects can be separated out from neuronal effects by 1) measures of isolated vascular signal, such as measures of CBF through Arterial Spin Labeling scans, or CVR through hypercapnic paradigms, 2) incorporating independent measures of neuronal function through fMRI-EEG or fMRI-MEG, or 3) formal modelling or statistical decomposition of the resulting BOLD signal (Tsvetanov, Henson, & Rowe, 2021).

Systemic physiology also changes with aging: heart rate and respiration decrease, and unintentional head movement is often seen in elderly populations, all resulting in other confounds with the BOLD signal. Studies have demonstrated that older adults tend

to demonstrate greater power in higher frequency bands relevant to this physiology (Zhong & Chen, 2022). However, studies have also reported neuronally-relevant aging changes in rs-brain networks. There are generally two age-related network trends that are reported: **compensation**, where activity in additional areas are recruited to compensate for functional deficits (Cabeza, 2002a; Davis et al., 2008; Park & Reuter-Lorenz, 2009) and **dedifferentiation**, which describes the loss of functional specificity within networks (J. R. Cohen & D'Esposito, 2016; Park et al., 2004). The Default Mode Network (DMN; Figure 2.2) has been highlighted in a number of studies as a potentially age-sensitive network implicated in cognitive processing (Baptista et al., 2026; Mevel et al., 2011), with decreased connectivity between cortical DMN regions with increasing age (Jones et al., 2011a; Persson et al., 2014). Although several studies have explored the relationship between functional network connectivity and cognition (Medaglia et al., 2015; Sala-Llonch et al., 2015), our understanding of how age-related alterations in networks relate to specific cognitive processes is still limited (Tomasi & Volkow, 2012a). Nevertheless, aging-related changes in network connectivity have been suggested to contribute to cognitive decline in older adults (Deery et al., 2023).

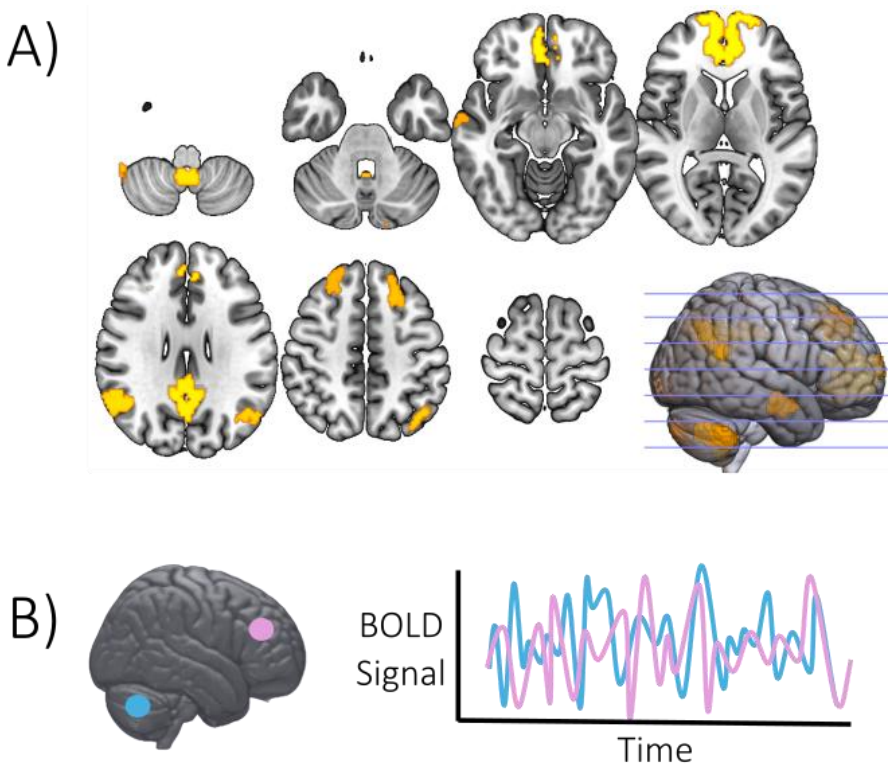


Figure 2.2 A) *The Default Mode Network (DMN) as defined by Yeo et al. (Thomas Yeo et al., 2011) in yellow, overlaid on a standard Montreal Neurologic Institute (MNI) brain. This reflects the regions that are functionally connected that make up the DMN.* ***B)*** *Schematic of functional connectivity calculation in a seed in the DMN. Signal in a seed region, indicated by pink, is compared to signal in a different region, indicated by blue. The correlation across the time series is evaluated, and used to determine connectivity. This process is repeated for different regions if conducting a region-to-region analysis, or computed at a voxel level if comparing a region to each voxel in the brain.*

2.5 Conclusions

The BOLD signal is reflective of the presence of oxygenated blood driven by neuronal and vascular components, both of which are differentially affected by aging. Metrics such as functional connectivity and (f)ALFF capture this underlying biology and reflect how different brain regions work together. These measures have been associated with cognitive function and will be utilized in the rest of this dissertation to assess aging-related changes networks correlated with motor memory.

Chapter 3 – Neural underpinnings of learning in dementia populations: a review of motor learning studies combined with neuroimaging

3.1 Introduction

Dementia is a progressive deficit in cognitive functions (e.g., memory, executive function, attention, language, visuospatial ability) that interferes with every day function (Gale et al., 2018). Alzheimer's Disease (AD) is a type of dementia characterized by a decline in episodic memory that results in cognitive and behavioral impairment, neurodegeneration, and ultimately death (Porsteinsson et al., 2021; Soria Lopez et al., 2019). Mild Cognitive Impairment (MCI) is objective cognitive impairment in at least one memory (amnestic) or non-memory (non-amnestic) cognitive domain that is less severe than what is observed in AD. While their impaired cognition may have a negative impact on everyday functioning, individuals with MCI largely function independently, unlike those with AD. Populations that develop MCI have a high risk of converting to AD (Dubois et al., 2010; Liss et al., 2021). This risk increases with a diagnosis of amnestic MCI (a-MCI) (Albert et al., 2011). Early, asymptomatic stages of AD, sometimes referred to as preclinical-AD or at-risk AD, do not present any detectable cognitive changes on standard assessments. However, this preclinical population often has a family history of AD, may carry the apolipoprotein E (APOE) ε4 allele, and may exhibit hallmark pathology: accumulation of amyloid beta (Aβ) in cerebrospinal fluid and neuronal injury or death caused by tau deposits (DeTure & Dickson, 2019; Dubois et al., 2010; Scheltens et al., 2016).

While the physiological progression of AD may be monitored by detection of amyloid, tau, and structural degeneration of the brain, these markers do not necessarily

result in clinical AD development (Shaw et al., 2007). Additionally, the diagnostic process and screening of these biomarkers often does not start until severe changes in symptoms such as agitation and delusions, in addition to cognition, particularly memory loss, are noticeable by the patient or an informant (Alberdi et al., 2016). This late diagnosis prevents early interventions that slow cognitive decline, improve independence, and reduce caregiver burden. Given that behavioral changes initiate clinical intervention and that behavioral detection is not typically studied in AD research (Alberdi et al., 2016), this article explores motor learning as a sensitive AD screening tool that can measure multiple cognitive domains simultaneously. These tasks may function as a supplement to traditional neuropsychological assessments that focus on individual domains but not necessarily how these domains interact together.

Motor Learning and Cognition

Motor learning tasks are paradigms in which there is measured improvement in motor performance with practice. They can be broken down into four main types of tasks. Motor acuity: the effect of practice on an action's accuracy and precision; de novo learning: associating a discrete set of stimuli with discrete or continuous actions; sequence learning: operations that must be performed in a particular order; and adaptation: the adjustment of a practiced action to complete a task in response to, usually, an environmental change. A more in-depth review of these motor learning domains, their classifications, and their analyses can be found in Krakauer et al. (Krakauer et al., 2019).

Motor actions in healthy populations have well-studied functional network substrates involving structures such as the cerebellum (Llinás & Welsh, 1993; Sakai et al., 2004), motor cortex (Tanji & Mushiake, 1996), basal ganglia (Doyon et al., 2009),

hippocampus (Albouy et al., 2008), and regions within the frontal lobe (Halsband & Lange, 2006). Given the similarities between the neural substrates for motor control and cognition (see (Funahashi & Andreau, 2013; Opitz, 2014; Rosch & Mostofsky, 2019; Schmahmann, 2019) for reviews of these brain areas and their contributions to cognition), it is no surprise that skill acquisition is connected to cognitive functioning. Cognitive processes crucial to the regulatory means of motor execution and responses (movement selection, generalization, etc.) include various combinations of attention and concentration, executive functioning, processing speed, and memory (Ren et al., 2013). These control processes affect motor performance and learning efficiency.

How are these cognitive domains applicable to a motor learning task? In a novel motor learning paradigm, a subject may be instructed to complete a task 'as quickly and accurately as possible', and their reaction time recorded, to assess processing speed. Distracting information may be presented to test selective attention, which can be quantified by the number of correct or incorrect movements. The ability to reduce incorrect movements is indicative of inhibition, a type of executive function (Harvey, 2019). Planning or working memory, another subdomain of executive function, contributes to the subject's execution or suppression of goal-directed movement (Mirabella et al., 2014). As the subject makes their movement, they will have various contributions of 'explicit', or conscious, and 'implicit', or unconscious, changes. With repetition, the contribution of implicit and explicit knowledge varies, and the rate of change in movement across repetitions is used to indicate learning. Moreover, as the subject repeats the movement, they will have to remember what sequence of actions resulted in successful task completion.

Cognitive faculties typically decline in healthy aging (Salthouse, 2019; Y. Yang et al., 2023; S. Zhao et al., 2023). As a result, it would be expected that the rate at which motor learning occurs is somewhat slower for older adults than for young adults. This may be reflected in the rate of change in motor metrics (e.g., reaction time, errors made, movement efficiency) over the duration of the task. In MCI patients, impairment may be less obvious through neuropsychological tests, but made clearer by consideration of overall motor learning: the accrued effect of all cognitive domains working together to successfully complete a task. In AD patients, we would expect a more impaired learning rate compared to healthy counterparts. However, the contribution of each domain to overall task learning will vary depending on the paradigm employed, as will be investigated in this chapter.

Neural imaging/recording

It is not possible to assign one aspect of cognition to a single motor learning task. Similarly, it is not possible to ascribe one brain region to one aspect of motor learning. The contributions of neural systems as a whole are highly interconnected and task-dependent (Thomas Yeo et al., 2015). Neural imaging can provide additional information to motor learning tasks by identifying task-specific regions. Subsequent analysis of these regions can then reveal mechanisms for performance differences between clinical populations. We will briefly discuss some common modalities used to identify motor learning-related brain activity in addition to the MRI techniques described in previous chapters of this dissertation: electroencephalography (EEG) and magnetoencephalography (MEG). This section summarizes imaging information that is

directly relevant to the studies analyzed in this review paper, and is not a holistic overview of neural recording techniques.

MRI is a popular choice in motor learning studies due to high spatial resolution that allows for visualization of the brain. Performance measures may be correlated with structural characteristics of the brain such as gray and white matter volume, the physical size of specific structures, the integrity of white matter fiber tracts, or measurements of white matter hyperintensities (lesions in white matter that suggest neuronal demyelination). Brain activity can also be measured with MRI through functional imaging (fMRI). This technique records the blood oxygen level-dependent, or BOLD, signal during task execution to observe task-related neuronal changes. However, fMRI is an indirect method of measuring neuronal activation, as it measures regional changes of cerebral blood flow and oxygen demand, not neuronal firing, resulting in signals with lower temporal resolution. The small bore size, the need to restrict head motion for imaging, and the strong magnetic field of the MRI restrict simultaneous motor learning studies. Investigators must build or purchase specialized, non-ferrous instruments to record physical movement and limit tasks to small hand motions (i.e., button pushes in a Serial Reaction Time task, knob rotations) or recording of eye movements (e.g., saccades). Unfortunately, even small movements inside the scanner can cause head displacement on the scale of millimeters, resulting in artifacts of the BOLD signal. Some studies navigate around these movement and apparatus constraints by utilizing resting state fMRI (rs-fMRI), an fMRI scan conducted while a participant is at rest. Resting state data is correlated with behavioral performance measures and used to indicate a 'prediction' of task performance. While rs-fMRI is a well-studied technique, it is still to be determined

if resting state imaging is sufficient at predicting behavior outcomes (Ikeda et al., 2022; Tavor et al., 2016; Q. Zou et al., 2013), or if this is better done through task-based imaging (Gal et al., 2022; W. Zhao et al., 2023).

EEG is another popular recording technique for motor learning studies. Task-based recordings are more common in this modality, as it is portable, wearable, and does not require dedicated hardware or specially built spaces like MRI machines (most caps have software that can be implemented on laptops). Not only is task-based recording more feasible, but this recording can also be implemented during tasks that involve large movements, like reaching or grasping. Brain activity recorded using this modality has high temporal resolution but considerably lower spatial resolution when compared to MRI, as EEG measures the difference of electrical potential between large neuronal populations found closer to the skull. However, resting-state EEG has also been used to study neuronal activity in AD populations (Jafari et al., 2020). Activity can be quantified through measurement of local field potentials (LFPs), which are neuronal oscillatory rhythms (e.g., alpha, beta, or gamma waves).This activity contributes to information coding in the brain (Lopes da Silva, 2013). Activity can also be measured through event-related potentials (ERPs), which are voltage changes evoked from several million neurons that are time-locked to sensory and cognitive processes.

Although MEG is most commonly used for clinical applications in epilepsy (Singh, 2014), this modality has also been used to study neuronal change due to learning. MEG produces recordings of high temporal resolution through direct measurement of induced magnetic fields from current changes caused by neuronal firing. The neuronal oscillations seen in MEG are referred to as local magnetic fields (LMFs), which are analogous to LFPs. MEG is similar to MRI imaging in the requirement of specialized equipment, housing,

and head restraints that limit large movements. As a result, motor tasks conducted in junction with MEG are similar to tasks with MRI: either conducted separately from the scan or limited to small movements during the scan. Typically, structural MRI is obtained in addition with MEG data to obtain structural references.

Information gathered from these imaging modalities have contributed to our current understanding of how typical aging causes structural and functional changes in the brain. Gray and white matter volumes throughout the brain naturally atrophy, with the most prominent degradation occurring in frontal areas and in the hippocampus (Burke & Barnes, 2006; MacDonald & Pike, 2021a). In general, segregated networks dedifferentiate, or become more homogenous, both structurally and functionally with age (Koen & Rugg, 2019). Furthermore, evidence of neural compensation and reorganization has been found, and is typically reported as a compensatory mechanism for dedifferentiation (Morcom & Johnson, 2015). In AD, neurodegeneration occurs faster than healthy aging, with most significant volumetric changes in medial temporal regions (Chandra et al., 2019). There are mixed findings regarding AD-specific regions that demonstrate functional change and their trends (Chandra et al., 2019), but most findings implicate disrupted connectivity within the default mode network (DMN), a brain network that is most active during periods of rest (Smallwood et al., 2021). Resting state EEG studies commonly find that overall increased power in low neuronal frequencies correlate with diagnosis (Jafari et al., 2020).

The combination of imaging and motor learning in AD

Motor tasks are cognitively demanding tasks that can provide insight into areas of cognitive decline (Ansai et al., 2018; Aslan et al., 2021; Montero-Odasso et al., 2014; Wu

et al., 2016). Therefore, investigation of both motor learning capabilities and their neural underpinnings across the AD spectrum has important consequences. First, as mentioned earlier, behavior is often not considered in AD detection. Currently, general behavioral as well as Activities of Daily Living (ADL) questionnaires are popular and well-understood methods used to monitor behavioral symptoms of AD (Robert et al., 2010). Other behaviors such as speech and gait have been investigated as quantitative behavioral markers of disease progression (Belghali et al., 2017; Petti et al., 2020), but further investigation is needed to identify unique AD characteristics from other neurodegenerative diseases. Understanding motor learning differences in patient populations will inform our knowledge about learning capabilities of AD patients, and may become a quantifiable screening technique that assesses the interaction of multiple cognitive domains at once. The analysis of learning informs cognitive-motor therapies that are employed to reduce behavioral symptoms of AD (Cao et al., 2023; Ries, 2018). These therapies are important in helping maintain quality of life and independence of patients, while reducing caretaker burden. In parallel, analysis of neural circuits that contribute to learning may help infer neuronal degeneration simply from behavioral measures. Additionally, neural-motor analysis may help differentiate between typical age-related brain changes and changes caused by disease. Collectively, this information may help distinguish why certain populations go on to develop AD while others maintain largely normal cognitive function.

The aim of this chapter is to summarize the current understanding of overall learning capabilities in AD, and to highlight areas in which learning metrics may be a useful screening technique for early points of the disease (in MCI or at-risk populations). We will summarize relevant neural mechanisms found in comparison of these learning

differences, motor metrics that are correlated with these mechanisms, and comment on the current understanding of learning abilities of AD and MCI populations. This review also seeks to provide a more cognitive perspective of motor learning metrics and the interactions of relevant cognitive domains, which may help guide future learning studies in MCI and AD populations.

3.2 Methods

A search on Pubmed and Web of Science was conducted using three groups of search terms: (1) “motor”, “visuomotor”, “visuospatial” (2) “EEG”, “imaging”, “PET”, “MRI” (3) “skill”, “task”. The “OR” function was used within each group, and the “AND” function was used between the three groups. These terms were searched with either “Alzheimer” or “MCI”. An initial search was conducted in July of 2022. A second search was conducted in August of 2023 to include “learning” and “adaptation” in addition to the classifiers for group 3. A summary of the searches and the results can be found in Figure 3.1.

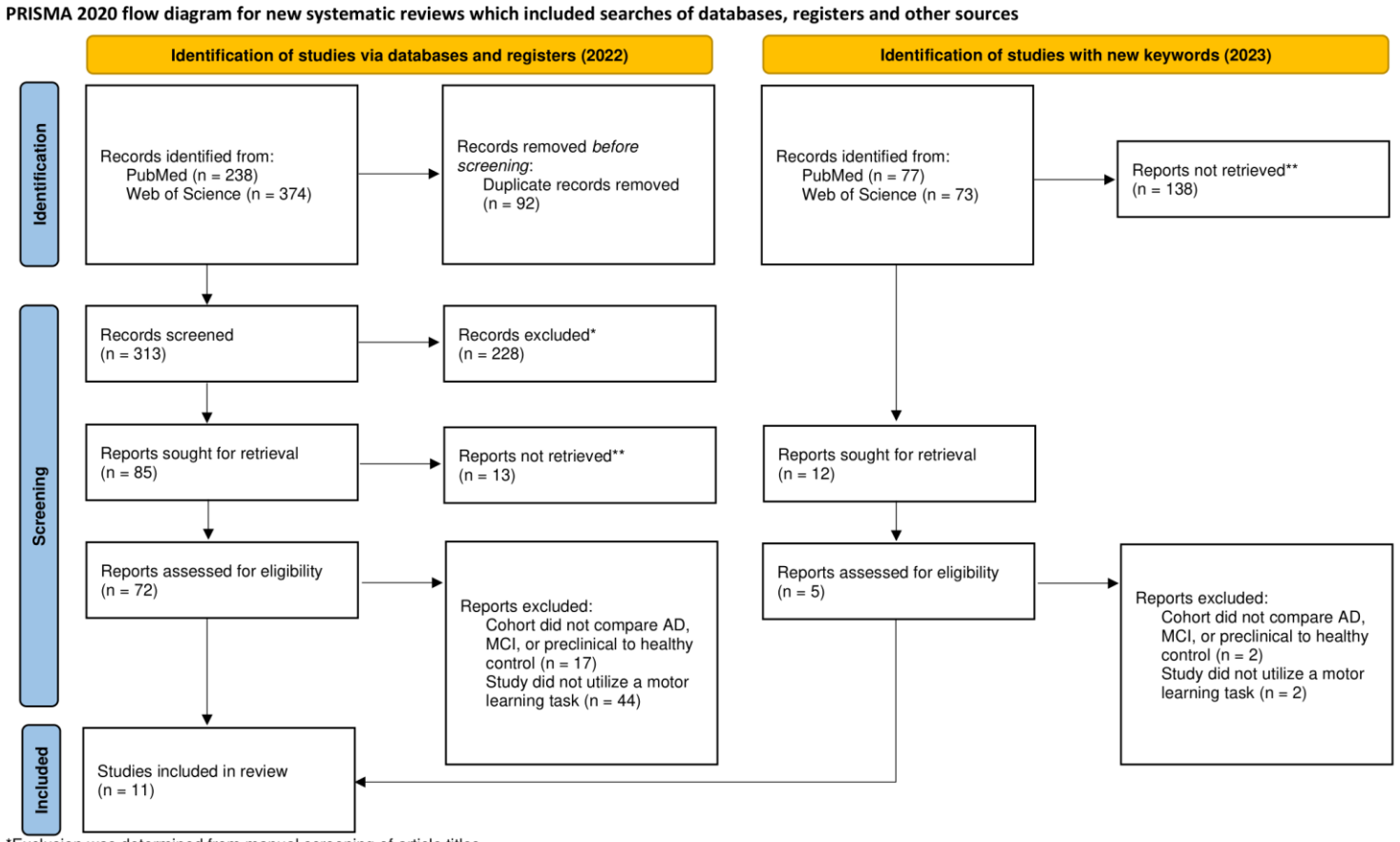


Figure 3.1 PRISMA Flow diagram.

Inclusion criterion

Studies were included in this review if they met all the following criteria: (1) The study compared (a) healthy elderly and MCI/AD subjects or at-risk AD subjects or (b) differences between MCI and AD, or at-risk AD. (2) The study compared performance between groups in a novel motor learning task. (3) The study used a neuromonitoring modality. Overall, seven studies were found to align with all three criteria, the general summaries for which can be found in Table 1. Studies that fulfilled criteria (1) and (2), but not (3) were not part of the main analysis but were also summarized to highlight areas in which imaging may be used to further understand the neural circuitry of learning in MCI or AD populations. These studies can be found in Table 2. Other reviews have previously investigated motor learning within AD populations and its implications for implicit learning (Aslan et al., 2021; Van Halteren-Van Tilborg et al., 2007), and readers are encouraged to reference these papers for additional motor learning AD articles that were not produced from our search terms.

3.3 Results

3.3.1 Participant screening criteria

All studies were case-control studies of Level III evidence (Burns et al., 2011). Except for Mollica (2017) and Eslinger (1986), studies in this review utilized either the MMSE or MoCA to identify the cognitive status of all the participants. In general, a subject was assigned to the AD group if the MMSE was less than 20, or if the MoCA was less than 22. Single domain amnestic MCI (sda-MCI) and multi domain amnestic (mda-MCI) scored 1.5 standard deviations below healthy age- and education-matched peers on the MMSE (these healthy scores were between 24-30), while the MoCA was not used in this

population. MCI participants underwent functional assessments to ensure that cognitive impairment did not interfere with daily activities. Tables 1 and 2 summarize other tests used to validate assignment to control, MCI, or AD groups. These tests were also used to ensure consistency with clinical criteria and exclude other causes of dementia. AD, and particularly an MCI diagnosis, has varied criteria across studies (Anderson, 2019). The Trail-Making Test (TMT; Part A and/or Part B) and/or the Wescheler Adult Intelligence Scale (WAIS) was used in Schaefer, Mollica and Wiesman (either explicitly stated or indicated via the Alzheimer's Disease Neurological Institute procedures) to test for visuomotor ability and visuomotor attentional differences between diagnostic groups. Vecchio indicated that visuomotor/visuoconstruction abilities were measured, but the specific tests were not listed. All other studies did not state whether visuomotor abilities were tested.

Table 3.1 Preclinical/MCI/AD Studies of Motor Learning with Neuromonitoring

Author	Motor Task/ Motor Learning Category	Neuromonitoring Technique	Population Size	Screening Methods	General Findings
Cespón (2013)	Simon task / De novo motor task	Task-based EEG	25 controls (11F, 14M, mean age: 65.2); 17 single-domain aMCI (7F, 10M, mean age: 67); 13 mdaMCI (7F, 6M, mean age: 71)	MMSE California Verbal Learning Test Cambridge examination for mental disorders in elderly (CAMDEX-r) Questionnaire on subjective memory complaints IADL GDS Questionnaire with socio-demo-graphic and clinical data	Speed of attentional shifts to target stimuli is not affected in either type of MCI, but the reduced amplitude of event-related potentials within temporal and parieto-occipital regions for mdaMCI patients suggests a reduced allocation of attentional resources.
Hawkins (2014)	Novel Visuomotor Reaching Task / Motor adaptation	Structural MRI (diffusion tensor imaging)	30 participants: 10 young (mean age: 26), 10 mild at-risk (mean age: 58); 10 high at-risk (mean age: 58). All subjects were female.	MoCA High-risk: reporting either a maternal, multiple, or early-onset family his-tory of AD, no cognitive impairment Low -risk: age-matched with high-risk participants, no family history, no abnormal memory complaints Saliva samples for APOE-e4 carriers	Subjects with increased AD risk demonstrated more age-related WM integrity decline, with a significant association between WM compromise and cognitive motor performance.

Hawkins (2016)	Novel Visuomotor Reaching Task / Motor adaptation	Resting-state fMRI	30 participants: 10 young (mean age: 26), 10 mild at-risk (mean age: 58); 10 high at-risk (mean age: 58). All subjects were female.	MoCA High-risk: reporting either a maternal, multiple, or early-onset family his-tory of AD, no cognitive impairment Low -risk: age-matched with high-risk participants, no family history, no abnormal memory complaints Saliva samples for APOE-e4 carriers	DMN functional connectivity correlated with kinematic measures of cognitive motor performance, despite no cognitive or basic motor impairment. AD-risk participants demonstrated reduced resting-state functional connectivity in the following areas: parietal-frontal, interhemispheric, and temporal-subcortical connections.
Rogojin (2023)	Novel Visuomotor Reaching Task / Motor adaptation	Structural MRI (gray matter volume, diffusion tensor imaging)	49 participants: 25 high at-risk (12F, 13M, mean age: 58); 24 low at-risk (12F, 12M, mean age: 58)	MoCA High-risk: reporting either a maternal, multiple, or early-onset family his-tory of AD, no cognitive impairment Low -risk: age-matched with high-risk participants, no family history, no abnormal memory complaints Saliva samples for APOE-e4 carriers	High-risk subjects with APOE-e4 allele demonstrated correlation between lower WM integrity and gray matter in temporal regions and poorer performance scores in the non-standard portion of the task. These subjects also demonstrated poorer performance in the non-standard task with lower gray matter in temporal regions.

Schaefer (2022)	Novel Upper Extremity Motor Task / Motor Acuity	Structural MRI (gray matter volume)	54 participants: 15 cognitively unimpaired (13F, 2M, mean age: 71.9); 24 aMCI (16F, 8M, mean age: 74.1); 15 AD (7F, 8M, mean age: 78.6)	MMSE Clinical status was confirmed with the ADNI classification battery Clinical Dementia Rating Scale Wechsler Memory Scale–Revised Logical Memory II Paragraph A	Motor task acquisition was a significant predictor of hippocampal volume, with worse task acquisition (i.e. more variable performance) being associated with lower hippocampal volume after adjusting for demographic and clinical variables. Controls had better acquisition (less variability in performance) and the AD participants had worse acquisition (more variability) across trials.
Vecchio (2018)	Sensory Motor Learning (SmoL) task of visual rotation paradigm / Motor adaptation	Resting-state functional EEG	86 subjects: 22 normal (mean age: 68.3), 47 aMCI (mean age: 72.8), 17 AD (mean age: 70.1)	MMSE Diagnosis was based on National Institute on Aging-Alzheimer's Association workgroups DSM-IV-TR criteria Neuropsychological testing to assess memory, attention, executive function, visuospatial construction abilities	Significant differences between healthy elderly, MCI and AD patients were demonstrated by showing that physiological brain aging shows characteristic small world EEG rhythms, i.e. being lower in alpha bands.

Wiesman (2021)	Visuospatial discrimination task / De novo motor task	Task-based MEG	35 subjects: 20 healthy controls (12F, 8M, mean age: 72.7), 17 aMCI (mean age: 69.3), 21 probable AD (mean age: 69.3)	MMSE & MoCA IADL, FAQ PET scan to identify amyloid-positive groups Battery of cognitive tests to assess verbal memory, language, processing speed, learning, attention, and executive function	Subjects on AD spectrum demonstrated lower theta and alpha responses and stronger gamma frequency synchronizations, which correlated with performance on cognitive screening tests. No note of specific brain structures that are affected.

Abbreviations: AD = Alzheimer Disease, ADNI = Alzheimer's Disease Neuroimaging Initiative, aMCI =amnestic mild cognitive impairment, DSM-IV-TR = text revision of the Diagnostic and Statistical Manual of Mental Disorders IV, DMN = Default Mode Network, FA = Fractional Anisotropy, FAQ = Functional Activities Questionnaire, GDS = Geriatric depression scale, IADL = Instrumental Activities of Daily Living, MCI = Mild Cognitive Impairment, mdaMCI = multiple domain-amnestic MCI, MMSE = Mini-Mental State Exam, MoCA = Montreal Cognitive Assessment, PET = positron emission tomography, sdaMCI = single-domain amnestic MCI, WM = white matter

Table 3.2 Preclinical/MCI/AD Studies of Motor Learning Without Neuromonitoring

Author	Motor Task/ Motor Learning Category	Subjects	Screening Methods	Summary of Findings
Eslinger (1986)	Angular rotary pursuit task/ Motor adaptation	16 subjects: 8 healthy controls (mean age: 70.8); 8 AD subjects (mean age: 71.4)	NINCDS-ADRDA 1984 criteria (McKhann et al., 1984)	Memory loss in AD affects mostly declarative memory, which is primarily associated with corticotemporo/limbic structures. Procedural knowledge is more dependent on corticocerebellar/striatal structures, and is preserved in AD.
Hong (2020)	Serial Reaction Time Task (SRTT) / Sequence learning	42 subjects: 22 controls (8M, 14F, mean age: 67.6); 20 MCI (13M, 7F, mean age: 66.7)	MMSE Neuropsychological tests to assess global cognitive function, premorbid intelligence, four specific cognitive domains	MCI subjects performed poorer than healthy controls in reaction time, commission errors, and omission errors in the SRTT. However, learning slopes in randomized blocks were similar between healthy and MCI subjects, pointing to retained implicit memory.
Mollica (2017)	Visuomotor coordination task (VMC) / De novo motor task	81 subjects: 47 controls (mean age: 65.4); 19 'pre-clinical' (mean age: 67.4); 15 AD (mean age: 68.1)	CSF p-tau, tau testing Depression and anxiety assessments Self-rated subjective cognitive decline questionnaires Neuropsychological tests to assess recall, total recall, learning, total learning, semantic fluency, visual object and space perception battery	Reaction time was longer than controls in pre-clinical AD, and even longer in AD. This was the only behavioral measurement that was significantly different when compared to the control group. Visuomotor dysfunction occurs at earlier stages of AD and may be associated with cerebrospinal fluid Aβ42 protein deposition.

Yan (2006)	Novel motor reaching task / Motor acuity	88 subjects: 31 controls (23F, 8M, mean age: 71.6), 29 MCI (13F, 16M, mean age: 73.9), 28 AD (10F, 18M, mean age: 77.4)	Diagnostic criteria for probable AD developed by the NINCDS and the ADRDA Functional deficits: BADLS, FAQ, NPI No history of chronic alcoholism, psychiatric illness, or other neurological disorders CDR scale Hachiniski Ischemic Scale Tested for Vitamin B-12 deficiency, thyroid-stimulating hormone MRI, SPECT to identify atrophy and presence of amyloid of tau	Learning was quantified by improvement of movement from baseline trial to final trial. Practice in a simple motor reaching paradigm allowed MCI participants to reduce jerk and movement time, while AD subjects only improved movement time.

Abbreviations: AD = Alzheimer's Disease, ADRDA = Alzheimer's Disease and Related Disorders Association, BADLS = Bristol Activities of Daily Living Scale, CDR = Clinical Dementia Rating, CSF = Cerebrospinal Fluid, MCI = Mild Cognitive Impairment, MMSE = Mini-mental state exam, MoCA = Montreal Cognitive Assessment, MRI = Magnetic resonance imaging, P-tau = phosphorylated tau, NINCDS = National Institute of Neurological and Communicative Disorders and Stroke, NPI = Neuro-Psychiatric Inventory, SPECT = single-photon emission computed tomography

The overall age of participants in these studies ranged between 60 and 80 years old for controls, MCI, and AD. Subjects in these studies were also closely balanced in sex, apart from Hawkins (2014 and 2016), where all subjects were female, and in Mollica and Eslinger, where subject sex was not reported or clearly delineated within cognitive groups. Regarding subject demographics, only Schaefer et al. stated the race and ethnicity of the participants. Overall, all participants were right-handed, identified either through testing (Edinburgh Handedness Inventory Scale) or self-report. The largest cohort that underwent motor testing and neuromonitoring was in Vecchio et al., with 86 total participants. The smallest subject group was in Vidoni et al., with 19 total subjects to undergo neuroimaging and motor testing. None of the studies reported a power analysis for the motor learning nor for the imaging results.

Given the relationship between motor learning and cognitive functioning, and given the wide array of motor tasks that can be employed, under each category of motor task we have separated the different imaging and behavioral results into cognitive domains so that results can be more easily compared (Figure 3.2). It should be noted that each motor task category can contain various combinations of the cognitive domains listed. However, the motor results that are most correlated to specific cognitive domains have been presented.

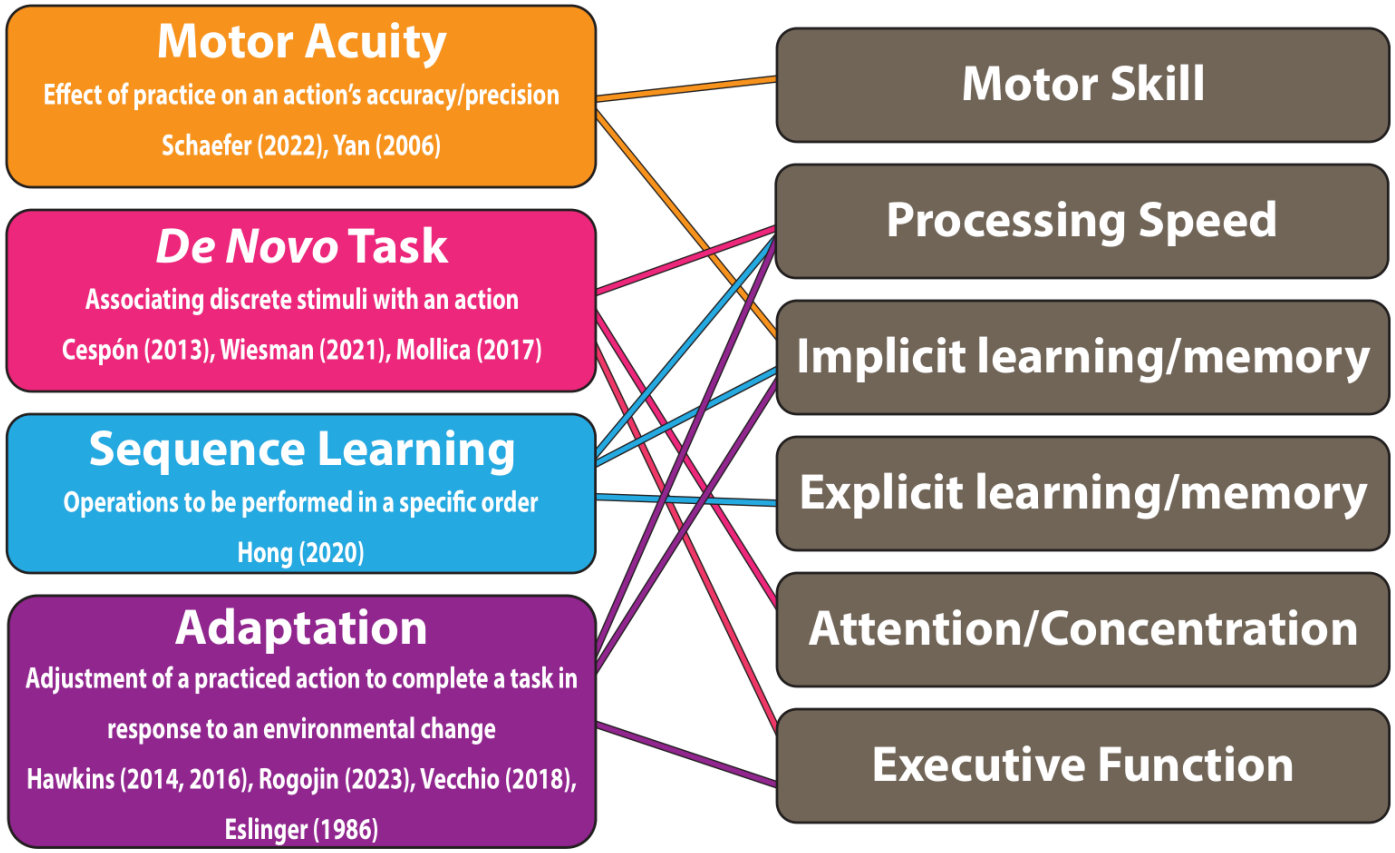


Figure 3.2 Cognitive domains assessed by each motor task. *Figure adapted from Krakauer (Krakauer et al., 2019). Each motor task can assess multiple cognitive domains listed. Definitions obtained from Harvey (2019), Zucchella and colleagues (2018), and Baggetta and Alexander (2016).*

3.3.2 Motor Acuity

Motor acuity, also referred to as motor accuracy or precision, is mainly assessed with prehension tasks (reaching and grasping) in animal models (Krakauer et al., 2019), with a focus on how movement variability decreases or how efficiency increases. Motor acuity tasks are not typically studied in human clinical populations as they do not carry large cognitive demands. Nevertheless, these types of experiments provide insight into neural connections that may generalize to motor skill learning. These tasks are also reflective of motor skill maintenance (increased accuracy and precision) due to practice.

Task descriptions

(J. Yan & Dick, 2006) required participants to move a stylus on a tablet from a centered starting position away from their body and 'land' within a target. AD, MCI, and healthy controls were all compared. Half of the participants were allowed practice before recording, and half had their attempts recorded directly. This paradigm was repeated over the course of 5 days. The following metrics were recorded: 'jerk' (the number of corrections made to move in a straight line), movement time, and percent primary submovement (the first point at which acceleration changes from negative to positive divided by overall movement time).

(Schaefer et al., 2022) looked at correlations between a simple reaching task and hippocampal atrophy. The motivation for analysis of reaching and hippocampal volume come from previous evidence demonstrating the contributions of the hippocampus in sequence learning (Albouy et al., 2008; Long et al., 2018) and movement execution (Burman, 2019) combined with well-established patterns of atrophy in the hippocampus in AD (de Flores et al., 2015). An upper extremity reaching task was used to observe the

effects of practice in AD populations. This task required participants to pick up a bean with a spoon in their non-dominant hand, extend their hand to one of three target cups to drop the bean, and return to the center. This was repeated to each different cup, and the duration of each trial was recorded. Learning was quantified as the acquisition 'slope', or the difference in mean acquisition time between the first and the last trial.

Motor skill

Motor skill is often assessed in a neuropsychological setting by observing fine motor abilities: finger tapping, pegboard tasks, and assessment of grip strength (Harvey, 2019). Yan et al. quantified motor skill with jerkiness in a simple arm reaching movement. The authors found that jerkiness was mainly affected by AD diagnosis, while movement time differed between all three diagnosis groups. However, practice was found to improve only movement time across all groups. Movement time also correlated with MMSE scores, with higher cognitive functioning subjects performing the task faster. Although no neural recording was conducted in conjunction with this task, the correlation between movement time and MMSE scores suggests potential neural differences between diagnostic groups may be caused by changes in brain regions related to active motor control. Schaefer's reaching task measured the number of errors, or number of incomplete reaches. However, there was no difference across diagnostic groups, suggesting that motor skill was similar across all groups.

Learning and memory – implicit learning

Yan's task used primary submovement to evaluate motor planning, sometimes referred to as 'offline' planning (Khan & Franks, 2003). This is a measure of the initial control plan made prior to visual feedback (Fradet et al., 2008). As a result, an increase in primary submovement after repeated attempts is a measure of retention of motor

experience (Thomas et al., 2000). No significant effect was found between offline planning and diagnostic group nor practice groups, in contrast to other experiments that have found a correlation between practice and primary submovement (M. F. Ghilardi et al., 2000; J. H. Yan & Zhou, 2009).

In Schaefer et al., the movement acquisition slope (a measure of the change in movement time) was the only metric that significantly correlated with hippocampal atrophy for AD and healthy participants. Higher intra-subject variability (amount of time to complete the movements) but a higher measure of improvement between the first and last trial correlated with lower hippocampal volume. This finding suggests that motor practice may be affected by hippocampal atrophy. Contributions of the temporal lobe to visuomotor coordination is relatively understudied, but previous studies have demonstrated recruitment of the hippocampus and other temporal regions for visuomotor coordination (Onuki et al., 2015; Tankus & Fried, 2012). Combined with known deficits in AD subjects' learning ability due to deteriorated visuomotor networks (Oki et al., 2021; Salimi et al., 2019), the authors point to a potential mechanism through which hippocampal atrophy in AD may affect visuomotor ability.

Motor acuity summary

Both paradigms found inherent motor performance differences across diagnostic groups, but also demonstrated preservation of learning by measured improvement with practice. These results are similar to previous findings that have noted decreased motor skill in AD patients but large effects of practice (Willingham et al., 1997). However, the two studies provided here demonstrate that practice only improves certain metrics of performance. In Yan, movement jerkiness did not improve with practice; similarly, the variability in movement time did not improve in Schaefer's paradigm. The effect of

hippocampal atrophy as a mechanism for movement variability has also been found in gait studies (Tian et al., 2017), and may be reflective of spatial navigation deficits in AD (Allison et al., 2016, 2019; Jin et al., 2020; Parizkova et al., 2018).

In general, it is difficult to draw conclusions about the effect of practice in dementia populations from these two studies. As will be discussed later, findings regarding the preservation of implicit learning across the AD spectrum is not consistent. Overall performance can be improved by continually practicing movements, but even with practice, MCI and AD participants display noticeable deficits even in simple movements.

3.3.3 *De novo* tasks

De novo tasks require participants to make associations between arbitrary stimuli (either visual, like a specific type of shape, or audio, like a specific tone of a beep) and a motor action. This type of learning is distinct from adaptation studies as it requires subjects to generate a completely new feedback controller to successfully complete the task (C. S. Yang et al., 2021). In other words, a participant cannot depend on performance of a previously learned skill to carry out their movement. As a result, this specific motor learning task is one that depends mostly on explicit, or conscious, learning abilities without interference from previously learned skills (Krakauer et al., 2019). Therefore, *de novo* tasks may be more representative of learning capacities in AD and MCI populations.

Task descriptions

A Simon task was the *de novo* paradigm used in Cespón et al. (Cespón et al., 2013), where participants were presented two arrows in different locations, with different colors, oriented in different directions. Participants were ascribed either to healthy controls, single-domain amnestic MCI (deficit in only memory; sda-MCI) or multi-domain

amnestic MCI (deficits in multiple cognitive domains including memory; mda-MCI). Subjects had to select the appropriate response only regarding color, not arrow direction or location. This task observes the effect of distractions on performance, which is termed as the 'Simon Effect' for this specific paradigm (Cespón et al., 2020). The authors reported on the percentage of errors (percentage of incorrect button presses), reaction time, and 'interference', the interaction effect on performance caused by the Simon Effect.

In Wiesman's task (Wiesman et al., 2021), subjects were grouped into cognitively normal or 'AD spectrum' (these participants either had a diagnosis of aMCI or mild probable AD). The task required volunteers to select one of five buttons that corresponded with various positions of a black and white grid. MEG was used to observe neural activity during the task.

Mollica (Mollica et al., 2017) did not image participants, but utilized a visuomotor coordination task (VMC) that required participants to press a key that corresponded with an on-screen target position. The experiment was designed to develop a standard test for visuomotor coordination, an execution of motor task that is determined by processing speed (Tankus & Fried, 2012), while simultaneously reducing the contribution of other cognitive domain activity such as executive functioning. The task measured the response times, errors, and omission rate for healthy, pre-AD (participants in the preclinical stage of AD), and AD subjects. Differences between subjects were evaluated using mean response time of correct responses.

Processing speed

In Mollica et al., mean response time in AD patients were significantly slower than pre-AD and control subjects. Correlations between cerebrospinal fluid Aβ42 levels, an amino acid that is a biomarker of AD, and response times were shown across all subjects.

However, Cespón and Wiesman did not find response times nor movement latency to be affected by diagnosis. While the differences in findings may be due to inherent motor skill deficits across the AD spectrum, (it is unclear if Cespón evaluated visuomotor ability, while Wiesman did not conduct subtests for visuospatial processing), the VMC was developed to minimize executive function contribution. Performance differences in these *de novo* tasks may be partially explained by the varied contribution of executive functions.

Attention/concentration

Cespón and Wiesman's groups did not find attentional differences as reflected in behavioral outcomes. However, Cespón found that EEG posterior contralateral negativity (N2pc) ERP amplitude was significantly affected by diagnosis. Control groups demonstrated higher amplitudes than the mdaMCI group. The N2pc is elicited in the posterior region of the brain, contralaterally to the target location. In discrimination tasks, this N2pc has been found to reflect attentional selection of task-relevant stimuli (Eimer, 1996). Therefore, the lower N2pc amplitude of mdaMCI subjects may suggest decreased attentional resource availability in demented populations to achieve the same level of behavior.

The VMC task also utilizes a spatial attentional component; however, there was no reported measure for the attentional shifts between the screen and button pressing, which is typically achieved with saccade recordings (Birmingham & Kingstone, 2009).

Executive function - interference control

Interference control, or inhibitory control of attention, is a type of executive function that allows for selective attention while suppressing attention to other stimuli (Diamond, 2013). Wiesman and Cespón found the number of errors to significantly correlate with diagnosis. In the Simon Task, the heightened error rate may be indicative

of a lack of inhibition of irrelevant information in sdaMCI or mdaMCI populations (Cespón et al., 2020). Additionally, the authors found that diagnosis was associated with response-locked lateralized readiness potential (LRP-r): EEG measurements of processes that make distinctions between perceptual and response preparation (Mordkoff & Gianaros, 2000). Although more work is needed to parse out the relationship between LRPs and the Simon Task, a recent hypothesis is that the varying LRP amplitudes indicate inhibition control (Cespón et al., 2020), with lower amplitude indicating less inhibition.

In Wiesman's experiment, MEG was used to observe alpha band activity during the visuomotor task. Like N2pc ERPs, MEG alpha band activity in the posterior region and contralateral to stimuli has been linked to visuospatial attention. The amplitude of these waves increase to inhibit non-relevant stimuli (Bacigalupo & Luck, 2019; Doesburg et al., 2016). When compared to healthy controls, subjects with more advanced AD biomarkers exhibited lower amplitudes of alpha waves in the lateral occipital regions during the task, but higher gamma amplitudes in the primary occipital cortices. The alpha and gamma oscillations significantly predicted the diagnosis of the participants, suggesting that subjects on the AD spectrum demonstrate differences in functional selection of visual information and decreased ability to represent stimulus information in visuospatial processing.

Although Mollica et al. designed the VMC to limit the contribution of executive functions, the authors noticed that commission errors (clicking the wrong button) were significantly higher for AD patients than controls. Conversely, omission errors (lack of response) did not reveal any significant performance differences. Combined, these errors indicate that AD patients may have difficulty with inhibiting unwanted responses, or disinhibition, in motor learning.

De novo learning summary

These studies demonstrated that patients along the AD spectrum have different neural resources for attention and inhibition, as measured through EEG and MEG. This was evident in neuromonitoring data, despite a lack of behavioral performance differences, in tasks that recruited executive function in addition to attention and processing speed. The results from Wiesman and Cespón point to attentional deficits on the neural level, as opposed to the behavioral level, at earlier stages of AD, suggesting that neural changes in regions related to attention may help identify MCI development. These mechanistic results align with other imaging studies that have found functional and structural differences in regions responsible for attention and inhibitory control in early AD (Jacobs et al., 2015; Prvulovic et al., 2002).

3.3.4 Sequence learning

Learning the sequences of actions is an important aspect in daily functioning and is a major component of Instrumental Activities of Daily Living (ADL) assessments administered in dementia clinics. IADL assessments measure an individual's capability to complete everyday tasks (e.g.: making coffee or tea, paying bills, preparing a balanced meal). Such tasks have a critical order of steps that need to be taken to be successfully completed. Similarly, sequence learning paradigms with discrete steps can assess the implicit and explicit learning capability of novel tasks. Despite the popularity of sequence learning studies on AD participants, our search did not produce any articles in which neural imaging was conducted in conjunction with these tasks. As a result, proposed mechanisms will be summarized, and we will provide a brief overview of overall findings.

Task description

Hong (Hong et al., 2020) employed a well-studied behavioral paradigm, the serial reaction time task (SRTT), to study learning deficits in MCI populations compared to healthy counterparts. This task requires participants to press one of four buttons that correspond with an on-screen position as quickly and accurately as possible. Certain blocks of the SRTT have a pre-determined pattern, while other blocks had a random pattern. Participants are not made aware of the pre-determined button pattern. As a result, this task analyzes processing speed, implicit learning, and explicit learning (Moisello et al., 2009). Typically, the SRTT has several random pattern blocks followed by several patterned blocks. Hong's paradigm interleaved random and patterned blocks. Both the random and sequenced portions of the paradigm were designed to have an 'equal probability of button pressing'. These modifications produce larger contributions of implicit as opposed to explicit learning.

Processing speed

Regardless of the block type, MCI participants had significantly slower mean reaction times compared to healthy counterparts. While the overall times were significantly slower for MCI than controls, there was no significant difference in the effect of practice, a finding that aligns with (J. Yan & Dick, 2006).

Learning and memory – implicit and explicit learning

This study measured implicit learning through commission and omission errors (incorrect button press or failing to press the response button in a predetermined amount of time, respectively) in each block. Despite comparable accuracy between MCI and healthy subjects, MCI participants demonstrated higher commission errors per block.

Both groups demonstrated greater improvement in randomized blocks than the sequenced blocks, pointing to preservation of implicit learning in MCI.

3.3.5 Motor Adaptation

Adaptation paradigms reveal ways in which people modify existing controllers to novel situations. A short-term example of this might be cursor drift from a computer mouse, while a long-term example might be the effect of injury on body movements. These studies focus on how the brain accounts for error in movement and analyze the adjustments used to maintain performance. Typically, learning strategies are referenced as having implicit and explicit contributions, which reflect sensory prediction error and higher-order cognitive processes, respectively (Bindra et al., 2021b; Taylor et al., 2014b). However, the studies presented here did not differentiate between the two strategies. As a result, task errors have been interpreted to be a result of cognitive flexibility, and actual hand or arm movement to reflect implicit learning.

Task descriptions

In Vecchio (Vecchio et al., 2018), the motor adaptation paradigm, Sensory Motor Learning task (SMoL), required participants to adapt their reaching movements to different targets on a screen by countering an induced 90° rotation of the movement feedback. The study measured the number of successfully reached targets. To mitigate a ceiling effect, learning was also quantified by comparing the direction of the initial four movements to the final four movements. The subjects' resting-state EEG was obtained before and after the task occurred. The activity between motor learning activated regions (Heitger et al., 2012) was then analyzed using the small world metric. This technique is utilized in graph theory analysis and characterizes networks through examination of

functional integration and segregation (Latora & Marchiori, 2001), with higher small world values indicating an optimal balance between global integration and local connectivity (Bassett & Bullmore, 2017; Watts & Strogatz, 1998).

The adaptation task used by (Hawkins & Sergio, 2014) assessed generalization of learning across contexts. This was the only task that did not examine the rate of improvement in motion but measured how a single movement translated to various environments. Participants learned to move toward a target on the same plane as their hand, and then were trained to move toward a target while their hand was on a different plane. Participants also underwent trials in both planes with reversed feedback, where successful completion required hand movement in the opposite direction of the target. Subjects were always made aware of the task requirements and were given practice trials before movement recording. The z-scores of overall error (the averages of accuracy, precision, and corrective path length, respectively) and performance timing (the averages of movement time and reaction time, respectively) were calculated for each healthy young, low-risk AD, and high-risk AD subject in the standard plane/standard movement task and the dissociated plane/feedback reversal task. The accuracy and precision of this type of task has been suggested to be reflective of motor planning (Messier & Kalaska, 1997). Performance was correlated with diffusion imaging analysis, which measures restricted diffusion of water molecules to identify WM fiber tracts. A later study by the same group (Hawkins & Sergio, 2016) utilized the same paradigm, but analyzed rs-fMRI taken at a later time to correlate behavioral measures. Similar to Hawkins & Sergio (2014), (Rogojin et al., 2023) utilized the same task and conducted diffusion MRI analysis, but also compared hippocampal subfields and gray matter atrophy.

Eslinger and Damasio (Eslinger & Damasio, 1986) utilized practice in a rotorary pursuit task to evaluate learning. This paradigm required participants to maintain contact on a target that rotated around a surface. The authors recorded the time on target and number of rotary pursuit impulses (number of times the stylus lost and regained contact with the target) and compared the improvement in performance over each trial.

Processing speed

Hawkins' task was the only adaptation task to have a metric to assess processing speed. The z-scored performance timing metric demonstrated a significant difference between high-risk AD and young participants, but no difference between high-risk and low-risk (healthy older) adults. These results align with the *de novo* tasks that included some form of executive functioning. The correlational results for Hawkins' fMRI and DTI analysis aligned with results for cognitive flexibility, as will be explained in the following section.

Executive function – cognitive flexibility

Cognitive flexibility can be thought of as the ability to switch from one way of thinking to another. In Hawkins' (2016) task, this would be the ability to switch from same plane/same direction to offset plane/opposite direction tasks. The subjects at high risk of AD demonstrated significantly larger error scores when the plane and direction were offset when compared to healthy controls and low-risk AD subjects. This points to an impairment in high-risk AD populations in generalizing or translating motor planning to different contexts. These errors correlated with decreased connectivity within the default mode network, as identified through seed-based analysis of resting state fMRI. The greatest correlation between error score and decreased connectivity was located between the right middle temporal gyrus and the right thalamus.

Diffusion analysis by the Hawkins group (2014) demonstrated lower fractional anisotropy (FA; where high FA values indicate fiber tracts with high directionality) in low-risk AD, higher radial diffusivity, and lower axial diffusion in the forceps minor, corpus callosum, and the corticospinal tract. These findings in low-risk participants point to age-related changes in anterior WM tracts. When high-risk AD subjects were compared to young subjects, these structural changes were found to be more severe, with the white matter changes also identified in the hippocampus and posterior white matter tracts. The severity of white matter hyperintensities in these regions correlated significantly with task performance, indicating that white matter changes in normal aging occur in the anterior portions of the brain. In contrast, white matter changes were more prominent in posterior regions in subjects with AD, which appeared to reduce motor planning capability.

The analysis by Rogojin et al. (2023) demonstrated similar correlations between visuomotor performance and decreased WM integrity throughout most WM tracts, but particularly the inferior fronto-occipital fasciulus. Volumetric analysis also revealed that gray matter atrophy in the parahippocampal gyrus and entorhinal cortex also predicted poorer performance. However, this correlation was only seen in high-risk participants that also carried the APOE-e4 allele.

Learning and memory – implicit learning

The SmoL task revealed that MCI and AD subjects were unable to successfully complete as many movements as their healthy counterparts. Healthy controls also demonstrated significant learning as reflected by the difference in the number of successful target completions for the initial and final trials, while AD and MCI participants showed little difference between the beginning and end of the paradigm. Graph analysis of resting-state EEG found that learning in the SmoL task correlated with

alpha 2 band small world index. More specifically, lower alpha 2 small world measures prior to behavior testing predicted higher rates of learning in the task. These low small world values indicate less 'random' connections and more uniformity in participants that showed learning. In EEG, high frequency alpha waves reflect semantic processing (Klimesch, 1997, 1999) and have been proposed to reflect facilitation and inhibition of sensorimotor information (Uusberg et al., 2013). Other resting state EEG studies have noted a decreased power in alpha band frequencies in MCI and AD participants (Jafari et al., 2020). Collectively, this suggests that MCI or AD participants had lower uniformity within posterior networks, or a decreased ability to inhibit irrelevant sensorimotor information, which impaired implicit learning.

While Eslinger et al. (1986) found that AD patients demonstrated greater improvement with practice than healthy controls (similar to Schaefer (2022)), retention of the motor skill (time on target) did not differ between controls and patients with AD. This contrasts with Vecchio's findings, and suggests that implicit learning is maintained throughout AD. The authors proposed that cortico-cerebellar and striatal structures, neural connections required for implicit learning, are spared in AD progression.

Adaptation summary

The adaptation studies presented here did not differentiate between explicit and implicit learning. Metrics taken to imply implicit learning, the change in overall movement in Hawkins (2014, 2016), Rogojin (2023), and Vecchio (2018), indicated that implicit learning is not preserved in AD. However, these tasks draw on spatial processing abilities, while the rotary pursuit task in Eslinger (1986) reflects more perceptual motor skill learning (Sarazin et al., 2002). This may contribute to the different conclusions about AD learning. Notably, although Hawkins' and Rogojin's participants did not include

people with cognitive impairment, at-risk subjects displayed greater difficulty in successfully completing the task and were slower than low-risk controls. As a result, executive functions related to spatial processing may be an early indicator of AD progression, but further study is required in high-risk populations to confirm this association.

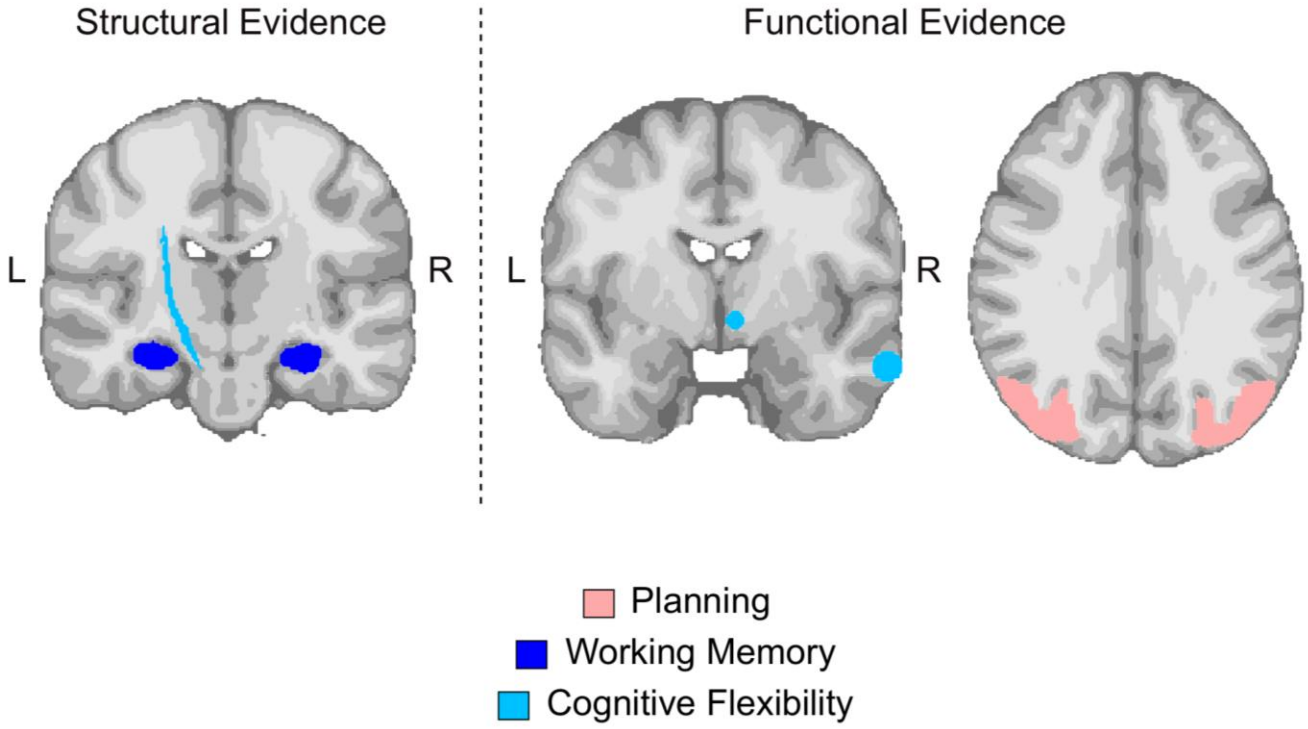


Figure 3.3 Brain regions that correlate with participant diagnosis. *Tasks that evaluated planning produced decreased amplitude within posterior regions (P07 and P08 electrode pair) as noted through EEG (Cespón et al., 2013). Behavioral output measuring working memory correlated with hippocampal size (Schaefer et al., 2022). Hippocampal size also correlated with VMC performance (Rogojin et al., 2023). Cognitive flexibility as measured through movement errors were most strongly associated with left cerebrospinal tract integrity (left image; negative association [Hawkins & Sergio, 2014]) and with default mode connectivity (middle image; decreased connectivity between a seed in the right thalamus and the right middle temporal gyrus [Hawkins & Sergio, 2016]). Although tasks examining cognitive flexibility noted several other regions that correlated with performance, these regions demonstrated the strongest correlations.*

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3.4 Discussion

The aim of this review was to summarize findings from imaging and motor learning studies in at-risk, MCI, and AD populations. Seven studies met all our search criteria, and an additional four non-imaging studies were included. All studies were of level III evidence given the comparison of disease or at-risk groups to healthy controls.

Limitations

A first limitation of this review is the small number of papers that met the screening criteria. Only seven articles were included, and additional articles that did not include neuroimaging were also compared. These studies used varied screening criteria for preclinical, MCI, or AD participants. As mentioned earlier, diagnosis across AD development, particularly MCI diagnoses, can differ between clinics and physicians. This makes it difficult to draw conclusions about behavioral differences with AD progression and may be reason for inconsistent findings between studies. Additionally, despite the use of motor learning tasks, only four studies specifically assessed visuomotor abilities through the Trails Making Test or through subtests of the Wechsler Adult Intelligence Scale-IV (WAIS-IV). Nonetheless, to some degree, all studies found motor learning behavioral differences that were characteristic of at-risk, MCI, or AD populations.

Summary of Main Results

Rogojin and colleagues (2023), Wiesman and colleagues (2021), Vecchio and colleagues (2018), Hawkins (2014, 2016), and Cespón and colleagues (2013) had tasks that recruited executive function skills and had metrics of errors. A summary of the brain regions relevant to executive function and error metrics can be found in Figure 3.3. Even in at-risk populations, movement errors were significantly greater than healthy controls. Although these errors may be caused by increased cognitive workload, Mollica and

colleague's (2017) task did not have as great of a demand on executive function and still induced greater commission errors in AD patients compared with controls. However, these errors were not obvious in MCI populations. In Yan, jerkiness of movement, or the initial change in direction made in a simple reaching motion, was also significantly correlated with diagnosis. These results may reflect disinhibition in information discrimination (an inability to filter out irrelevant stimuli) or in movement selection (inability to move in a controlled way). These articles provide evidence that disinhibition can be quantified in motor learning studies and may be a metric by which early AD progression can be identified. Notably, disinhibition has also been found in other nonmotor studies of attention in AD (Firbank et al., 2016; Verheij et al., 2012; Fernandez-Duque & Black, 2006).

Trends in neural changes underlying motor learning differences in AD

A large portion of the articles presented here provide evidence of anterior-posterior connectivity changes with AD progression, also referred to as the 'disconnection hypothesis' (Delbuck et al., 2003; Reuter-Lorenz & Mikels, 2005). Vecchio (2018) found differences in neural activity within posterior regions between healthy, MCI and AD subjects that corresponded with implicit learning ability. Hawkins (2014) noted structural changes in anterior regions for healthy aging subjects, while the degeneration moved more to more posterior regions in at-risk AD participants. Such changes were tied to deficits in cognitive flexibility. Moreover, Cespòn (2013) and Wiesman (2021) found a lack of inhibitory LRPs and oscillatory activity in posterior regions near the visual cortex.

While this begins to build a complementary narrative for neural changes in AD, there are still unanswered questions and conflicting evidence between other

neuromonitoring-motor learning studies. Motor studies that did not include any form of neural recording still suggest that neural differences arise in regions strongly associated with their task (Mollica (2017) points to the posterior parietal cortex, Hong (2020) points to the basal ganglia and cerebellum, and so on). The mechanism for these changes can be revealed if the task is conducted in junction with whole brain neuromonitoring. Furthermore, brain structures related to domains other than memory should and can be explored in motor learning studies. As seen in our comparison across articles, there may be increased sensitivity in brain areas or networks concerning implicit learning or attention. Additionally, questions regarding generalization, adaptation processes, temporal stability, forward and inverse models, and sensory prediction errors are probed in typical motor learning settings (Alhussein et al., 2019; Bindra et al., 2021a; McKenna et al., 2017; Nguyen et al., 2019; M. A. Smith et al., 2006a; Wagner & Smith, 2008; W. Zhou et al., 2017, 2022) but are limited in their combination with neuroimaging, especially in dementia cohorts.

Brain regions for future investigations

As mentioned earlier, the preservation of implicit learning in AD is debated but generally agreed to be preserved (Van Halteren-Van Tilborg et al., 2007). This type of learning is highly dependent on the function of subcortical structures including the basal ganglia, the thalamus, and the cerebellum (Clark et al., 2014). The rate of improvement in implicit performance between healthy, MCI, and AD patients was comparable throughout the motor learning studies presented in this review, which suggests that these structures and their projections to the cortex are preserved throughout the disease progression. Similar findings have been demonstrated in other non-motor studies (Eldridge et al., 2002; Phillips et al., 2017; Poe & Seifert, 1997). However, recent evidence

has shown that structures like the cerebellum are not 'silent bystanders' in AD (Schmahmann, 2016). In general, decreased cerebellar gray matter (Venneri et al., 2011) (Venneri, Dos Santos, Baldacara, Lojkowska, Thomann), decreased cerebellar white matter integrity (Fukutani et al., 1996; Rohn et al., 2012; Toniolo et al., 2020), and lower cerebellar functional activity (Binnewijzend et al., 2012; Castellazzi et al., 2014; Cha et al., 2015) and decreased gray and white matter volume in the basal ganglia (Cho et al., 2014; Wurst et al., 2023) correlate with AD diagnosis and MMSE scores. These subcortical regions are understudied in AD investigations due to the belief that amyloid and tau do not affect these areas (Jacobs et al., 2018) combined with the difficulty in imaging such structures (Diedrichsen et al., 2010; Hoch & Shepherd, 2022). Discrepancies in implicit learning maintenance in MCI/AD patients as revealed by the variable performance in Schaefer (2022), or the lack of improvement in Vecchio (2018), may be explained by activity changes in the aforementioned subcortical regions (Bernard, Seidler, Hassevoort, Benson, Welsh, Lee Wiggins, et al., 2012; Eldridge et al., 2002). Utilization of high spatial resolution imaging for these regions specifically within AD populations has not been reported but would provide the information necessary to analyze cerebellar or basal ganglia structures. Understanding the contribution of these regions to cognitive decline may provide further insight into progression from MCI to AD and the preservation of learning ability in AD (Knopman & Nissen, 1987; Van Tilborg et al., 2011).

3.5 Conclusions

The high cognitive demand from motor learning tasks produces behavioral measures that are sensitive to age and disease-related changes. When paired with neuroimaging, such tasks can provide insight into mechanistic changes underlying cognitive and learning deficits. The regions highlighted in this article are not new

discoveries of affected areas in MCI and AD patients, but these findings are significant in that they begin to demonstrate how AD affects typical learning processes. Even within preclinical populations, brain structure and connectivity is different from healthy counterparts, and results in measurable behavioral differences. Overall, the combination of imaging with motor learning tasks has application both in basic science and in clinical settings, and will provide insight into how changes in neural mechanisms affect cognition, which in turn impacts behavior.

Chapter 4 – Age-related low frequency amplitude differences in resting-state blood oxygenation level-dependent signal in the cerebellum

4.1 Introduction

In typical aging, a number of behavioral processes are maintained, such as implicit (unconscious) sensorimotor adaptation (J. Huang et al., 2017; Reuter et al., 2018; Vachon et al., 2020), and predictive timing (Filip et al., 2019; Johari et al., 2018), all of which are supported by cerebellar circuitry (M. King et al., 2023; Nettekoven et al., 2024; Stoodley, 2012; Stoodley & Schmahmann, 2009). Yet the cerebellum undergoes large neuronal loss with age, particularly of Purkinje and granule cells (Andersen et al., 2003; Hogan et al., 2011; Walløe et al., 2014). The concept of cerebellar reserve, the ability of the cerebellum to compensate for pathological changes, highlights the cerebellum's potential to support neural processes in aging and disease (Mitoma et al., 2021, 2023). However, a majority of functional cognitive aging studies do not include the cerebellum in their analysis (MacDonald & Pike, 2021b). As a result, there has been growing interest to understand the effect of aging specifically on cerebellar function (Arleo et al., 2024; Bernard, 2022) and how these changes contribute to broader circuitry variations.

Resting-state functional magnetic resonance imaging (rsfMRI) is a neuroimaging technique commonly used to study the functional dynamics of elderly cohorts as it is non-invasive, not confounded by task demands (i.e., task differences that may reflect physical aging as opposed to cognitive aging) and can be used to study the functional dynamics that support neural function *in vivo*. While most rsfMRI studies measure blood oxygenation level dependent (BOLD) signal changes using functional connectivity (FC; (B. Biswal et al., 1995; B. B. Biswal et al., 2010; Smitha et al., 2017)), voxel-wise measures

such as the amplitude of low-frequency fluctuations (ALFF; (Yu-Feng et al., 2007)) and fractional-ALFF (fALFF) capture the intensity of BOLD signal fluctuations between 0.008-0.1 Hz, reflecting spontaneous neural oscillations. These measures exhibit high reproducibility (Cahart et al., 2023; Golestani et al., 2017; X.-N. Zuo et al., 2010) and demonstrate characteristic differences across various brain disorders (Hrybouski et al., 2025; H. Zhang et al., 2019), suggesting they contain neuronal and physiological information that differ in clinical populations. Aging-related cortical changes have also been identified using ALFF and similar metrics, with older adults producing lower amplitude of BOLD within 0.01-0.1 Hz (A. C. Yang et al., 2018a; Zhong & Chen, 2022). Cerebellar aging has primarily been studied through cortico-cerebellar FC (Bernard et al., 2013, 2020; Gellersen et al., 2021; Hausman et al., 2020; Uwisengeyimana et al., 2020). To our knowledge, no study has explicitly focused on aging-related changes of (f)ALFF in the cerebellum.

Prior work has reported positive associations between ALFF and FC, raising the possibility that regions with greater low-frequency BOLD amplitude may also exhibit stronger functional coupling (Di, Kim, et al., 2013; Mascali et al., 2015; Tommasin et al., 2017). However, neurovascular reactivity, the ability of cerebral blood vessels to dilate in response to a stimulus, can also influence both BOLD amplitude and inter-regional correlations, providing a physiological mechanism by which (f)ALFF and FC may covary independently of neuronal coupling (Liu et al., 2017). In the context of aging, older participants demonstrate decreased BOLD amplitude and variability (Garrett et al., 2010, 2013; Millar et al., 2020) as well as decreased long-range FC (Z. Zhou et al., 2023). Aging can also reduce the hemodynamic response through decreased neurovascular coupling

(Tarantini et al., 2017; Yabluchanskiy et al., 2021), which in turn can reduce the BOLD amplitude and SNR, resulting in lower FC (Liu et al., 2017). Age-related changes in cerebellar-cortical connectivity appear to differ across cerebellar sub-lobular regions, with some studies reporting increased FC to the cortex in older adults (Mccarthy et al., 2014; Tomasi & Volkow, 2012b), potentially reflecting regional preservation, compensatory recruitment, or changes in neurovascular dynamics. Together, these findings indicate that local BOLD amplitude differences in the cerebellum may be indicative of age driven shifts in its connectivity to cortical regions.

The goal of this study was to identify a robust metric for studying functional differences within the cerebellum associated with age. To compare differences between young adults and older adults, we utilized data from a public cohort of rsfMRI data via the Human Connectome Project (HCP) Young Adult S1200 and Aging datasets. Our first step consisted of a control analysis. In both cohorts, we evaluated and compared potential physiological/data quality confounds with our metrics of interest, ALFF and fALFF, within the cerebellum. After characterizing these differences, we calculated regional ALFF and fALFF within the cerebellum to identify aging-related BOLD frequency differences within the cerebellum, accounting for the potential confounds identified in our control analysis. Next, we conducted a repeatability and reliability assessment to establish the reliability of age group differences across scan sessions. We then explored aging-related differences in functional connectivity between key cerebellar regions identified using resting-state frequency-based metrics and the cortex.

4.1 Materials & methods

Participants

The HCP Young Adult S1200 has an available database of 860 participants acquired on a Siemens 3T Connectom scanner at Washington University (Marcus et al., 2011) while HCP-Aging has 726 participants acquired on Siemens 3T Prisma across 4 different sites (Harms et al., 2018), 338 of whom are 60 and older. An *a priori* power analysis was conducted to determine the required sample size using a two-tailed independent samples t-test with target power of 0.8 and a significance level of 0.05. Required sample sizes were estimated across a range of effect sizes (Cohen's d). A minimum of 100 participants (50 per group) was required to detect group-level differences at a reasonable effect size (d= approximately 0.5). To accommodate potential exclusions during quality control, we randomly selected data from 70 young adults (YA; 35 female) and 70 older adults (OA; 35 female) from the HCP Young Adult S1200 and Aging datasets. All YA were between 18 and 35 years old, while OA were between 65 and 79. Participants were considered if they successfully completed 2 resting-state scanning sessions on 2 separate days for a total of 4 rsfMRI scans and HCP documentation indicated no quality issues during scan acquisition. Quality control included: visual inspection to ensure adequate rsfMRI coverage of the cerebellum, removal of participants with large amounts of movement (described below), and hand-correcting cerebellum white/gray matter segmentation. After quality control, 61 YA and 59 OA subjects remained.

Imaging data

Details on the acquisitions for HCP-YA 1200 can be found in (Glasser et al., 2016; Van Essen et al., 2012). Briefly, each participants' T1-weighted MPRAGE scan (0.7mm isotropic), T2-weighted FLAIR scan (0.7mm isotropic), 1 baseline resting state (rs) scan

(TR: 720ms, phase-encoding: R-L, spatial resolution: 2mm isotropic, duration: 14.4 minutes, multi-band factor: 8) and 1 follow-up rs-scan separated by at least one day were used for analysis. YA rsfMRI data was truncated to the first 541 samples (a duration of approximately 6.5 minutes) to achieve a scan duration comparable to OA acquisition.

For OA, the T1-weighted MPRAGE (0.8mm isotropic), T2-weighted FLAIR (0.8mm isotropic), and 2 separate rsfMRI acquisitions on 2 separate days (TR: 800ms, phase-encoding: P-A, spatial resolution: 2mm isotropic, duration: 6.5 minutes, multi-band factor: 8) for a total of 4 rsfMRI images were used for analysis (Fig 1B). Further details on the acquisitions for HCP-A can be found in (Bookheimer et al., 2019).

Image preprocessing

Distortion effects were corrected using spin echo scans acquired on the same day, processed with FSL's topup. Preprocessing of the distortion-corrected rsfMRI followed the minimal preprocessing pipeline (Glasser et al., 2013), which includes: correction for head movement and spatial distortion, registration to structural data, rigid alignment to the MNI152 atlas, and functional artifact removal. No smoothing was performed. The first 5 timepoints were discarded to account for initial relaxation effects. CONN (RRID:SCR_009550) release 20.a (Nieto-Castanon & Whitfield-Gabrieli, 2020) was used for preprocessing. Frame outliers were identified in the Artifact Detection Tools (ART) toolbox within CONN and was defined by movement greater than ±0.5mm or global BOLD signal changes above 3 SD. Subjects that had greater than 10% frame outliers in an individual session were removed from analysis. Framewise displacement (FD) was computed using CONN. This was performed in subject space at each timepoint by considering a 140x180x115mm bounding box around the brain and estimating the largest

displacement among six control points placed at the center of these bounding-box faces (Nieto-Castanon, 2020).

Denoising was conducted in CONN and did not include detrending, as previous methodological studies have found that detrending can bias (f)ALFF metrics and decrease repeatability (Woletz et al., 2019). Six principal components were included as confound regressors, derived from: linear regression of movement, CSF, and white matter (Woletz et al., 2019). The denoised signal was then Fourier transformed and bandpass filtered to [0.008 0.1] Hz. Voxel-wise maps of ALFF were calculated as the average power in the frequency filtered spectrum (Figure 4.1). fALFF was similarly calculated by dividing the average power in the [0.008 0.1] Hz range by the power across the full, non-filtered spectrum. (f)ALFF maps were normalized to the average whole brain (f)ALFF to enable comparison across participants (Küblböck et al., 2014; Xi et al., 2012).

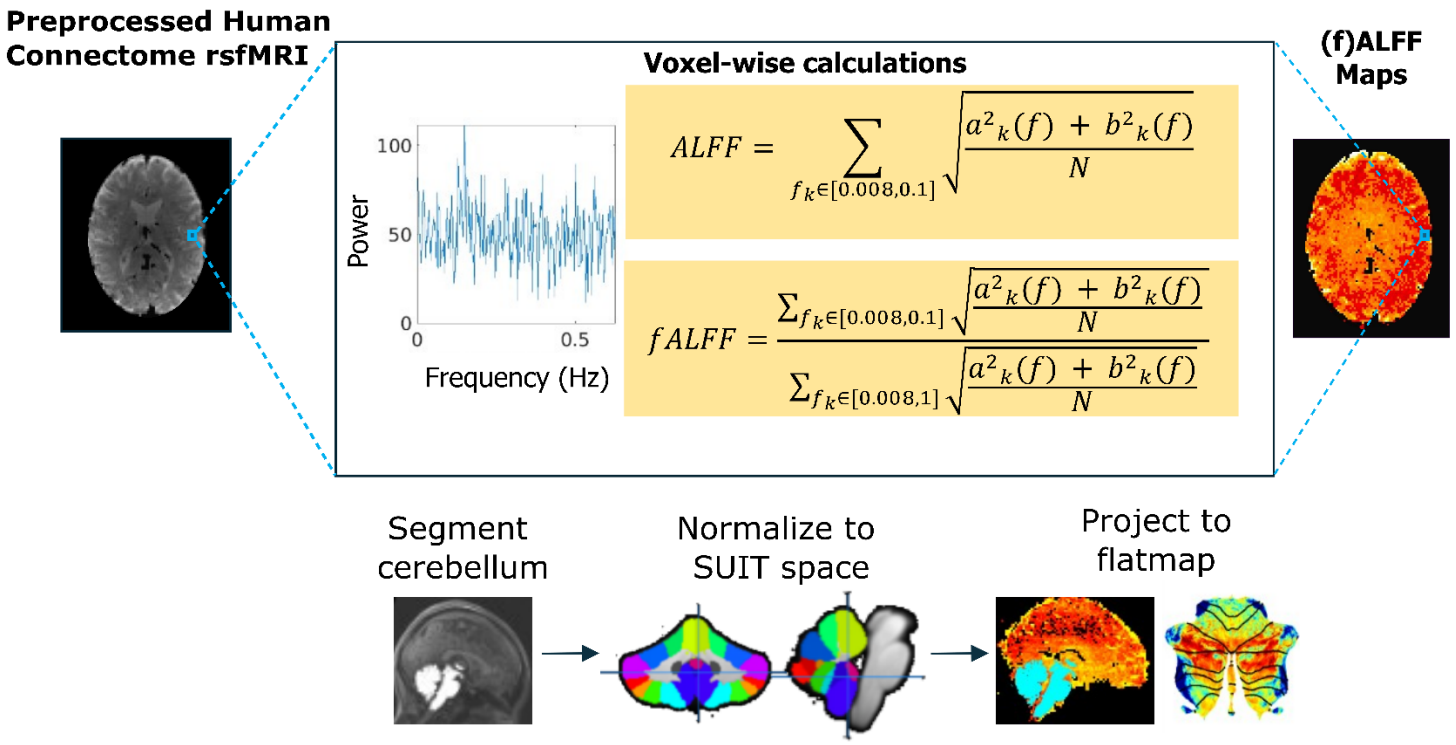


Figure 4.1. Analysis of ALFF and fALFF measures. *(A) Schematic for the voxel-wise calculation of the Amplitude of Low Frequency Fluctuations (ALFF) and fractional ALFF (fALFF). (B) Processing steps for isolating the cerebellum using the Spatially Unbiased Infra-tentorial Template (SUIT) atlas*

Statistical analyses

After (f)ALFF normalization, cerebellar segmentation, and removal of movement outliers, SPM12 (RRID:SCR_007037) (Penny et al., 2006) release 12.7771 was used to register structural and functional maps to the Spatially Unbiased Infra-tentorial Template (SUIT) cerebellum lobular template (Diedrichsen, 2006; Diedrichsen et al., 2009) (Fig. 1B). This atlas and normalization method was developed for more accurate spatially normalized functional analyses. The resolution of the scans is sufficient to reflect volumetric results at sub-lobular levels (the average volume of each lobule being approximately 114 cm^3 (Diedrichsen, 2006; Zheng et al., 2023), and similar resolution has been used at this level of analysis – e.g., (M. King et al., 2019)). SPM12 was used for all group-level statistical comparisons. Statistical results were projected onto SUIT flatmaps to enable visualization (Diedrichsen & Zotow, 2015). This flatmap reflects the average over several folia for each lobule, and is used only for visualization of results.

Control analysis

The BOLD signal is aliased with physiological effects such as heart rate and respiration [0.05-0.15 Hz] (Attarpour et al., 2021; Q. N. Lee et al., 2023) due to low sampling rates (Liu et al., 2017; Power et al., 2017). Compared to cortical regions, BOLD signal in the cerebellum exhibits similar heart rate-related fluctuations but is more sensitive to respiration (van der Zwaag et al., 2015), with inferior regions being particularly vulnerable to these physiological confounds. Aging has been found to increase cardiac effects in the BOLD signal of white matter regions (Viessmann et al., 2019); moreover, cortical BOLD amplitude is highly associated with cardiovascular and cerebrovascular factors (Tsvetanov, Henson, Jones, et al., 2021). All of this indicates that

the cerebellar BOLD signal is susceptible to respiratory and cardiac effects, which are differentially affected by aging and will affect resulting (f)ALFF values. Accordingly, we wanted to evaluate how physiology may explain group-level differences in cerebellar ALFF/fALFF measures. To do this, global BOLD (gBOLD), the average BOLD signal across the whole brain, was correlated with cerebellar BOLD at a voxel level. gBOLD signal is reflective of a multitude of factors such as vascular coupling, scanner noise, head movement, and even potentially neuronally-driven slow oscillations, but is often attributed to "physiological noise" (Addeh, Williams, et al., 2025; Keilholz et al., 2017). Physiological noise typically references systemic effects from heart rate (Chang et al., 2009) and respiration (Liu et al., 2017; Raitamaa et al., 2021), two factors highly affected by age. gBOLD was used as a proxy of physiology as opposed to direct measurements from HCP data due to the low number of participants with usable recordings (J. Fan et al., 2025). Results were evaluated using a lenient threshold (uncorrected $p<0.001$, cluster size > 10) (Bernard et al., 2013; Kwak et al., 2010). Additionally, differences in gray matter volume probability (GMVp) maps were compared between groups to identify areas where age-related structural degradation may contribute to frequency differences. Finally, the temporal signal-to-noise (tSNR) ratio was calculated for each participant's scan to address potential BOLD amplitude differences between cohorts. This is a voxel-wise metric calculated after preprocessing the data, and is the mean BOLD signal divided by the standard deviation over the scan duration. Again, a lenient threshold was used to evaluate group-level statistics.

Analysis

ALFF and fALFF ((f)ALFF) maps were compared between younger versus older groups to identify cerebellar regions that are sensitive to age using a voxel-wise one-way t-test. All statistical analyses were evaluated with a family-wise error (FWE) height correction of p-FWE<0.05. Only clusters a minimum voxel size of 10 voxels are shown graphically and considered for FC analysis. Mean framewise displacement as reported by CONN, cerebellar gray matter probability volume, and correlation with global BOLD were used as covariates for group comparisons.

Repeatability and reliability assessment

Repeatability refers to the variation of repeat measurements made on the same participant, while reliability refers to the inherent variability between participants (Bartlett & Frost, 2008). To quantify regional variability in ALFF/fALFF, each participant's cerebellar map was averaged within each SUIT anatomical ROI, excluding the dentate regions due to resolution constraints, for a total of 28 individual regions. For each ROI, we obtained one mean ALFF/fALFF value per participant for session 1 and session 2. Test-retest reliability was then assessed by computing an Intraclass Correlation Coefficient (ICC) value (Shrout & Fleiss, 1979) for each cerebellar ROI across participants, using the paired regional values from the two resting-state sessions. Additionally, Bland-Altman plots for (f)ALFF over the whole cerebellum were generated to compare repeatability of both metrics across separate sessions.

Functional connectivity analysis

To explore how local cerebellar BOLD dynamics relate to broader functional coupling, the largest cluster from fALFF group differences was selected as a seed region for functional connectivity (FC) analysis in CONN (region indicated by the red arrow in

Figure 4.3). Each individual's time series within this cerebellar ROI was extracted and used for voxel-wise correlation to the cortex. The resulting Fisher's correlation map was then normalized to the MNI152 atlas and smoothed with a 6-mm full-width at half-maximum (FWHM) Gaussian kernel. This process was repeated for each participant's separate resting-state session.

For each individual, the average connectivity between each cortical region defined by the Yeo/Buckner atlas (Buckner et al., 2011) and the cerebellar fALFF ROI was computed for each session. These values were then concatenated across sessions, resulting in FC of 104 separate regions with repeated observations per subject. A multivariate linear mixed effects model was generated with FC as the dependent variable and mean framewise displacement (mFD), sex, session, and group assignment (younger versus older, with Younger Adults as the reference group) in MATLAB, with participant as a random effect to account for 2 sessions per person. To control for multiple comparisons, a positive False Discovery Rate of p-FDR<0.001 (Benjamini & Yekutieli, 2005) was applied to the resulting correlations. ROIs that demonstrated significant group-level differences were reported.

4.2 Results

Control analysis

OA had significantly higher mFD than YA for session 1 (OA = 0.141±0.063, YA=0.087±0.026, p<0.0001) and session 2 (OA =0.142±0.056, YA =0.093±0.026, p<0.0001). GMVp was significantly higher in YA than OA in medial regions of Crus I/II (Figure 4.2A); however, correcting for GMVp in regions of ALFF and fALFF differences did not alter cluster extent of group differences. Correlation of gBOLD with voxel-wise

cerebellar BOLD was not significantly different between groups (Figure 4.2B). When the resulting group T-statistic map was visually compared with a venous probability map, there was high visual correspondence with venous locations (Supplementary Figure A4.1). To quantify similarity to group-level ALFF and fALFF differences, the resulting t-statistic map from gBOLD correlation analysis was binarized using an uncorrected threshold level of $p<0.05$. Binarized clusters from group-level ALFF and fALFF analysis were compared using a dice coefficient. ALFF t-statistic maps had a dice value of 0.404, while fALFF t-statistic maps had a dice value of 0.0196. tSNR comparison revealed that overall, OA had higher signal than YA (Figure 4.2C).

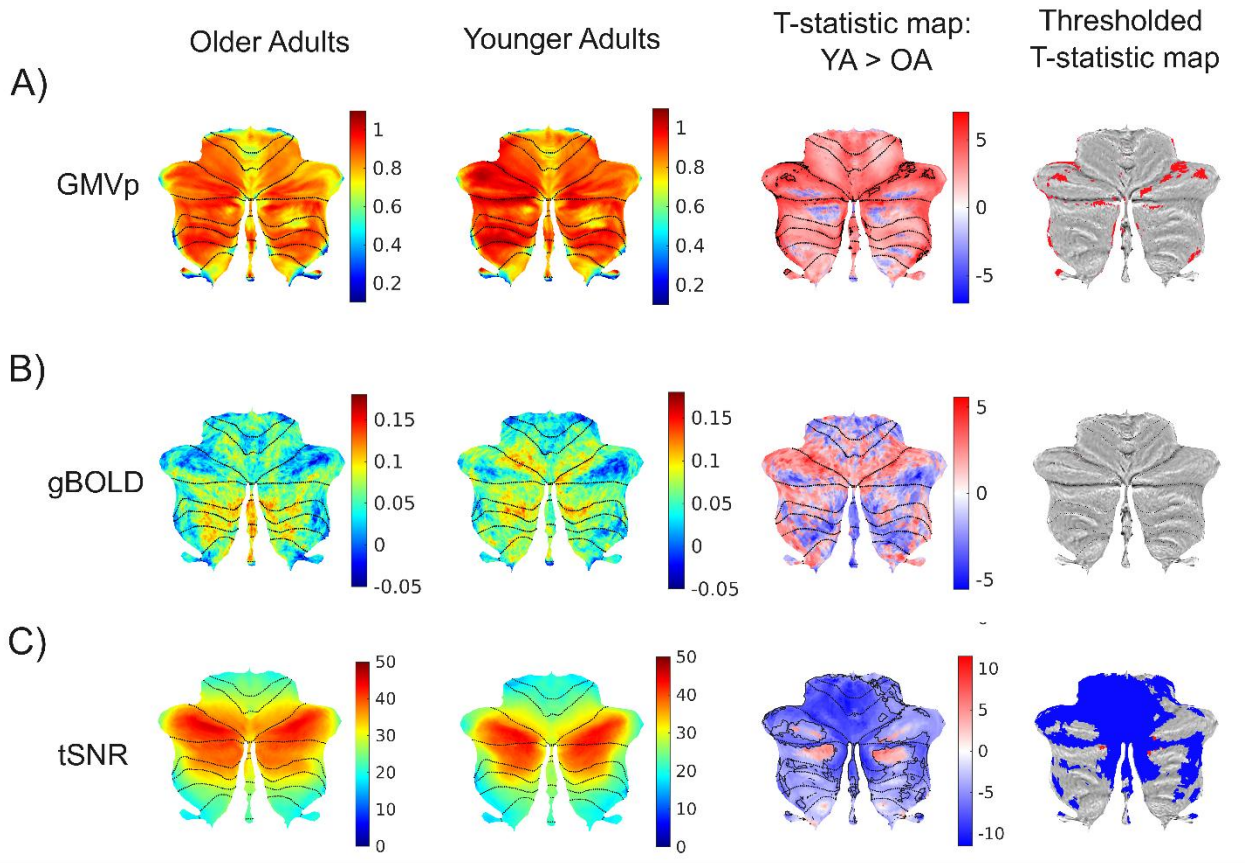


Figure 4.2 Comparison of global BOLD (gBOLD) correlation, cerebellar gray matter probability, and temporal signal-to-noise (tSNR) between age groups. *Group-averaged results for respective control analyses for Older Adults (OA; left column), Young Adults (YA; middle column), and the resulting t-statistic map (red indicates where YA > OA, blue indicates where OA > YA). The thresholded t-statistic results are shown in the right-most column. Areas where YA > OA are shown in red, while OA > YA is shown in blue.* ***(A)*** *Group-level gray matter volume probability (GMVp) map comparisons. Areas that passed multiple comparison correction are outlined in black. The largest of these clusters is 16 voxels, suggesting minor differences between the two groups.* ***(B)*** *Resulting beta values of the correlation of gBOLD signal with voxel-wise cerebellar BOLD between OA and YA. There were no voxels that survived the lenient threshold (p < 0.001, p-FWE < 0.05, cluster size > 10 voxels).* ***(C)*** *Group-level temporal signal to noise ratio (tSNR) map comparisons. Overall, OA had greater tSNR than YA. Regions that survived the lenient threshold (p < 0.001, p-FWE < 0.05, cluster size > 10 voxels) are outlined in black in the t-statistic column and highlighted in the thresholded column.*

Aging-related differences in cerebellar BOLD low-frequency amplitude

ALFF revealed significant differences between OA and YA within the cerebellum after cluster correction. Specifically, YA clusters exhibited significantly higher ALFF than OA in bilateral Lobules I–V, VIIIB, IX, and X (p-uncorrected<0.001, p-FWE<0.05, cluster size>10; Figure 4.3A). Cohen's effect size of group differences (d = 0.54) suggests a moderate practical significance. No significant clusters remained when the t-test was conducted in the opposite direction.

OA had higher fALFF in Crus I and II across both hemispheres as compared to YA after multiple comparison correction (p-uncorrected<0.001, p-FWE<0.05, cluster size>10; Figure 4.3B). Cohen's effect size value (d = 0.16) suggests that this group difference is more difficult to detect. No significant clusters remained when the t-test was conducted in the opposite direction. The largest cluster in Crus I/II was used for subsequent functional connectivity analysis.

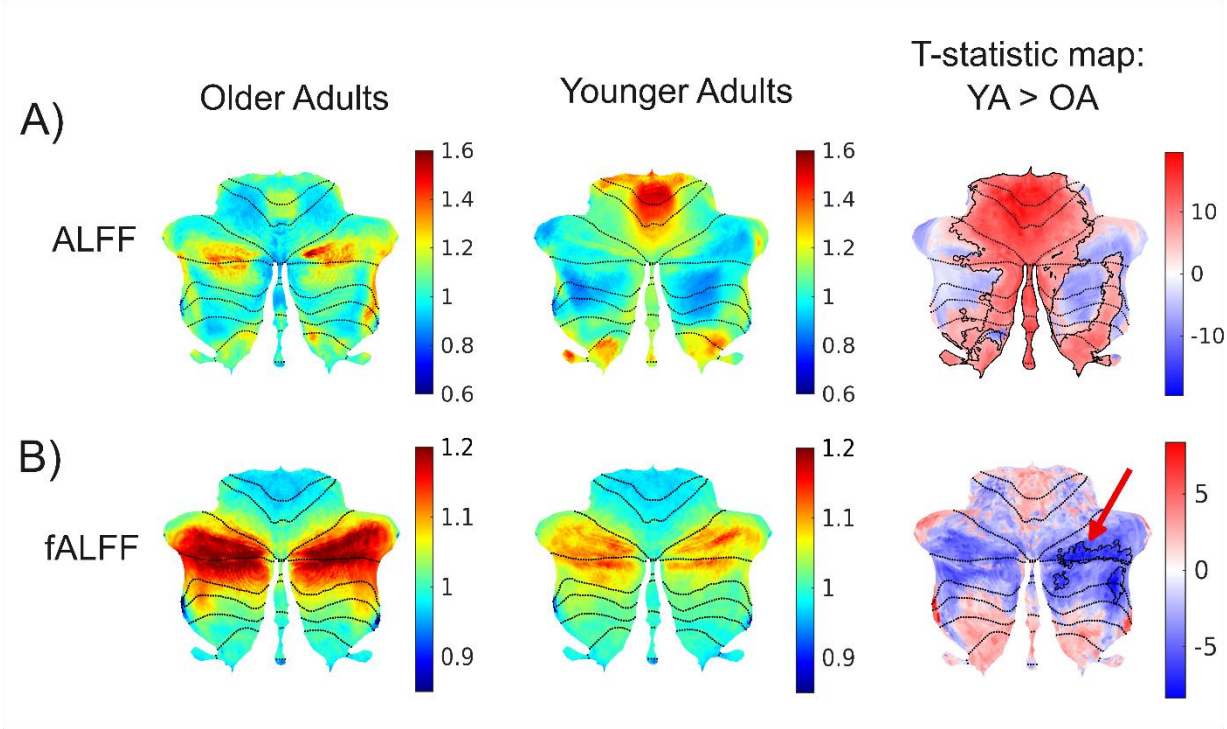


Figure 4.3 Age-related differences in regional cerebellar ALFF and fALFF values. *Group-averaged ALFF maps for Older Adults (OA; left column), Young Adults (YA; middle column), and the resulting t-statistic map after accounting for covariates (p-uncorrected < 0.001, p-FWE < 0.05, minimum extent of 10 voxels; right column). Red values indicate areas where YA had higher ALFF than OA, while blue indicates the reverse. Regions that survive cluster correction are outlined in black on the t-statistic map. (A) Regions that demonstrate significant group differences for ALFF values are located medially in Lobules I-V, and laterally in Lobules VIIIB, IX and X. In these clusters, YA had higher ALFF (Mean = 1.920, SD = 0.829, 95% CI: [1.712, 2.128]) than OA (Mean = 1.527, SD = 0.613, 95% CI: [1.371, 1.683]). (B) Regions that demonstrate significant group differences in fALFF values are located laterally in Crus I, Crus II and Lobule VIIB. In these clusters, OA had higher fALFF (Mean = 1.675, SD = 0.888, 95% CI: [1.448, 1.902]) than YA (Mean = 1.543, SD = 0.816, 95% CI: [1.338, 1.748]). The red arrow indicates the Crus I/II cluster used for functional connectivity analysis.*

.

Repeatability and reliability assessment

Bland-Altman plots of average cerebellar ALFF showed clear group-level differences (OA N = 59, μALFF = 0.824; YA N = 61, μALFF = 0.927), with YA demonstrating greater differences across rs-sessions (OA Δ ALFF= -0.022, YA Δ ALFF = -0.006) (Figure 4.4A). 48% of OA and 79% of YA had an ICC value of 0.8 or greater, indicating moderate to high repeatability for a majority of participants.

Conversely, OA and YA showed similar average cerebellar fALFF across both rs-sessions (Figure 4.4B; OA μfALFF = 0.886, YA μfALFF = 0.905) but smaller inter-session differences (OA Δ fALFF = -0.004, YA Δ fALFF = -0.002). Average cerebellar ICC values increased for both groups with 93% of participants in both groups demonstrating an ICC of at least 0.8, indicating high repeatability. The increased repeatability of fALFF motivated its use for defining an ROI for FC analysis.

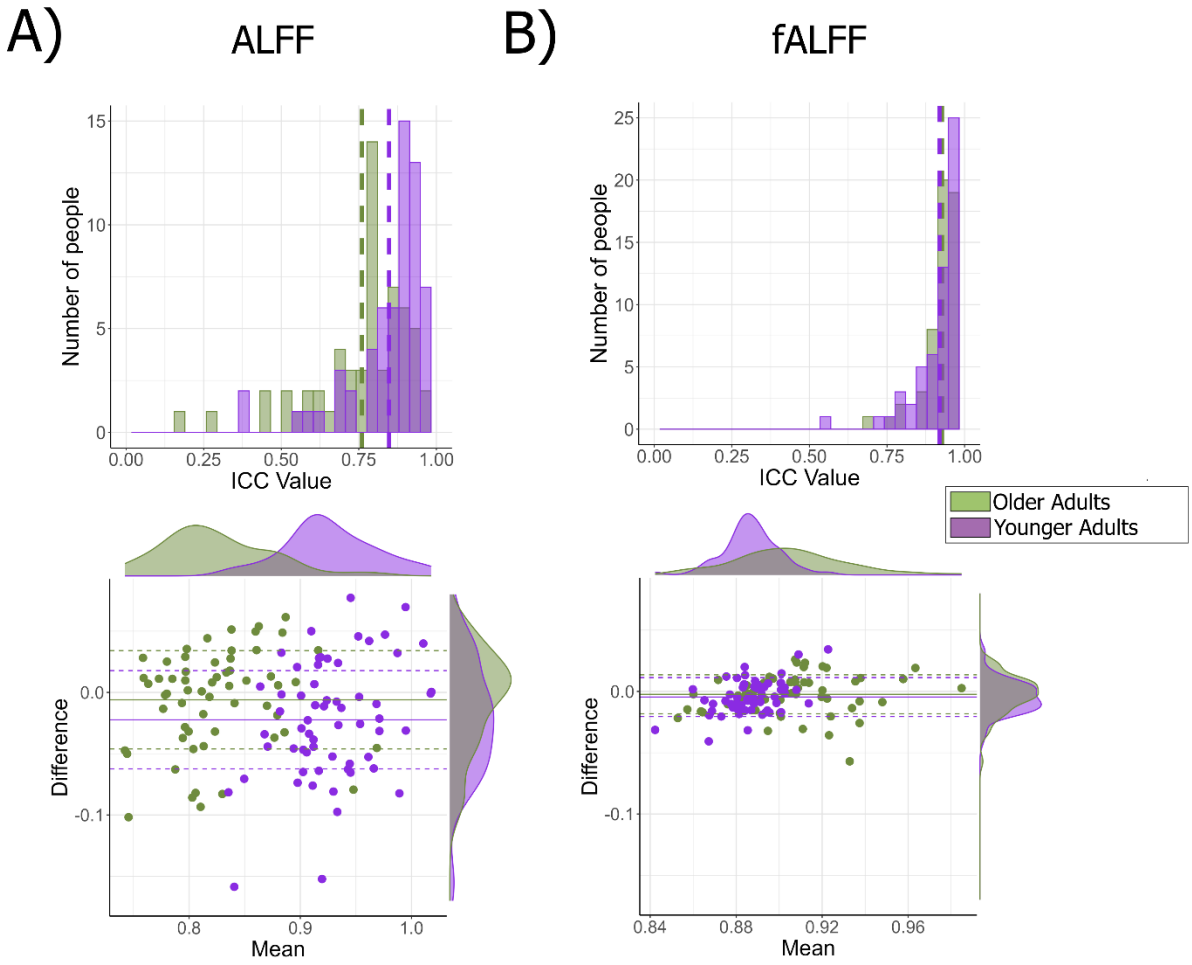


Figure 4.4 Reproducibility assessment of ALFF and fALFF. *Assessment of cerebellar ROI reproducibility using Intraclass Correlation Coefficients (ICCs) for ALFF (left column) and fALFF (right column) in the cerebellum for OA and YA. ICC values and Bland–Altman plots are reflective of repeatability over the entire cerebellum for each participant. (A) Cerebellar ICC and average inter-session Bland–Altman for ALFF. (B) Cerebellar ICC and average inter-session Bland–Altman for fALFF*

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Functional connectivity analysis

Using the fALFF Crus I/II seed as indicated in Figure 4.3 for FC analysis, regions within the DMN demonstrated significant group-level differences in functional connectivity after p-FDR correction across both resting state sessions (Table 4.1). OA demonstrated greater connectivity to cortical regions compared to YA. These regions were located in the right frontal pole (MNI coordinates: x=61, y= -6, z= -18), the posterior cingulate gyrus (MNI coordinates: x=52, y= -56, z=28), and the right lateral occipital cortex (MNI coordinates: x=23 y=36, z=43). Regions that survived a more lenient threshold of p-FDR<0.05 can be found in Supplementary Table A4.1. Sex, session, and head movement measured by mFD did not demonstrate a significant correlation with FC.

Table 4.1 *Multi-linear mixed-effects model reporting group-level differences of FC from the cerebellar seed region, with group as a categorical variable (YA as the reference group) and sex, mFD, and session as covariates for the selected cohort after controlling for random effects (N=120; YA = 61, OA = 59 after quality control). In this model, FC between the Crus II cerebellar seed and the listed ROIs are the dependent variables. Only ROIs that pass p-FDR<0.001 for the group effect are shown. The independent variables are listed below.*

Effect	β	± SE	*T*	*p*-value	*p-FDR corrected*
	Right frontal pole (MNI: x= 61, y= -6, z= -18) Network 16				
Group[a]	1.167	0.219	-5.327	0.0000	0.0000
mFD	-4.438	2.008	-2.210	0.0280	0.1620
Sex[b]	0.423	0.193	2.188	0.0297	0.2318
Session	0.018	0.138	0.129	0.8972	0.9771
	Right lateral occipital cortex (MNI: x= 23, y= 36, z= 43) Network 16				
Group[a]	1.104	0.229	-4.814	0.0000	0.0001
mFD	-3.569	2.104	-1.696	0.0912	0.3282
Sex[b]	0.167	0.202	0.824	0.4110	0.6678
Session	0.073	0.146	0.503	0.6154	0.9688
	Posterior cingulate gyrus (MNI: x= 52, y= -56, z= 28) Network 16				
Group[a]	1.519	0.280	-5.424	0.0000	0.0000
mFD	-2.103	2.573	-0.818	0.4145	0.6890
Sex[b]	0.255	0.247	1.034	0.3024	0.6047
Session	0.151	0.179	0.842	0.4005	0.8723

mFD: mean framewise displacement; β: standardized beta coefficient; SE: standardized error; p-FDR: positive false discovery rate

[a]*The difference in the reported ROI between age groups, with Young Adults as the reference group.*

[b]*The difference in the reported ROI between sex, with male participants as the reference group.*

4.3 Discussion

This study evaluated ALFF and fALFF as potential biomarkers of healthy aging in the cerebellum. ALFF demonstrated significant group-level differences in Lobules I-V, IX and X (Fig. 4.3) along with a moderate effect size, suggesting fair sensitivity (Sullivan & Feinn, 2012) to aging differences. However, these measures were less reproducible when compared to fALFF metrics, as shown in ICC calculations and Bland-Altman plots (Fig. 4.4). fALFF was robust and was greater bilaterally in Crus I and II within the cerebellum in older populations (Fig. 4.3) as a potential spatial signature of typical aging. The largest significant cluster of group-level fALFF differences in right Crus I/II revealed that OA generally has lower FC to this region, particularly within the Default Mode Network (DMN).

Physiological interpretation of ALFF and fALFF

ALFF and fALFF quantify the BOLD signal and reflect both neuronal and cerebrovascular contributions. ALFF is the absolute amplitude of low-frequency BOLD fluctuations (0.008-0.1 Hz) and is therefore sensitive to vascular and venous influences, including cardiac and respiratory effects (Birn et al., 2006; Chang et al., 2009; Esteves et al., 2025; Tong et al., 2012), pulsatility (Glover et al., 2000; Kassinopoulos & Mitsis, 2021), and proximity to draining veins (Di, Kannurpatti, et al., 2013; X.-N. Zuo et al., 2010). In contrast, fALFF expresses low-frequency power as a ratio to the entire frequency spectrum, reducing the effect of systemic noise (Egorova et al., 2017; Huck et al., 2023; X.-N. Zuo et al., 2010). It should be noted that venous influences on the BOLD signal are not restricted to one frequency band. They affect the whole spectrum, meaning normalization does not fully eliminate their impact. However, studies investigating

venous bias on different BOLD metrics have found that this effect is significantly reduced in fALFF compared to ALFF (Huck et al., 2023). This is especially relevant for the cerebellum, which contains numerous draining veins within its compact structure (de Miquel, 2021).

BOLD sign and magnitude are affected by cerebrovascular factors such as cerebral blood flow (CBF) (Shin et al., 2007) and cerebrovascular reactivity (CVR) (De Vis et al., 2018; Y. Gao et al., 2025), resulting in corresponding changes in (f)ALFF magnitude. Notably, these cerebrovascular measures are affected by age, where CBF and CVR decrease with greater age (Tsvetanov, Henson, & Rowe, 2021). Studies that have investigated BOLD amplitude (specifically, resting state functional amplitude; RSFA, a measure of BOLD amplitude that is proportional to ALFF (Chen & Gauthier, 2021; Kannurpatti & Biswal, 2008)) have attributed age-related RSFA differences to physiology as opposed to neuronal influence (Garrett et al., 2017; Henson et al., 2024; Tsvetanov et al., 2015). A study by Tsvetanov and colleagues (Tsvetanov, Henson, Jones, et al., 2021) found that measures of cardiovascular health and CBF were sufficient to account for variance in RSFA across age. Atrophy was not sufficient in explaining age-related differences in RSFA, suggesting limited neuronal contributions to the BOLD amplitude. In the context of understanding group-level differences, this information suggests that while ALFF may contain neuronal information, it is likely to be dominated by physiology. On the other hand, while fALFF is more likely to reflect neuronally relevant information, it does not completely remove cerebrovascular or venous effects.

Interpretation and reliability of ALFF results

Based on our findings and existing work regarding aging and BOLD amplitude, we believe that cerebellar ALFF primarily reflects vascular differences between age groups. YA showed greater ALFF in medial cerebellar regions, which are proximal to the fourth ventricle. Signal measured in these regions of the cerebellum may be particularly susceptible to acquisition-related effects, including T2* decay and spatial blurring along the phase-encoding direction, resulting in greater apparent BOLD signal amplitude and reduced spatial specificity. Consistent with this interpretation, clusters that showed group-level ALFF differences (YA > OA) had a large overlap with regions that showed a gBOLD correlation in the same direction. These regions had a strong visual correspondence with regions of high venous probability (Huck et al., 2019), suggesting confounds with vascular signal. Moreover, OA demonstrated greater tSNR group-level differences than YA. This suggests that lower ALFF in OA is unlikely to reflect reduced data quality, and instead may reflect reduced low-frequency neural variability with age, or increased vascular stiffness resulting in more stable signal baseline and lower ALFF.

The latter interpretation is consistent with prior work that has found ALFF to be more sensitive specifically to venous bias than fALFF (Huck et al., 2023). The contributions of physiology to ALFF serve as a potential explanation as to why test-retest reliability was lower for both groups, as reflected in ICC values and Bland-Altman plots (Figure 4.4). However, the effect size of ALFF differences (d=0.54) indicates a meaningful difference in physiology between YA and OA. Controlling for GMVp did not change the spatial extent of age-related ALFF clusters, suggesting that BOLD amplitude differences are not influenced by structural differences. Although ALFF showed spatial similarity to gBOLD correlations, gBOLD did not significantly correlate with ALFF; therefore, there is

no strong bias from scanner drift, head movement, or physiological noise. Measures of CVR and CBF influence the amplitude of the BOLD signal and would help to disentangle this interpretation. Moreover, these factors are influenced by aging but were not included in this study due to available scan limitations. Future work investigating these physiological metrics and ALFF in the cerebellum can more directly confirm the extent to which ALFF patterns reflect vascular or neuronal aging.

Interpretation and reliability of fALFF results

We identified greater lateralized fALFF in OA within Crus I and II regions (Figure 4.3), regions that have demonstrated the greatest functional correlation/structural connection between prefrontal/frontal regions (Alasmar et al., 2025; Bernard, Seidler, Hassevoort, Benson, Welsh, Wiggins, et al., 2012; Buckner et al., 2011; Krienen & Buckner, 2009; O'Reilly et al., 2010). Given that aging is associated with disrupted DMN integrity and reduced spontaneous cortical activity (Sambataro et al., 2010; Schroeter et al., 2004; Vidal-Piñeiro et al., 2014; X.-X. Xing, 2021; Zhong & Chen, 2022), we anticipated reduced fALFF in cerebellar DMN regions. Instead, we observed higher fALFF in OA. It is important to note that higher fALFF values reflect differences in the relative contribution of low-frequency power rather than a direct measure of neuronal activity alone. A decrease in high-frequency BOLD signal amplitude can also lead to lower ALFF values while simultaneously elevating fALFF. fALFF values demonstrated high test-retest reliability (Figure 4.4) and cluster extents of group differences were not affected after taking GMVp or gBOLD into account (Figure 4.2). Regions that demonstrated fALFF group-level differences did not overlap with regions that showed tSNR differences; however, OA overall demonstrated greater tSNR across the cerebellum. Higher tSNR may

reflect reduced high-frequency noise, increasing the relative contribution of low-frequency power and resulting in higher fALFF values.

Low frequency amplitude and functional connectivity

Our findings demonstrate elevated cerebellar BOLD signal in OA and increased connectivity between fALFF-defined cerebellar regions and subregions within the DMN. Previous studies have noted decreased DMN connectivity with age (Damoiseaux, 2017; Jones et al., 2011b; Park & Reuter-Lorenz, 2009; Varangis et al., 2019). However, fALFF is typically interpreted to reflect increased spontaneous neural activity partly influenced by functional connectivity (Q.-H. Zou et al., 2008). Age-related changes in FC are not uniform across all regions or networks, and have been reported to vary within the DMN itself with aging (Campbell et al., 2013; C.-C. Huang et al., 2015). Moreover, FC differences with age are heterogeneous, with longitudinal studies reporting non-linear relationships between FC and age (Luo et al., 2019; Malagurski et al., 2022) as well as cerebellar structure and age (Romero et al., 2021b). FC analysis of cortico-cerebellar networks by Bernard and colleagues (Bernard et al., 2013) reported that older adults were more likely to demonstrate increased connectivity to frontal regions, a pattern interpreted as reflecting altered or increased engagement of cerebellar networks. Our observed increase in FC associated with fALFF-defined regions may reflect similar alterations in cortico-cerebellar connectivity across age groups.

There are several non-neuronal explanations as to why we see increased rather than decreased FC in OA. Reduced BOLD signal variability in OA (as indicated by increased tSNR and decreased ALFF), greater head motion (with Crus II demonstrating increased sensitivity to slow head motion (Tomasi & Volkow, 2012b)), or differences in

vascular compliance may all result in spurious long-range connectivity. Notably, while both groups demonstrated minimal head motion, both OA and YA had a negative correlation between mFD and FC. Van Dijk (Van Dijk et al., 2012) found that head motion resulted in varied functional connectivity changes depending on the network of interest, with DMN connectivity decreasing with increasing head motion. Together, these findings suggest that increased cerebellar FC in older populations may arise from a complex interaction between age-related network reorganization and non-neuronal age-related factors that influence BOLD variability and amplitude.

Limitations

There are several limitations to our study. First, image acquisition site and protocol are confounded with the separate age cohorts. YA were scanned at a single site with one protocol, while OA were scanned across multiple sites with a different protocol. The HCP site collection and data acquisition were developed to minimize differences between the separate datasets (Harms et al., 2018) but there remain inherent differences in signal due to protocol and hardware (Adhikari et al., 2019), that may be confounded with the separate cohorts. tSNR has been used to compare differences in HCP data quality attributes (Chan et al., 2026) and was used in our study to at least partially provide insight into image quality differences. Our finding of greater tSNR in OA aligns with other studies that have compared image quality between the HCP cohorts (Chan et al., 2026), however we cannot conclude if these differences are cohort- or acquisition-driven. Future studies with harmonized protocol would help to confirm our results.

Additionally, our sample size of N=120 is modest compared to larger fMRI studies. While this limits generalizability and statistical power, the effect size and our reliability

analysis suggests that these results are consistent and repeatable. As mentioned earlier, existing literature has reported differences within DMN connectivity with age (Sambataro et al., 2010; Schroeter et al., 2004; Vidal-Piñeiro et al., 2014; X.-X. Xing, 2021; Zhong & Chen, 2022), but we did not find group-level FC differences in our analysis. Other cortico-cerebellar FC studies have found connectivity differences with age (Bernard et al., 2013; Uwisengeyimana et al., 2020). This may reflect methodological differences, as these studies used whole cerebellar anatomical lobules as seed regions and used voxel-wise comparison, while we used a data-driven approach to define a seed and conduct seed-to-ROI analysis. It is also important to note that using group differences in fALFF may bias our FC analysis to reflect group differences. While prior work has utilized similar methods (Di, Kim, et al., 2013; L. Fan et al., 2019; Wang et al., 2021), future work should employ independent datasets or cross-validation approaches to confirm our results. Additionally, to provide a physiological interpretation of cerebellar (f)ALFF, we used gBOLD as an indirect measure of physiology. Direct physiological measures such as breathing and heart rate recordings can be used, but these can be corrupted and difficult to use for removal of physiological confounds (Addeh et al., 2023; Addeh, Vega, et al., 2025). gBOLD has been used as a general measure of physiology (Liu et al., 2017). We did not regress this signal out using global signal regression as it can contain information important to aging effects, but included it as a covariate in our analysis. Future studies with a larger cohort, direct measurements of physiology, and complementary FC approaches will be important in confirming the findings presented here.

4.4 Conclusions

Our study provides a potential biomarker of healthy aging in the cerebellum using ALFF as a measure of vascular differences and fALFF as a potential measure of neuronal cerebellar differences. In the context of aging, there are several hypotheses as to how circuitry within the brain varies; however, these hypotheses are limited to cortical regions (Cabeza, 2002b; Davis et al., 2008; Reuter-Lorenz et al., 1999; Reuter-Lorenz & Cappell, 2008) and do not include subcortical regions (MacDonald & Pike, 2021b). In summary, we found that increased BOLD fluctuations in subregions of the cerebellum with age coincides with an increased relative FC to the cortex. Our findings highlight the need to include the cerebellum, among other subcortical structures, in functional models of compensatory or dedifferentiation changes in aging.

Chapter 5 – Effects of aging on long-term consolidation and retention of motor adaptation

5.1 Introduction

Although older adults (60 years and older; OA) often learn novel tasks at slower rates compared to their younger counterparts (18-35; younger adults, YA), procedural learning and memory is posited to be preserved with age (Churchill et al., 2003; Mitchell, 1989; C. D. Smith et al., 2005). This stands in contrast to other memory systems that are negatively affected by aging. Preserved motor learning is essential for maintaining independence in older adulthood, allowing individuals to adapt movements to changing physical capabilities and recover function following injury or disease. Motor learning/memory tasks are often characterized as mainly procedural systems; however, work over the last several decades has demonstrated that motor learning requires both implicit (procedural) and explicit (declarative) learning components (Maresch et al., 2021; Morehead et al., 2017; Taylor et al., 2014a; Tsay et al., 2024). As a result, similar overall motor performance may conceal age-related differences in how the task is learned or memorized.

Age-related effects on motor adaptation, a specific type of motor learning, are heterogeneous, with studies reporting preserved or impaired learning depending on the task and learning process examined (E. A. Christou, 2011; Fernandez-Duque & Black, 2006; Vachon et al., 2020; Zvornik et al., 2024). Visuomotor adaptation tasks provide a well-established model for investigating age-related changes in motor learning as implicit and explicit components can be measured independently (Taylor et al., 2014a). In these tasks, performance is generally thought to be similar between YA and OA, which is mainly

attributed to OA's greater dependence on implicit processing (Vandevoorde & Orban de Xivry, 2019, 2020). Studies that have looked into retention of motor adaptation in OA are limited (B. R. King et al., 2013). OA have demonstrated motor transfer, the ability to learn new task variants, between different magnitudes of perturbation even after testing 1-2 days following initial training (Bock & Schneider, 2002; Seidler, 2007), suggesting that retention of motor adaptation is not impaired in OA. However, this hypothesis has not been directly tested, and it remains unclear whether age-related differences in motor adaptation are expressed in the longer-term stability of the motor memory (B. R. King et al., 2013). Examining adaptation following a one-week interval provides an opportunity to investigate whether age-related differences emerge after an extended period of motor memory retention. The use of a counter-perturbation (a perturbation in the opposite direction) in the following session provides a behavioral assessment of how prior adaptation influences relearning, probing how retention and subsequent adaptation is affected by age.

Retention of visuomotor adaptation tasks is attributed to cortico-cerebellar networks (Attwell et al., 2002; Hadjiosif et al., 2024; Okamoto et al., 2011), while the exposure phase (early trials) of adaptation are associated with function in cortico-striatal and frontal networks (Della-Maggiore et al., 2015; Gentili et al., 2011; Koralek et al., 2012). Behavior in these initial trials and the associated neural correlates are proposed to be more susceptible to aging effects (Bakkum et al., 2021), resulting in OA demonstrating reduced initial performance during re-exposure. Resting state fMRI (rsfMRI) provides an opportunity to examine resting-state (rs) patterns associated with individual differences in longer-term retention and subsequent adaptation. This *in vivo* neuroimaging

technique has previously been used to detect offline changes in spontaneous functional activity as a result of motor learning, potentially reflecting networks that predict learning and adapting of motor skills (Cassady et al., 2018; Della-Maggiore et al., 2015). The fractional Amplitude of Low Frequency Fluctuations (fALFF) is a semiquantitative metric that demonstrates high repeatability across sessions (Cahart et al., 2023; Golestani et al., 2017; X.-N. Zuo et al., 2010) driven in part by connectivity to associated networks (X.-N. Zuo et al., 2010), and has been used to capture age-related changes in the low-frequency power of blood oxygenation-level dependent (BOLD) signal (Korte et al., 2026; A. C. Yang et al., 2018b; Zhong & Chen, 2022). As a result, the combination of semi-quantitative rsfMRI with behavioral performance in the same participant may provide insight into the neural correlates of motor adaptation retention across extended periods.

The main goal of this study was to assess long-term consolidation and retention of motor adaptation task in OA compared to YA, and to identify associated neural markers. Given the effect of age on explicit contributions (Anguera et al., 2011; Vandevoorde & Orban de Xivry, 2019, 2020), we hypothesized to observe age group distinctions to be seen when comparing performance of overall and explicit learning during later testing sessions. By introducing an opposite perturbation during the second session, we expected minimal improvement in OA's overall performance during session 2, potentially driven by reduced consolidation processing in OA (Brown et al., 2009; Roig et al., 2014). We further hypothesized that poorer performance would be driven by decreased explicit contributions. In contrast, we expected YA to demonstrate faster re-learning due to greater explicit contributions. We planned to explore associated neural correlates of these performance differences by conducting rsfMRI in a subset of individuals.

5.2 Methods

Participants

Participants were recruited from the local Davis and Sacramento area, as well as through the University of California Davis (UCD) Alzheimer's Disease Research Center (ADRC). All participants were healthy and reported no history of neurological or psychiatric disorder. If recruited through the UCD ADRC, cognitively normal participants were confirmed through a battery of tests, including the Montreal Cognitive Assessment (MOCA) and consensus diagnosis at clinical case conference with neurological evaluation. If recruited outside of the UCD ADRC, participants self-reported no neurological conditions and underwent the Mini-Mental State Exam (MMSE) testing, as well as the Trails Making Task (TMT) A and B. Participants signed a consent form approved by the UC Davis Institutional Review Board. Two younger adults and one older adult were excluded due to failure to follow instructions in the motor task or poor task performance. A total of 30 YA and 27 OA were included for analysis (Table 1).

Visuomotor Rotation Apparatus

The visuomotor rotation task set-up is similar to what has been previously described (Bindra et al., 2021a). Briefly, participants sat at a horizontal 27-inch LCD monitor (refresh rate, 60 Hz) mounted 10 inches above a Wacom digitizing tablet (12 by 19 inches, Inutos 4, Wacom, 200 Hz sampling rate) (Figure 5.1A). A custom handle containing the tablet stylus was used to control a 0.3 cm diameter cursor on the screen. Each participant's hand location was occluded by the monitor, and subjects were instructed to only look at the screen. The midline of the participant was aligned with the

midline of the screen. A rotation knob was provided to the left of the tablet (3.8 cm diameter) for subjects to select their aiming direction prior to each reaching movement.

Visuomotor Rotation Paradigm

On each trial, participants reached from a starting position located at the center of the screen to a target presented 10cm away along the midline. At the start of the trial, an orange arrow was presented to the participant with a rotational axis located at the starting position. The arrow direction could be changed using the associated knob presented to participants (Figure 5.1A). Subjects were instructed to rotate the arrow to indicate their aiming direction for the planned reaching movement, so that the cursor landed inside of the target. After selecting the position using the dial, participants made their reaching movement. Feedback on the speed of reaching movement was given for each trial and was indicated by changing the color of the target. Blue was used to indicate a movement that was too slow (< 200 ms), red indicated too fast (> 800 ms), and green indicated the ideal speed (< 800 ms, > 200 ms). This feedback corresponded only with speed, and not with movement accuracy.

On perturbed trials, after the reaching movement exceeded the target distance, static end-point visual feedback was provided. Following one second of end-point feedback, the cursor disappeared and a circle appeared that scaled with the hand distance from the starting position. As participants' hand distance moved back towards the start, the radius of the circle became proportionally smaller. Once the hand was within 2 cm of the start, the cursor reappeared so that subjects could enter the start target to begin the next trial.

The task structure was maintained across groups and sessions (Figure 5.1B). This included 20 familiarization trials of veridical feedback, 40 baseline trials of veridical feedback (20% of which randomly had visual feedback removed), followed by 65 training trials (5 veridical, 60 perturbed). The perturbed trials had an offset of 45 degrees from the actual movement trajectory. The first session was randomly selected to be either a perturbation clockwise or counterclockwise. The second session had a similar task structure, but was counter-balanced in direction. The initial 65 veridical trials of the second session were treated as a washout block in between competing perturbation directions.

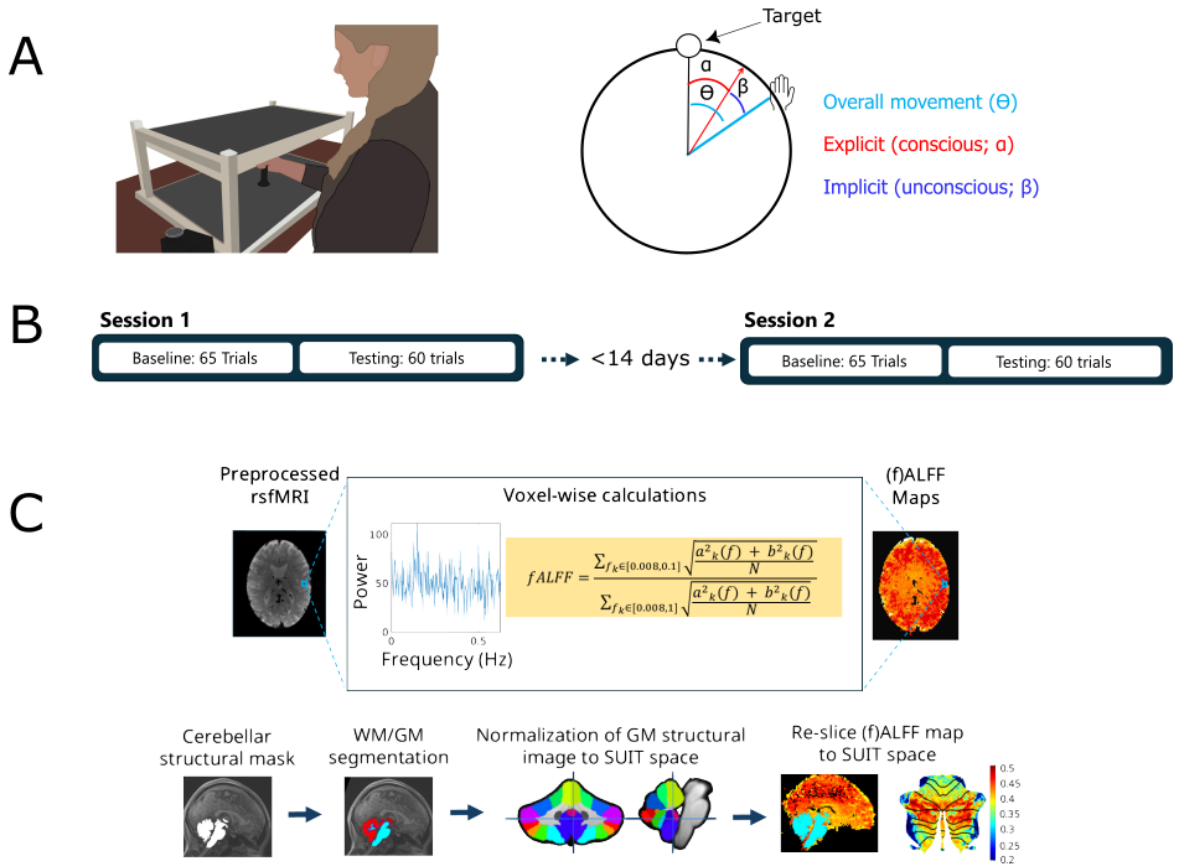


Figure 5.1 Task set-up and rsfMRI preprocessing steps. A) *Left: A schematic of a participant at the visuomotor rotation (VMR) set-up. Right: Implicit, explicit, and overall movement directions were measured by the angle offset from the target presentation, positioned directly in front of the midline, 10cm away from the starting point. Implicit learning is determined by the difference between overall hand movement and explicit movement selection.* ***B)*** *Task structure for all participants. Veridical feedback was provided for the first 60 trials in the first block. The second block consisted of 5 veridical trials followed by 60 trials of perturbed feedback at 45. Participants returned within a 14 day time period for re-testing in a similar block setup, but with a counter-perturbed direction.* ***C)*** *Top row: A schematic for voxel-wise fALFF calculations. Bottom row: cerebellar segmentation steps utilizing the SUIT atlas (adapted from (Korte et al., 2026)). The cerebellum was segmented using the SUIT toolbox, and white/gray matter was segmented. The SUIT atlas was warped to each individual participant, and the deformation applied to the relevant atlas..*

Behavioral Analysis

Data was analyzed offline using MATLAB 2021b and R Studio version 4.5.1. Trials that had too slow or fast movement speeds (peak speed <0.2 or > 0.5 m/s), long selection time (selection time > 30s), reaching movement before aiming selection, or overall movement outliers (±3 S.D. from a moving mean window of 3 trials) were excluded (13% of total trials from YA and 18% from OA over both sessions).

The average learning of early trials (trials 5-10 after perturbation onset) was calculated for each individual's overall, implicit, and explicit traces, for each session. Savings, a measure of how quickly performance is relearned upon re-exposure, was calculated using the difference in average early trials between sessions. A second metric of savings was evaluated using the change in the rate of learning across sessions. To do this, a simple exponential (Equation 1) was fit to each individual's overall, implicit, and explicit performance during the perturbation block of each session. The amount of learning (y) over each trial *t*, depends on the rate of learning (k) and the scaling terms (y_1 and y_2), where y_1 determines the asymptote. Savings was then evaluated as the difference in the *k* rate between sessions. The data was fit using the *lsqcurvefit* function in MATLAB with an initial starting point of [45, -1, 0.1] for y_1, y_2, and k, respectively. As a result, savings values were computed at an individual level.

$$Equation\ 1.\ y = y_1 - (y_1 - y_2) \cdot e^{-k \cdot t}$$

Each participant's relative performance was also calculated as the percentage contribution of the 'final adaptation': the average overall performance of the last 5 trials in the perturbation block. This was done to account for individuals that could not adapt to the 45° perturbation during the testing session, and to visualize relative contributions

of implicit and explicit mechanisms across the testing period. The final behavioral metrics used for correlation with imaging were: $\Delta k_{implicit}$, the difference in rate of learning between sessions for the implicit component; $\Delta \mu_{explicit}$, the difference between sessions of early trials of the explicit component; and $\Delta \mu_{overall}$, the difference between sessions of early trials of the overall learning.

rsfMRI Data Acquisition

Resting state functional MRI was collected from a subset of participants with either a 3T Siemens Prisma or a 3T Siemens Skyra scanner in Sacramento or Davis, respectively. 11 younger (21.4 ± 4.6 years, 3 females) and 11 older adults (73 ± 7.4 years, 5 females) consented to return after behavioral testing for a rsfMRI scan. All participants signed an MRI consent form approved by the University of California Davis Institutional Review Board. An EPI-BOLD resting state fMRI scan (TR: 825 ms, TE: 35 ms, flip angle: 50 degrees, phase encoding direction: P-A, voxel size: 2.5 mm^3, 64 axial slices), T1-weighted MPRAGE (TR: 2300 ms, TE: 2.98 ms, flip angle: 9 degrees, voxel size: 1 mm^3, 256 axial slices), and a T2-FLAIR (TR: 5000 ms, TE: 3.93 ms, flip angle: 90 degrees, voxel size: 1 mm^3, 208 axial slices) were obtained from each participant. For the resting state scan, participants were instructed to lay awake in the scanner and to not think about anything.

rsfMRI Preprocessing

Distortion effects were corrected using field mapping scans acquired in the same session, processed using FSL's *feat* command. Preprocessing of the distortion-corrected rsfMRI followed a minimal preprocessing pipeline and followed steps outlined in our previous rsfMRI study (Korte et al., 2026). Briefly, after artifact removal and rigid alignment to the MNI 152 atlas, preprocessing was conducted in CONN

(RRID:SCR_009550) release 20.a (Nieto-Castanon & Whitfield-Gabrieli, 2020). Frame outliers were identified in the Artifact Detection Tools (ART) toolbox within CONN and was defined by movement greater than ±0.5mm or global BOLD signal changes above 3 SD (Nieto-Castanon, 2020). Denoising included identifying six principal components for confound regressors derived from linear regression of movement, cerebrospinal fluid (CSF), and white matter. All subsequent analysis was conducted in each individual's T1 anatomical space.

Imaging analysis

For quality assessment, each participant's gray/white/CSF segmentation was visually inspected. After visual inspection, the temporal signal-to-noise (tSNR) for each voxel was calculated. tSNR was calculated for each voxel by measuring the voxel's average signal and dividing by the standard deviation of the signal (Welvaert & Rosseel, 2013). One younger adult was excluded from analysis due to poor segmentation, while another older adult was excluded from analysis due to poor overall tSNR resulting in a total of 10 participants in each group.

fALFF was computed at the voxel level by conducting a Fourier transform of the denoised signal, and bandpass filtering to [0.008 to 0.1] Hz. The average power of this frequency band compared to the average power of the full, non-filtered spectrum is calculated for each voxel. The resulting fALFF map is then normalized to the average whole-brain fALFF (Figure 5.1C; (Küblböck et al., 2014; Xi et al., 2012)). After calculating fALFF maps, the deformation of the Spatially Unbiased Infratentorial Template (SUIT) cerebellar atlas was calculated for each participant's T1w-image (Diedrichsen, 2006) and applied to the Nettekoven asymmetrical atlas (Nettekoven et al., 2024), while the 17-

network Yeo atlas (Thomas Yeo et al., 2011) was warped to individual space for cortical ROI analysis.

Behavior-imaging analysis

We selected between-session differences of early adaptation as our primary behavioral outcome as this captures the initial expression of previously acquired motor memories following the multiple day delay, making it well suited for investigating age-related differences in motor relearning. Behavioral analysis was correlated with imaging metrics on an ROI basis, using the individual regions of the Yeo 17-network atlas to calculate ROI fALFF. Analysis of underlying neural contributions to $\Delta\mu_{overall}$ focused on fALFF in default mode network (DMN) regions, given the association between DMN connectivity and offline motor adaptation learning (Cassady et al., 2018). A Bonferroni correction of alpha=0.0056 was used to evaluate these correlations. For explicit savings, ROIs corresponding to the left and right dorsolateral prefrontal cortex (DLPFC) were selected for comparison to $\Delta\mu_{explicit}$, as medial frontal regions are recruited in early adaptation and associated with explicit processes (Anguera et al., 2010; Ikkai & Curtis, 2011; Seidler et al., 2012). We correlated fALFF with savings metrics, accounting for age group and time in between sessions as covariates (Equation 2).

After identifying fALFF in the left DLPFC was associated with $\Delta\mu_{explicit}$, another seed-to-voxel analysis was performed using the left DLPFC as the seed region. Connectivity associated with $\Delta\mu_{explicit}$ was examined while controlling for age group. Again, because of the small sample size, we used a lenient threshold to identify regions (p-uncorrected <0.001, cluster size >30).

$$Equation\ 2.\ Behavior = fALFF_{ROI_x} + age\ group + Time\ between\ sessions$$

Because no significant age-group differences were observed in implicit performance and that the cerebellum is central to the formation and retention of internal models, we next examined whether intrinsic cerebellar activity was associated with implicit metrics. Cerebellar ROIs within anterior motor-associated regions (i.e., lobules I-IV and V) and posterior cognitive-associated regions relevant to adaptation (i.e., working memory regions within Crus I and II) were considered, for a total of 8 regions. A linear model with behavior ($\Delta k_{implicit}$) as the dependent variable, and fALFF and time between sessions as dependent variables was compared to a model that contained age group as an additional dependent variable (Equation 2). Equation 2 had the lower AIC value and was used for further analysis. Significant ROIs were evaluated using a Bonferroni correction of alpha = 0.00625.

After identifying fALFF in the right Crus I was associated with the change in implicit rate of learning, fMRI data was normalized to the MNI atlas and a seed-to-voxel analysis was performed using right Crus I as the seed region. Connectivity associated with $\Delta k_{implicit}$ was examined while controlling for age group. Given the small sample size, we used a lenient threshold to identify regions (p-uncorrected <0.001, cluster size >30).

5.3 Results

Motor adaptation

A two-sample t-test revealed significant group-level differences in the amount of time between testing sessions with OA having a longer duration between testing sessions than YA (p=0.021). OA also performed slower on the TMT-A (p=0.00081) and TMT-B (p=0.0024), but groups demonstrated similar MMSE scores (Table 1). Both absolute and

relative measures of overall movement (Figure 5.2) demonstrated similar learning during session 1 across age groups.

Faster relearning in YA was captured in early trial savings of overall performance (Figure 5.3, p=0.0031). When comparing relative and absolute measures, YA demonstrated greater explicit contributions during session 2 compared to OA (Figure 5.3, p=0.001), but implicit contributions were similar between groups across both sessions. Additionally, OA did not demonstrate greater rates or contributions of implicit learning during the second session. As the amount of time between sessions was different between groups, the effect of time between sessions and the amount of savings was evaluated for each group. There was no significant association between any savings metric and the amount of time in between testing sessions, but there was a correlation between TMT-A performance and explicit performance, $\Delta\mu_{explicit}$ (p=0.0397, Supplemental Figure A5.1).

Table 5.1 Participant demographic information. *MMSE, TMT-A, and TMT-B scores are from participants recruited outside of the UC Davis ADRC. There were significant differences between group performance of TMT-A (p=.00017) and TMT-B (p=0.0016), but not MMSE (p=0.78).*

	YA	**OA**
N; Female	30; 16 F	27; 16 F
Age (years)	21.4 ± 3.3	71.5 ± 7.1
Time between testing sessions (days)*	7.6 ± 4.2	9.4 ± 4.1
MMSE	29.4 ± 0.8 **(N = 17)**	29.3 ± 1.04
TMT-A (s) * **	20.1 ± 4.8 **(N = 17)**	29.7 ± 7.4
TMT-B (s)**	41.7 ± 10.2 **(N = 17)**	56.7 ± 12.4

*p<0.05

**p<0.01

***p<0.001

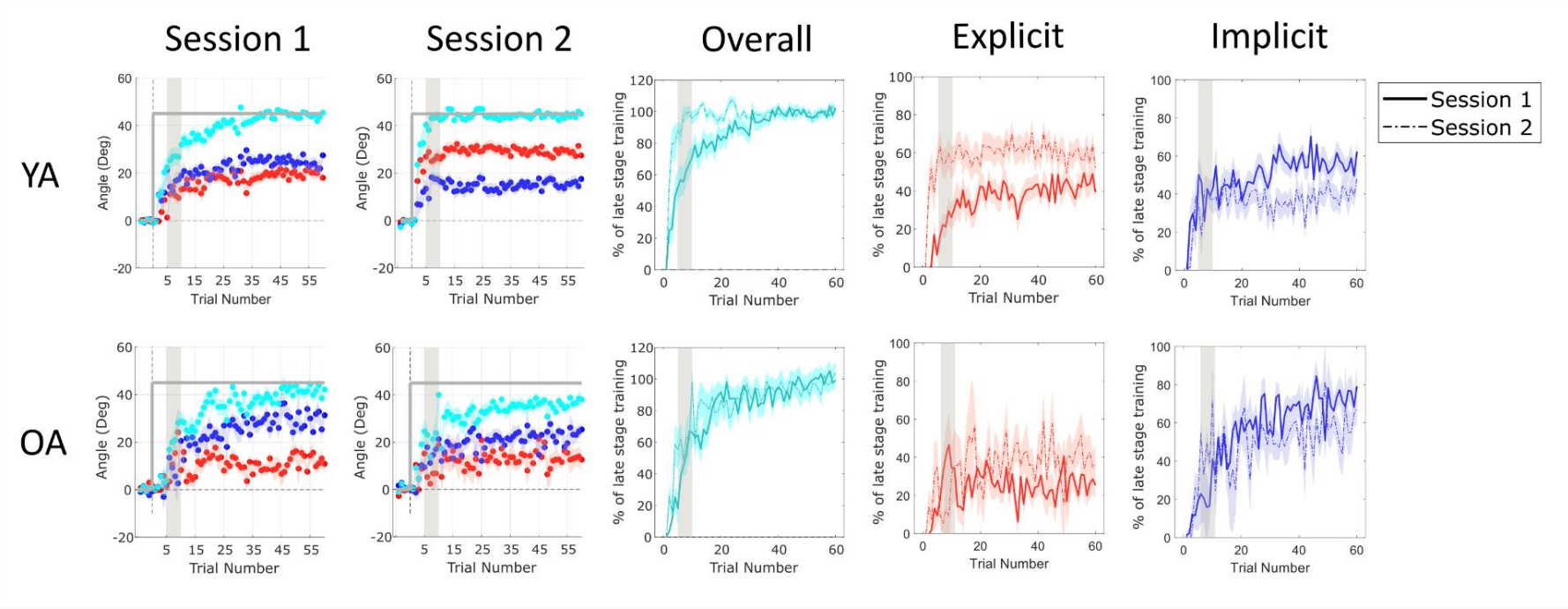


Figure 5.2 Overall, explicit, and implicit learning rates for younger adults *(YA) and older adults (OA). The top row displays the group-level performance of young adults (YA), while the bottom row reflects the group-level performance of older adults (OA). Columns 1 and 2 reflect the measured angle during sessions 1 and 2, where cyan reflects overall movement, red is explicit, and blue is implicit. The onset of the perturbation is indicated by the dark gray line. The following columns reflect the relative performance across all participants of the overall, explicit, and implicit components respectively, where performance is normalized to the final overall adaptation in each session (i.e., the average overall movement of the last 5 trials). Solid lines reflect relative performance during session 1, while dashed lines reflect session 2 performance. Shading around the lines denotes ± 1SEM. The gray rectangle indicates the 'early trials' – trials 5-10 following perturbation onset.*

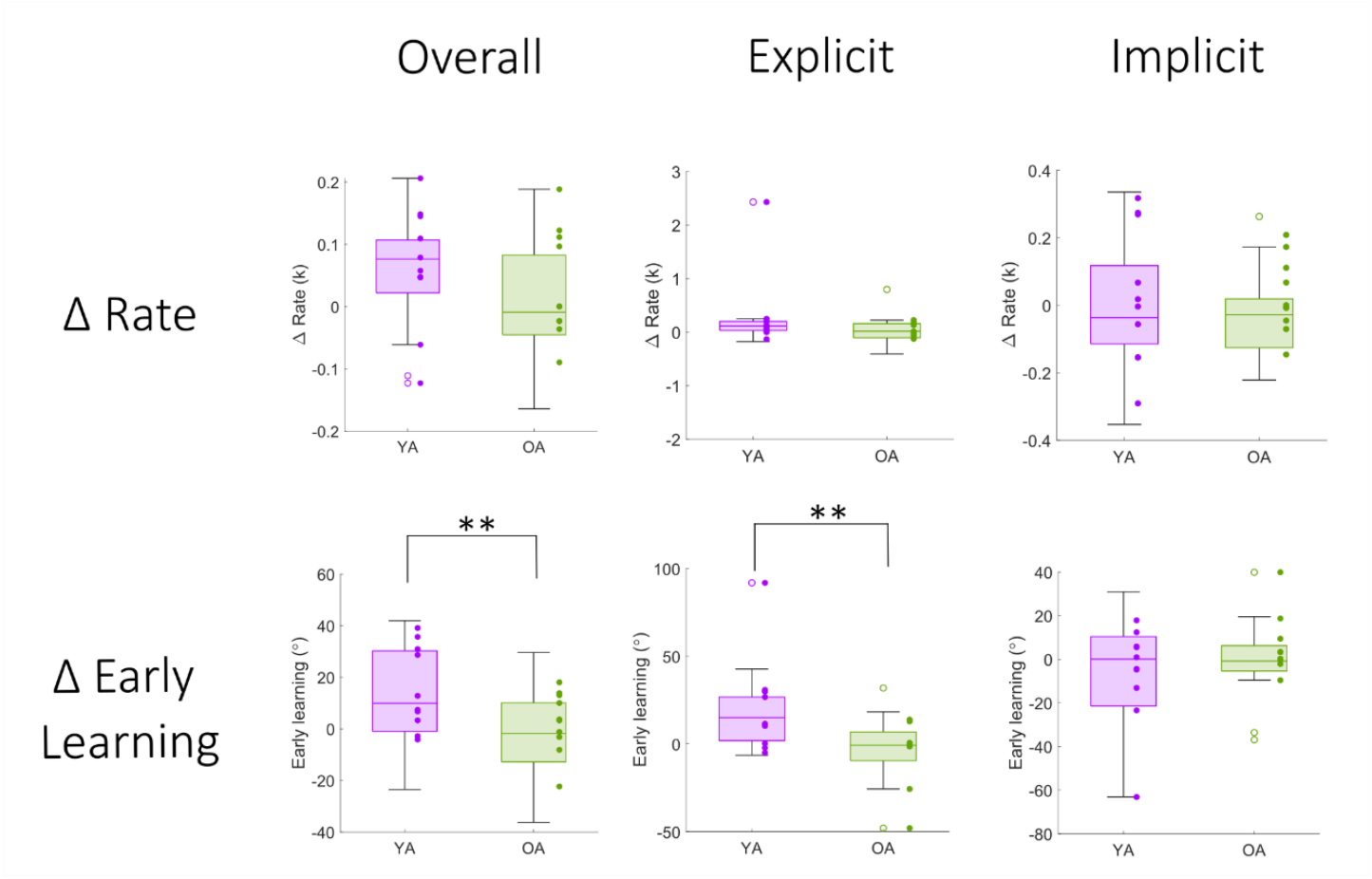


Figure 5.3 Quantification of the change in rate and early learning between sessions. *Absolute values (in degrees) were used to evaluate both the change in rate and the change in early trial performance. The change in rate of learning across sessions was not significantly different between groups; however, the overall learning rate trended higher for YA than OA. The change in overall (p=0.0031) and explicit (p=0.001) learning between sessions was significantly higher for YA than OA. Filled dots indicate performance for the subset of participants that also underwent rsfMRI.*

***p<0.01*

Changes in explicit learning correlated with fALFF in the left DLPFC (Table 5.2). In contrast, overall savings was not associated with fALFF in any DMN region. As a result, functional connectivity (FC) analysis focused on identifying neural correlates of explicit savings. The left DLPFC, identified in the fALFF analysis, was used as the seed for a seed-to-voxel analysis. FC between the left DLPFC and the rest of the brain was examined in relation to explicit savings while controlling for age group and time between sessions (Figure 5.4). Savings was positively correlated with FC between the left DLPFC and the left frontal medial cortex (MNI: x = -6, y = 58, z = -12; cluster size = 66), the right subcallosal cortex (MNI: x = 6, y = 12, z = -20; cluster size = 30), and the left cingulate gyrus (MNI: x = -8, y = 38, z = 18, cluster size = 75).

Table 5.2 *Linear mixed-effects model reporting differences in explicit savings associated with fALFF in the left DLPFC, with age and time in between sessions as covariates (N = 20).*

	β ± S.D.	***p-value***	***T-statistic***
fALFF*	114.9 ± 53.0	0.046	2.17
Group [a]*	-28.4 ± 10.4	0.015	-2.73
Time between sessions	0.098 ± 0.072	0.194	1.36

[a]*The difference in the measured savings metric (explicit savings, early trials) between age groups, with Young Adults as the reference group.*

*p<0.05

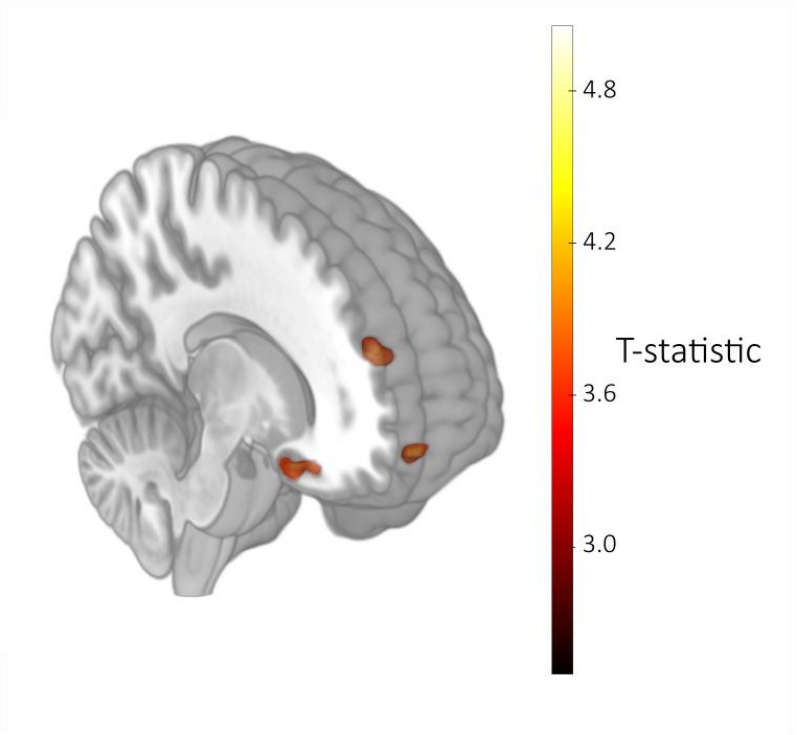


Figure 5.4 Regions where functional connectivity to the left DLPFC is associated with explicit savings. *Explicit savings was correlated with FC to the left DLPFC after controlling for age group, revealing three clusters with significant FC: the frontal medial cortex, the right subcallosal cortex, and the left cingulate gyrus (p-uncorrected<0.001, cluster threshold>30).*

There were no group differences in implicit measures; however, an exploratory analysis was conducted using this metric to identify regions associated with implicit measures. OA demonstrated similar cerebellar fALFF to YA, but trends were generally higher for OA, particularly in posterior cerebellar regions. Scan quality was comparable between the two groups, as demonstrated with tSNR assessment (Supplementary Figure A5.2). When correlating $\Delta k_{implicit}$ with cerebellar fALFF, only one subregion in right Crus I, region S3R, was significantly correlated with implicit learning rate changes (Table 5.3). Time between sessions also significantly correlated with $\Delta k_{implicit}$ ($p=0.0037$).

Table 5.3 *Linear mixed-effects model reporting differences in implicit savings associated with fALFF in right Crus I, with age and time in between sessions as covariates (N = 20).*

	β* ± *S.D.	***p-value***	***T-statistic***
fALFF**	3.39 ± 0.99	0.0046	3.421
Group[a]	-0.17 ± 0.08	0.057	-2.086
Time between sessions**	0.0025 ± 0.0007	0.0037	3.524

[a]*The difference in the measured savings metric ($\Delta k_{implicit}$) between age groups, with Young Adults as the reference group.*

**$p<0.01$

Based on this cerebellar finding, seed-to-voxel connectivity between right Crus I and the whole brain was conducted in additional exploratory analyses. Connectivity in relation to $\Delta k_{implicit}$ was assessed while controlling for group. A positive association was observed between right Crus I and left Crus I (MNI: x = -38, y = -76, z = -40), a region in the left temporal pole (MNI: x = -44, y = -12, z = -28; cluster size = 77), and the right caudate (MNI: x = 22, y = 26, z = 4; cluster size = 33) (Figure 5.5).

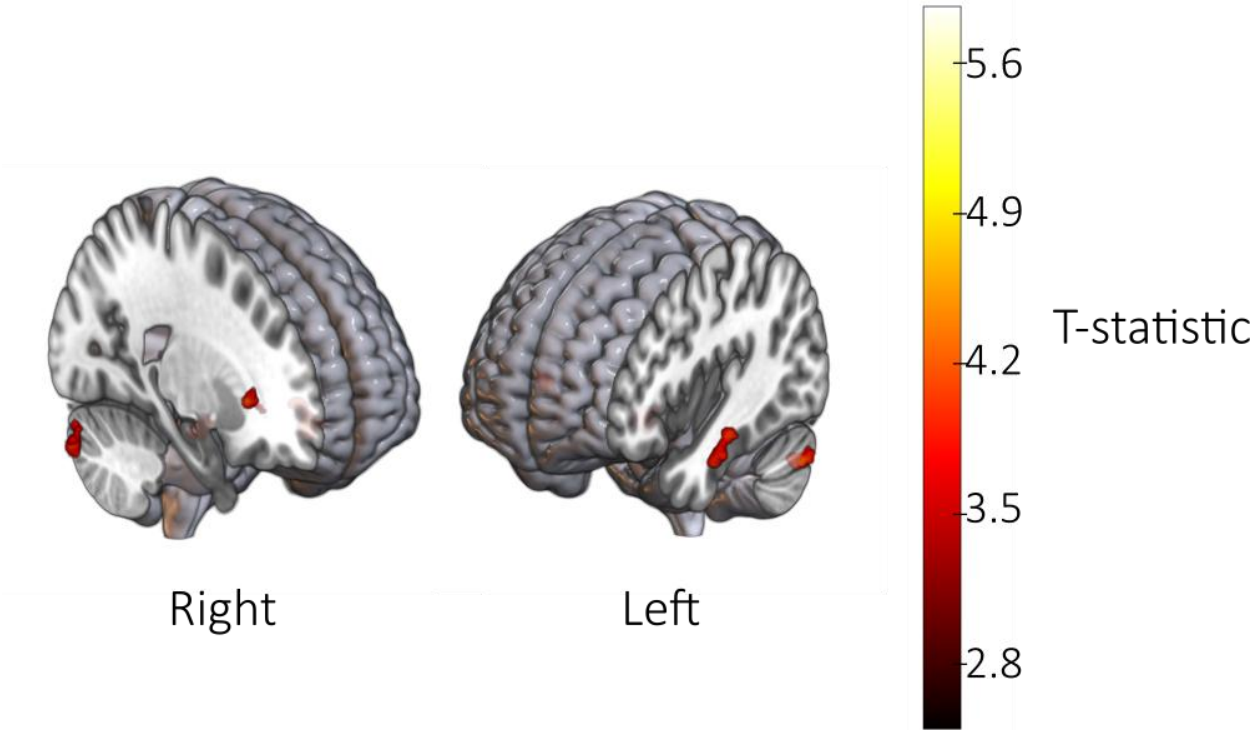


Figure 5.5 Regions where functional connectivity to the right cerebellar Crus I is associated with across-session changes in implicit rate of learning. *Explicit savings was correlated with FC to the right cerebellar Crus I after controlling for age group, revealing three clusters with significant FC: left Crus I, the left temporal pole, and the right caudate (p-uncorrected<0.001, cluster threshold>30).*

5.4 Discussion

Based on previous visuomotor adaptation studies, we hypothesized that OA would demonstrate minimal improvement during session 2 compared to session 1. Furthermore, we hypothesized that greater savings would be attributed to explicit contributions. We found that even in a counter-balanced adaptation task with long delays, YA demonstrated greater explicit contributions to overall performance across sessions compared to OA. Moreover, fALFF in the left DLPFC predicted explicit savings after controlling for age group and time between sessions. Explicit savings was also associated with stronger connectivity between the left DLPFC and medial frontal cortical regions. OA and YA did not differ in implicit contributions, but the rate of implicit learning correlated with fALFF in posterior cerebellar regions across groups.

Behavior

Most studies investigating interference effects have focused on opposite perturbations learned shortly after an initial learning task (V. S. Huang et al., 2011; Krakauer et al., 2005). Aging-related interference studies are limited but also focus on the effect of tasks learned in short succession (Roig et al., 2014). Our study introduces an opposing perturbation after a long duration (7-9 days), probing the extent a previously learned motor task continues to interact with subsequent learning. To distinguish different aspects of relearning, we quantified different timescales of the learning process: early training and trial-by-trial learning across sessions.

Previous studies in aging have reported that OA demonstrate lower explicit learning than YA (Heuer & Hegele, 2008; Vandevoorde & Orban de Xivry, 2019), yet we found that explicit learning was similar during session 1 for both age groups. Instead, age-

related deficits in explicit mechanisms were seen when comparing across-session changes, while implicit contributions were not different between groups (Figure 5.3). One interpretation of these results is that the difference in early explicit adaptation reflect consolidation differences between groups, where OA learn the appropriate explicit mapping, but fail to store the appropriate motor output. However, in healthy adults, consolidation of motor adaptation tasks occurs after 6 hours (Lerner et al., 2020), resulting in improved performance in a different perturbation days after experiencing the first task. These results may also reflect anterograde interference, as OA demonstrated negative explicit differences (i.e, lower explicit values during session 2 compared to session 1) when experiencing the counter-perturbation. This suggests that previously acquired sensorimotor mappings continue to interfere with subsequent adaptation in OA, a trend that has been observed in other motor memory tasks (Roig et al., 2014). However, washout blocks were introduced at the start of each experimental session, and both groups achieved a similar level of asymptotic adaptation during the initial session, suggesting that results are not affected by initial memory 'strength'.

Another interpretation for reduced explicit contributions in OA may be reduced flexibility or task switching. Explicit differences were correlated with performance in TMT-A, a test that reflects processing speed, attention, as well as cognitive flexibility (Stebbins, 2007). Future studies that modify the task used here can explore these potential causes. For example, employing multiple timescales (1 – 6 hours) of counter-perturbed visuomotor tasks or that undergo longer initial training may reveal if poorer task performance in OA is reflective of consolidation differences or anterograde interference (Krakauer et al., 2005). Furthermore, presenting multiple targets may

explore if OA demonstrate deficits in generalizing explicit strategy (McDougle et al., 2017).

The rate of implicit adaptation was similar across groups. Studies focusing on the neural correlates of adaptation suggest that as a motor task becomes consolidated, performance is more reliant on implicit processes supported by the motor cortex and cerebellum (Byczynski et al., 2025; Dahms et al., 2020; Shadmehr & Brashers-Krug, 1997a). Additionally, implicit adaptation is characterized by trial-by-trial updating. Although the implicit learning rate reflects a combination of trial-by-trial error reduction and forgetting (Lerner et al., 2020), we found that implicit learning is stable across groups: fast learners exhibited reduced implicit contributions during the second session, while slow learners demonstrated increased implicit contributions. This suggests that long-term differences in adaptation performance are driven less by continued changes in implicit adaptation and more by the recruitment or refinement of explicit strategies.

Imaging and behavior

Studies have shown that explicit strategies depend on working memory, reflecting a combination of visuospatial working memory (Anguera et al., 2010, 2011; Vandevoorde & Orban de Xivry, 2020) and response caching, or a mapping of appropriate action-outcome associations (Cisneros et al., 2026). Cisneros and colleagues proposed that age-related impairment in explicit contributions are more strongly attributed to working memory related to response-caching as opposed to visuospatial working memory, implicating frontal-hippocampal circuits rather than parietal-cerebellar circuits. The DLPFC is associated with spatial working memory (Barbey et al., 2013) along with its connectivity to parietal regions (Kosslyn et al., 1998). Response caching is also associated

with the DLPFC (Fresco et al., 2023; McDougle & Taylor, 2019b), as well as its connectivity to other frontal regions (Curtis & D'Esposito, 2003). Our imaging findings are consistent with the latter interpretation, as greater explicit savings was associated with intrinsic activity in the left DLPFC as well as stronger connectivity between the DLPFC and other medial frontal regions.

We demonstrated greater explicit savings is associated with greater fALFF, a measure influenced by FC (Q.-H. Zou et al., 2008). Previous studies have reported that resting-state DMN connectivity is a predictor of savings for YA (where in-between testing sessions was approximately 9 days, similar to our study) (Cassady et al., 2018). In Cassady et al., stronger DMN connectivity was associated with greater long-term savings. However, it is important to note that our task compares the effect of interference of an opposite perturbation direction and uses a task design that distinguishes between implicit and explicit learning. We also utilized different *a priori* ROIs for analysis. Nonetheless, DMN connectivity is associated with improved performance in a motor adaptation task. Specifically, within-network connectivity of the DMN has been suggested to play a role in offline learning and consolidation of motor learning (D. A. Cohen et al., 2005; Miall & Robertson, 2006). Notably, this network is commonly implicated in aging, where cortical connectivity within the DMN is lower with age (Damoiseaux, 2017; Park & Reuter-Lorenz, 2009; Varangis et al., 2019). If DMN connectivity is involved in offline learning and typically disrupted by aging, heterogeneity in DMN connectivity, as measured by fALFF, may explain why some OA demonstrate poorer savings than others.

We also found that changes in the rate of implicit learning were positively associated with individual differences in fALFF of cerebellar region Crus I. This region

has been implicated in predictive and adaptive computations beyond simple motor execution (Lesage et al., 2017; Sokolov et al., 2017). Connectivity analysis identified associations between Crus I and bilateral cerebellar regions, as well as cortical regions. FC between the posterior cerebellum and frontal regions have been reported in other non-motor implicit/explicit learning studies (Ma et al., 2023; L. Zuo et al., 2025). Future task-based studies that independently manipulate or measure implicit and explicit learning across acquisition and retention intervals will be important for determining the extent these neural associations are specific to a particular learning component or reflect broader mechanisms supporting offline motor learning.

Limitations

There are several limitations to our study. First, the number of subjects that participated in resting state scans (N=20) is small compared to other rsfMRI studies. While this limits statistical power, our effect size relating imaging and behavior is modest, suggesting that the relationship we see is beyond a spurious effect. Moreover, time between scanning sessions is variable between groups; however, the variable amount of time is taken into consideration in our linear model. The relationship between our imaging data and behavioral data is correlational, as testing is performed asynchronously from the scans. While this limits our understanding of neural mechanisms relating to online retrieval, our focus was on offline consolidation and understanding how network connectivity may reflect behavioral responses. Additionally, the design of our paradigm mainly addressed implicit and explicit contributions to adaptation and does not have a direct measure of other relevant learning processes that may be affected by age or demonstrate interindividual differences, such as reinforcement learning or use-

depending learning. Future work focused on isolating implicit and explicit contributions to motor adaptation could be utilized confirm our findings presented here.

5.5 Conclusions

Our work provides insight into functional measures that predict performance in a long-term, interfering motor adaptation paradigm. We found that OA demonstrate poorer recruitment of explicit mechanisms when faced with an opposite visual feedback perturbation in a sensorimotor adaptation task, and that low frequency amplitude of the BOLD signal in frontal regions are associated with explicit savings, while the rate of implicit learning was associated with frequency amplitude in right Crus I. This work provides insight into the mechanisms that support successful adaptation in older individuals. Establishing how motor learning and its neural substrates change in healthy aging is a critical first step toward distinguishing normative aging from pathological aging. By characterizing behavioral and neural mechanisms that support preserved motor learning in healthy older adults, this work provides a foundation for future investigations that can examine how changes in behavioral processes may serve as sensitive markers of early neurodegenerative disease.

Chapter 6 – General Discussion, Future Work, and Conclusions

6.1 Summary of Key Findings

The goal of our work was to understand how motor learning and its associated neural correlates are impacted by aging. The studies presented in this work suggest that age-related differences are best characterized by the individual components that contribute to overall learning. Specifically, implicit learning was relatively preserved across typical aging, whereas explicit learning demonstrated more apparent differences between younger and older adults. These findings provide a foundation for how motor learning may be altered in neurodegenerative disease, where changes in specific learning processes may provide information beyond traditional measures of cognitive function.

To establish this broader context, we first conducted a literature analysis to identify motor learning measures and associated neural underpinnings that are impacted in atypical aging, specifically in dementia. We found that metrics related to executive functioning demonstrated group-level differences, but that studies that measured function related to implicit learning were limited. Behavioral metrics indicated that these implicit functions may be impaired in AD. The subsequent studies focused on characterizing typical aging-related changes in implicit and explicit regions to understand the neural and behavioral signatures in typical aging.

The next study focused on age-related differences in intrinsic resting state fMRI in the cerebellum for a cohort of 120 participants. We found that the power in a low-frequency, neuronally relevant frequency band (fALFF) was greater in older adults than younger adults, and that this measure corresponded with the within-network functional connectivity of relevant networks, specifically the DMN. Moreover, fALFF demonstrated

high between-session repeatability, demonstrating a robust metric to assess these aging differences. As a result, the processing methods and the metrics used here were used as a foundation for the following analysis.

Our final study evaluated multiday performance differences in a visuomotor adaptation task between younger and older cohort. We found that initial learning was comparable between age groups, but early learning during the second session captured age group differences, particularly for explicit measures. The offline changes in implicit contributions to learning were similar across both groups, suggesting that this is an age-robust process. Subsequent rsfMRI analysis in a subset of participants demonstrated that early explicit learning was associated with fALFF in frontal cortical regions, while the implicit rate of learning was associated with fALFF in cerebellar regions, demonstrating that the frontal cortical region was sensitive to aging, while the cerebellar region was not.

6.2 Significance and contributions to the field

The findings of this work provide a behavioral-imaging framework to assess characteristics of healthy aging. In recent years, the cerebellum has been identified as a significant region of interest in the study of aging, as it contributes to higher-order processing related to social processing, language learning, and executive functioning, in addition to traditional association with gait, balance, and general motor function (Arleo et al., 2024; Nettekoven et al., 2024; Schmahmann, 2019; Sokolov et al., 2017). Our work adds to the growing body of research by identifying rsfMRI analysis techniques and processing methods that can robustly identify these age differences.

Regarding behavior, our study observes differences in a simple motor adaptation paradigm over multiple days and with opposing perturbations. Learning new motor skills

requires application over different days and in different contexts. By expanding the VMR paradigm to a longer time frame, we investigated persistent differences as opposed to short-term differences that may simply reflect slower learning (i.e., reaching the same level of performance at a slower rate) (Ranganathan et al., 2026). Utilizing longer time frames increases the relevance for tailoring rehabilitation programs which may require weeks of training (Olson et al., 2019), and highlights that the mechanisms through which older adults learn matter in the design of rehabilitation practices.

This dissertation characterizes neural changes that may accompany preserved motor learning in typical aging. Older adults demonstrated reliable differences in intrinsic cerebellar activity and its relationship with cortical networks, and these measures were integrated with specific motor learning processes. By having participants perform tasks outside of the MR scanner, we were able to separate intrinsic neural differences from age-related differences in task execution, resulting in a more accessible evaluation of networks that are preserved and susceptible to aging. Moreover, the final portion of this work began to highlight the individual nature of behavior and brain activity, demonstrating the need for individualized evaluation in order to better understand how behavior is related to neural function.

6.3 Future Directions

Task, analysis, and scanning modifications for future studies

There are several modifications that can be made to the existing paradigm, scanning, and analysis that may provide better clarity on the effect of age on offline motor learning. Multiple time points of behavioral assessment can be used to evaluate if behavioral differences are driven by changes in consolidation processes in older adults (e.g.,

experiencing the task after 6 hours as opposed to multiple days, or returning after a longer period of time has passed). The effect of the order of perturbation direction, experiencing different adaptation tasks (e.g., comparing performance in a force-adaptation task, or an implicit/explicit sequence learning task), and comparing multiple time points in interference may provide further evidence of the mechanisms that affect older adults' recall of motor tasks. Additionally, the findings in this dissertation should be explored utilizing more complex motor learning tasks that require coordination of multiple limbs, in order to generalize these findings to translational (i.e., rehabilitation) applications.

Additional resting state scans can be administered over the course of learning to assess how motor learning changes underlying neural function. A baseline scan, in addition to multiple scans after different learning sessions, can provide further insight into the specific network changes that underlie adaptation. Finally, different models can be used to evaluate learning. We used exponential models of learning as they are a relatively straight-forward method for quantifying learning; however, not all people learn in an exponential manner. Different quantification methods learning such as the state-space model (M. A. Smith et al., 2006b) that can identify 'fast' versus 'slow' learning processes, models that evaluate the contribution of proprioception to implicit adaptation (Z. Zhang et al., 2024), which may be relevant in aging changes, or even models that account for the exploratory nature seen in participants (Tsay et al., 2024) may better align with imaging markers. The neural underpinnings of these models can be further investigated by coupling task performance with task fMRI.

Assessing learning and memory changes in memory-impaired populations

We found that implicit-related metrics across long periods of time are robust to aging. Furthermore, our review of motor learning in dementia demonstrated that behavior related to implicit learning may be impaired in cognitively impaired populations. Studies have found that patients with MCI and AD also experience greater degeneration in lateral and posterior regions of the cerebellum. Motor learning paradigms that isolate implicit learning may provide better clarity to the degree to which aging-related changes in the cerebellum affect implicit learning (Cisneros et al., 2026; Morehead et al., 2017). This testing can be applied in MCI and AD populations to understand how this type of learning may be a behavioral marker of cognitive change.

We explored this preliminary idea using a visuomotor rotation task that isolates implicit contributions from Morehead et al. in typical aging older adults as well as one MCI patient (Figure 6.1). The task utilized a clamped visuomotor task, where the cursor is 'clamped' in one offset direction from a presented target, and the participant is made aware of the perturbation. Similar task formats have been used to investigate implicit learning changes in older adults, where older adults demonstrated overcompensation compared to younger adults (Cisneros et al., 2026). Our version of the implicit-only task used instructions that removed the abstract associations typically used in VMR tasks to assist with instruction memory. Instead, the cursor is presented as an airplane, and the goal of the task is presented as landing the airplane on the presented runway, inspired from (McDougle et al., 2022). Two different targets were presented, and the degree of offset over the course of the task was evaluated. General trends demonstrated lower implicit adaptation in the MCI patient compared to the age-matched healthy counterpart. Recruiting more participants and combining these results with rsfMRI can provide

further insight into the connection to associated neural underpinnings that may be associated with cognitive change in aging.

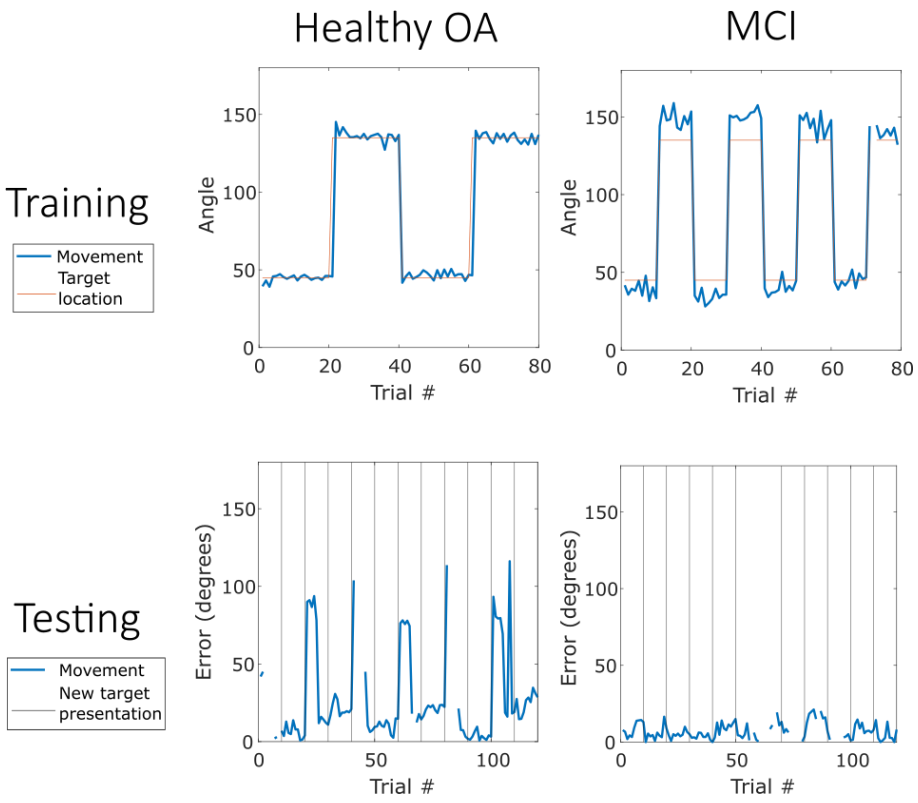


Figure 6.1. Preliminary data from a clamped VMR task with a health older adult (left) and an MCI patient (right). Top row*: performance during a veridical feedback baseline block, with the target locations presented in orange, and the participant heading angle indicated by the blue trace. The MCI patient was given more training targets after feedback from the healthy participant.* ***Bottom row:*** *The error deviation from the presented target during the clamped visual feedback testing session is indicated by the blue trace, while each different target presentation is marked by the vertical black line. During the clamped feedback trials, the healthy participant demonstrated compensation for the visual perturbation, while the MCI participant did not. This preliminary data highlights the potential of motor learning tasks to identify potential cognitive differences in older adults*

Application in rehabilitation

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6.4 Conclusions

Throughout this dissertation we investigated how aging affects learning and retention of motor tasks. Understanding motor learning processes improves outcomes of physical therapy, and also reveals how brain health is impacted in age. We first analyzed motor learning studies that have compared performance in dementia populations with age-matched healthy older adults, and found that measures of implicit behavior potentially demonstrated differences between cohorts. This motivated us to investigate functional differences in healthy older adults compared to younger adults in the cerebellum, a brain region typically implicated in implicit learning, proposed to be preserved in aging, but susceptible to aging degeneration. We utilized a semi-quantitative metric, fALFF, to demonstrate that the low frequency power in older adults is greater in posterior regions of the cerebellum compared to younger adults. Finally, we compared retention of a motor adaptation task across long intervals to assess age-related memory differences in motor learning. We identified group differences in explicit contributions, but no age group differences in implicit learning. We found that these metrics correlated with fALFF in the dorsolateral prefrontal cortex and the posterior cerebellum, respectively. In conclusion, we identified age-sensitive behaviors and associated neural mechanisms that may be used to inform better rehabilitation programs and even investigate behavioral differences in neurodegenerative disease.

References

2023 National Population Projections Tables: Main Series. (2025, February 12). United States Census Bureau. https://www.census.gov/data/tables/2023/demo/popproj/2023-summary-tables.html

Addeh, A., Vega, F., Medi, P. R., Williams, R. J., Pike, G. B., & MacDonald, M. E. (2023). Direct machine learning reconstruction of respiratory variation waveforms from resting state fMRI data in a pediatric population. *NeuroImage*, *269*, 119904. https://doi.org/10.1016/j.neuroimage.2023.119904

Addeh, A., Vega, F., Morshedi, A., Williams, R. J., Pike, G. B., & MacDonald, M. E. (2025). Machine learning-based estimation of respiratory fluctuations in a healthy adult population using resting state BOLD fMRI and head motion parameters. *Magnetic Resonance in Medicine*, *93*(3), 1365–1379. https://doi.org/10.1002/mrm.30330

Addeh, A., Williams, R. J., Golestani, A., Pike, G. B., & MacDonald, M. E. (2025). Physiological Confounds in BOLD-fMRI and Their Correction. *NMR in Biomedicine*, *38*(7), e70076. https://doi.org/10.1002/nbm.70076

Adhikari, B. M., Jahanshad, N., Shukla, D., Turner, J., Grotegerd, D., Dannlowski, U., Kugel, H., Engelen, J., Dietsche, B., Krug, A., Kircher, T., Fieremans, E., Veraart, J., Novikov, D. S., Boedhoe, P. S. W., van der Werf, Y. D., van den Heuvel, O. A., Ipser, J., Uhlmann, A., … Kochunov, P. (2019). A resting state fMRI analysis pipeline for pooling inference across diverse cohorts: An ENIGMA rs-fMRI protocol. *Brain Imaging and Behavior*, *13*(5), 1453–1467. https://doi.org/10.1007/s11682-018-9941-x

Alasmar, Z., Chakravarty, M. M., Penhune, V. B., & Steele, C. J. (2025). Patterns of Cerebellar–Cortical Structural Covariance Mirror Anatomical Connectivity of Sensorimotor and Cognitive Networks. *Human Brain Mapping*, *46*(1), e70079. https://doi.org/10.1002/hbm.70079

Alberdi, A., Aztiria, A., & Basarab, A. (2016). On the early diagnosis of Alzheimer's Disease from multimodal signals: A survey. *Artificial Intelligence in Medicine*, *71*, 1–29. https://doi.org/10.1016/j.artmed.2016.06.003

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., Gamst, A., Holtzman, D. M., Jagust, W. J., Petersen, R. C., Snyder, P. J., Carrillo, M. C., Thies, B., & Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, *7*(3), 270–279. https://doi.org/10.1016/j.jalz.2011.03.008

Albouy, G., Sterpenich, V., Balteau, E., Vandewalle, G., Desseilles, M., Dang-Vu, T., Darsaud, A., Ruby, P., Luppi, P. H., Degueldre, C., Peigneux, P., Luxen, A., & Maquet, P. (2008). Both the Hippocampus and Striatum Are Involved in Consolidation of Motor Sequence Memory. *Neuron*, *58*(2), 261–272. https://doi.org/10.1016/j.neuron.2008.02.008

Alhussein, L., Hosseini, E. A., Nguyen, K. P., Smith, M. A., & Joiner, W. M. (2019). Dissociating effects of error size, training duration, and amount of adaptation on the ability to retain motor memories. *Journal of Neurophysiology*, *122*(5), 2027–2042. https://doi.org/10.1152/jn.00387.2018

Allison, S. L., Fagan, A. M., Morris, J. C., & Head, D. (2016). Spatial Navigation in Preclinical Alzheimer's Disease. *Journal of Alzheimer's Disease*, *52*(1), 77–90. https://doi.org/10.3233/JAD-150855

Allison, S. L., Rodebaugh, T. L., Johnston, C., Fagan, A. M., Morris, J. C., & Head, D. (2019). Developing a Spatial Navigation Screening Tool Sensitive to the Preclinical Alzheimer Disease Continuum. *Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists*, *34*(7), 1138–1155. https://doi.org/10.1093/arclin/acz019

Andersen, B. B., Gundersen, H. J. G., & Pakkenberg, B. (2003). Aging of the human cerebellum: A stereological study. *Journal of Comparative Neurology*, *466*(3), 356–365. https://doi.org/10.1002/cne.10884

Anderson, N. D. (2019). State of the science on mild cognitive impairment (MCI). In *CNS Spectrums* (Vol. 24, Issue 1, pp. 78–87). https://doi.org/10.1017/S1092852918001347

Anguera, J. A., Reuter-Lorenz, P. A., Willingham, D. T., & Seidler, R. D. (2010). Contributions of spatial working memory to visuomotor learning. *Journal of Cognitive Neuroscience*, *22*(9), 1917–1930. https://doi.org/10.1162/jocn.2009.21351

Anguera, J. A., Reuter-Lorenz, P. A., Willingham, D. T., & Seidler, R. D. (2011). Failure to Engage Spatial Working Memory Contributes to Age-related Declines in Visuomotor Learning. *Journal of Cognitive Neuroscience*, *23*(1), 11–25. https://doi.org/10.1162/jocn.2010.21451

Ansai, J. H., Andrade, L. P. de, Rossi, P. G., Almeida, M. L., Carvalho Vale, F. A., & Rebelatto, J. R. (2018). Association Between Gait and Dual Task With Cognitive Domains in Older People With Cognitive Impairment. *Journal of Motor Behavior*, *50*(4), 409–415. https://doi.org/10.1080/00222895.2017.1363702

Arleo, A., Bareš, M., Bernard, J. A., Bogoian, H. R., Bruchhage, M. M. K., Bryant, P., Carlson, E. S., Chan, C. C. H., Chen, L.-K., Chung, C.-P., Dotson, V. M., Filip, P., Guell, X., Habas, C., Jacobs, H. I. L., Kakei, S., Lee, T. M. C., Leggio, M., Misiura, M., … Manto, M. (2024). Consensus Paper: Cerebellum and Ageing. *The Cerebellum*, *23*(2), 802–832. https://doi.org/10.1007/s12311-023-01577-7

Aslan, D. H., Hernandez, M. E., Frechette, M. L., Gephart, A. T., Soloveychik, I. M., & Sosnoff, J. J. (2021). The neural underpinnings of motor learning in people with neurodegenerative diseases: A scoping review. *Neuroscience and Biobehavioral Reviews*, *131*(December 2020), 882–898. https://doi.org/10.1016/j.neubiorev.2021.10.006

Attarpour, A., Ward, J., & Chen, J. J. (2021). Vascular origins of low-frequency oscillations in the cerebrospinal fluid signal in resting-state fMRI: Interpretation using photoplethysmography. *Human Brain Mapping*, *42*(8), 2606–2622. https://doi.org/10.1002/hbm.25392

Attwell, P. J. E., Cooke, S. F., & Yeo, C. H. (2002). Cerebellar Function in Consolidation of a Motor Memory. *Neuron*, *34*(6), 1011–1020. https://doi.org/10.1016/S0896-6273(02)00719-5

Bacigalupo, F., & Luck, S. J. (2019). Lateralized suppression of alpha-band EEG activity as a mechanism of target processing. *Journal of Neuroscience*, *39*(5), 900–917. https://doi.org/10.1523/JNEUROSCI.0183-18.2018

Bakkum, A., Gunn, S. M., & Marigold, D. S. (2021). How aging affects visuomotor adaptation and retention in a precision walking paradigm. *Scientific Reports*, *11*(1), 789. https://doi.org/10.1038/s41598-020-80916-8

Baptista, C., Vallesi, A., & Menardi, A. (2026). The default mode network throughout the lifespan: A state-of-the-art scoping review on its development and association to individual cognitive functioning. *Developmental Review*, *79*, 101250. https://doi.org/10.1016/j.dr.2026.101250

Barbey, A. K., Koenigs, M., & Grafman, J. (2013). Dorsolateral Prefrontal Contributions to Human Working Memory. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*, *49*(5), 1195–1205. https://doi.org/10.1016/j.cortex.2012.05.022

Bartlett, J. W., & Frost, C. (2008). Reliability, repeatability and reproducibility: Analysis of measurement errors in continuous variables. *Ultrasound in Obstetrics & Gynecology*, *31*(4), 466–475. https://doi.org/10.1002/uog.5256

Bassett, D. S., & Bullmore, E. T. (2017). Small-World Brain Networks Revisited. *The Neuroscientist : A Review Journal Bringing Neurobiology, Neurology and Psychiatry*, *23*(5), 499–516. https://doi.org/10.1177/1073858416667720

Belghali, M., Chastan, N., Cignetti, F., Davenne, D., & Decker, L. M. (2017). Loss of gait control assessed by cognitive-motor dual-tasks: Pros and cons in detecting people at risk of developing Alzheimer's and Parkinson's diseases. *GeroScience*, *39*(3), 305–329. https://doi.org/10.1007/s11357-017-9977-7

Benjamini, Y., & Yekutieli, D. (2005). False Discovery Rate–Adjusted Multiple Confidence Intervals for Selected Parameters. *Journal of the American Statistical Association*, *100*(469), 71–81. https://doi.org/10.1198/016214504000001907

Benson, B. L., Anguera, J. A., & Seidler, R. D. (2011). A spatial explicit strategy reduces error but interferes with sensorimotor adaptation. *Journal of Neurophysiology*, *105*(6), 2843–2851. https://doi.org/10.1152/jn.00002.2011

Bernard, J. A. (2022). Don't forget the little brain: A framework for incorporating the cerebellum into the understanding of cognitive aging. *Neuroscience and Biobehavioral Reviews*, *137*, 104639. https://doi.org/10.1016/j.neubiorev.2022.104639

Bernard, J. A., Nguyen, A. D., Hausman, H. K., Maldonado, T., Ballard, H. K., Jackson, T. B., Eakin, S. M., Lokshina, Y., & Goen, J. R. M. (2020). Shaky scaffolding: Age differences in cerebellar activation revealed through activation likelihood estimation meta-analysis. *Human Brain Mapping*, *41*(18), 5255–5281. https://doi.org/10.1002/hbm.25191

Bernard, J. A., Peltier, S. J., Wiggins, J. L., Jaeggi, S. M., Buschkuehl, M., Fling, B. W., Kwak, Y., Jonides, J., Monk, C. S., & Seidler, R. D. (2013). Disrupted cortico-cerebellar connectivity in older adults. *NeuroImage*, *83*, 103–119. https://doi.org/10.1016/j.neuroimage.2013.06.042

Bernard, J. A., & Seidler, R. D. (2013). Cerebellar contributions to visuomotor adaptation and motor sequence learning: An ALE meta-analysis. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00027

Bernard, J. A., & Seidler, R. D. (2014). Moving forward: Age effects on the cerebellum underlie cognitive and motor declines. *Neuroscience & Biobehavioral Reviews*, *42*, 193–207. https://doi.org/10.1016/j.neubiorev.2014.02.011

Bernard, J. A., Seidler, R. D., Hassevoort, K. M., Benson, B. L., Welsh, R. C., Lee Wiggins, J., Jaeggi, S. M., Buschkuehl, M., Monk, C. S., Jonides, J., & Peltier, S. J. (2012). Resting state cortico-cerebellar functional connectivity networks: A comparison of anatomical and self-organizing map approaches. *Frontiers in Neuroanatomy*, (AUG 2012). https://doi.org/10.3389/fnana.2012.00031

Bernard, J. A., Seidler, R. D., Hassevoort, K. M., Benson, B. L., Welsh, R. C., Wiggins, J. L., Jaeggi, S. M., Buschkuehl, M., Monk, C. S., Jonides, J., & Peltier, S. J. (2012). Resting state cortico-cerebellar functional connectivity networks: A comparison of anatomical and self-organizing map approaches. *Frontiers in Neuroanatomy*, *6*. https://doi.org/10.3389/fnana.2012.00031

Beurze, S. M., Toni, I., Pisella, L., & Medendorp, W. P. (2010). Reference Frames for Reach Planning in Human Parietofrontal Cortex. *Journal of Neurophysiology*, *104*(3), 1736–1745. https://doi.org/10.1152/jn.01044.2009

Bindra, G., Brower, R., North, R., Zhou, W., & Joiner, W. M. (2021a). Normal Aging Affects the Short-Term Temporal Stability of Implicit, But Not Explicit, Motor Learning following Visuomotor Adaptation. *eNeuro*, *8*(5), ENEURO.0527-20.2021. https://doi.org/10.1523/ENEURO.0527-20.2021

Bindra, G., Brower, R., North, R., Zhou, W., & Joiner, W. M. (2021b). Normal aging affects the short-term temporal stability of implicit, but not explicit, motor learning following visuomotor adaptation. *eNeuro*, *8*(5). https://doi.org/10.1523/ENEURO.0527-20.2021

Binnewijzend, M. A. A., Schoonheim, M. M., Sanz-Arigita, E., Wink, A. M., van der Flier, W. M., Tolboom, N., Adriaanse, S. M., Damoiseaux, J. S., Scheltens, P., van Berckel, B. N. M., & Barkhof, F. (2012). Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. *Neurobiology of Aging*, *33*(9), 2018–2028. https://doi.org/10.1016/j.neurobiolaging.2011.07.003

Birmingham, E., & Kingstone, A. (2009). Human Social Attention. *Annals of the New York Academy of Sciences*, *1156*(1), 118–140. https://doi.org/10.1111/j.1749-6632.2009.04468.x

Birn, R. M., Diamond, J. B., Smith, M. A., & Bandettini, P. A. (2006). Separating respiratory-variation-related fluctuations from neuronal-activity-related fluctuations in fMRI. *NeuroImage*, *31*(4), 1536–1548. https://doi.org/10.1016/j.neuroimage.2006.02.048

Biswal, B. B., Mennes, M., Zuo, X.-N., Gohel, S., Kelly, C., Smith, S. M., Beckmann, C. F., Adelstein, J. S., Buckner, R. L., Colcombe, S., Dogonowski, A.-M., Ernst, M., Fair, D., Hampson, M., Hoptman, M. J., Hyde, J. S., Kiviniemi, V. J., Kötter, R., Li, S.-J., … Milham, M. P. (2010). Toward discovery science of human brain function. *Proceedings of the National Academy of Sciences*, *107*(10), 4734–4739. https://doi.org/10.1073/pnas.0911855107

Biswal, B. B., & Uddin, L. Q. (2025). The history and future of resting-state functional magnetic resonance imaging. *Nature*, *641*(8065), 1121–1131. https://doi.org/10.1038/s41586-025-08953-9

Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine*, *34*(4), 537–541. https://doi.org/10.1002/mrm.1910340409

Bock, O., & Schneider, S. (2002). Sensorimotor adaptation in young and elderly humans. *Neuroscience & Biobehavioral Reviews*, *26*(7), 761–767. https://doi.org/10.1016/S0149-7634(02)00063-5

Boisgontier, M. P., & Nougier, V. (2013). Ageing of internal models: From a continuous to an intermittent proprioceptive control of movement. *AGE*, *35*(4), 1339–1355. https://doi.org/10.1007/s11357-012-9436-4

Bookheimer, S. Y., Salat, D. H., Terpstra, M., Ances, B. M., Barch, D. M., Buckner, R. L., Burgess, G. C., Curtiss, S. W., Diaz-Santos, M., Elam, J. S., Fischl, B., Greve, D. N., Hagy, H. A., Harms, M. P., Hatch, O. M., Hedden, T., Hodge, C., Japardi, K. C., Kuhn, T. P., … Yacoub, E. (2019). The Lifespan Human Connectome Project in Aging: An overview. *NeuroImage*, *185*, 335–348. https://doi.org/10.1016/j.neuroimage.2018.10.009

Brown, R. M., Robertson, E. M., & Press, D. Z. (2009). Sequence Skill Acquisition and Off-Line Learning in Normal Aging. *PLOS ONE*, *4*(8), e6683. https://doi.org/10.1371/journal.pone.0006683
Buckner, R. L., Krienen, F. M., Castellanos, A., Diaz, J. C., & Yeo, B. T. T. (2011). The organization of the human cerebellum estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(5), 2322–2345. https://doi.org/10.1152/jn.00339.2011
Burciu, R. G., Reinold, J., Rabe, K., Wondzinski, E., Siebler, M., Müller, O., Theysohn, N., Gerwig, M., Donchin, O., & Timmann, D. (2014). Structural correlates of motor adaptation deficits in patients with acute focal lesions of the cerebellum. *Experimental Brain Research*, *232*(9), 2847–2857. https://doi.org/10.1007/s00221-014-3956-3
Burke, S. N., & Barnes, C. A. (2006). Neural plasticity in the ageing brain. *Nature Reviews Neuroscience*, *7*(1), Article 1. https://doi.org/10.1038/nrn1809
Burman, D. D. (2019). Hippocampal connectivity with sensorimotor cortex during volitional finger movements: Laterality and relationship to motor learning. *PLOS ONE*, *14*(9), e0222064. https://doi.org/10.1371/journal.pone.0222064
Burns, P. B., Rohrich, R. J., & Chung, K. C. (2011). The Levels of Evidence and their role in Evidence-Based Medicine. *Plastic and Reconstructive Surgery*, *128*(1), 305–310. https://doi.org/10.1097/PRS.0b013e318219c171
Bursztyn, L. L. C. D., Ganesh, G., Imamizu, H., Kawato, M., & Flanagan, J. R. (2006). Neural Correlates of Internal-Model Loading. *Current Biology*, *16*(24), 2440–2445. https://doi.org/10.1016/j.cub.2006.10.051
Byczynski, G., Arulchelvan, E., Grootjans, Y., Scarlat, I.-M., Brady, S., Kamdar, S., & Vanneste, S. (2025). Neural signatures of online and offline motor learning: An ALE meta-analysis. *Imaging Neuroscience*, *3*, imag_a_00457. https://doi.org/10.1162/imag_a_00457
Cabeza, R. (2002a). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, *17*(1), 85–100. https://doi.org/10.1037//0882-7974.17.1.85
Cabeza, R. (2002b). Hemispheric asymmetry reduction in older adults: The HAROLD model. *Psychology and Aging*, *17*(1), 85–100. https://doi.org/10.1037/0882-7974.17.1.85
Cahart, M.-S., O'Daly, O., Giampietro, V., Timmers, M., Streffer, J., Einstein, S., Zelaya, F., Dell'Acqua, F., & Williams, S. C. R. (2023). Comparing the test–retest reliability of resting-state functional magnetic resonance imaging metrics across single band and multiband acquisitions in the context of healthy aging. *Human Brain Mapping*, *44*(5), 1901–1912. https://doi.org/10.1002/hbm.26180
Campbell, K., Grigg, O., Saverino, C., Churchill, N., & Grady, C. (2013). Age differences in the intrinsic functional connectivity of default network subsystems. *Frontiers in Aging Neuroscience*, *5*. https://doi.org/10.3389/fnagi.2013.00073
Cao, K., Bay, A. A., Hajjar, I., Wharton, W., Goldstein, F., Qiu, D., Prusin, T., McKay, J. L., Perkins, M. M., & Hackney, M. E. (2023). Rationale and Design of the PARTNER Trial: Partnered Rhythmic Rehabilitation for Enhanced Motor-Cognition in Prodromal Alzheimer's Disease. *Journal of Alzheimer's Disease : JAD*, *91*(3), 1019–1033. https://doi.org/10.3233/JAD-220783
Casellato, C., Pedrocchi, A., Garrido, J. A., Luque, N. R., Ferrigno, G., D'Angelo, E., & Ros, E. (2012). An integrated motor control loop of a human-like robotic arm: Feedforward, feedback and cerebellum-based learning. *2012 4th IEEE RAS & EMBS International Conference on Biomedical Robotics and Biomechatronics (BioRob)*, 562–567. https://doi.org/10.1109/BioRob.2012.6290791
Cassady, K., Ruitenberg, M., Koppelmans, V., Reuter-Lorenz, P., De Dios, Y., Gadd, N., Wood, S., Riascos Castenada, R., Kofman, I., Bloomberg, J., Mulavara, A., & Seidler, R. (2018). Neural predictors of sensorimotor adaptation rate and savings. *Human Brain Mapping*, *39*(4), 1516–1531. https://doi.org/10.1002/hbm.23924
Castellazzi, G., Palesi, F., Casali, S., Vitali, P., Sinforiani, E., Wheeler-Kingshott, C. A. M., & D'Angelo, E. (2014). A comprehensive assessment of resting state networks: Bidirectional modification of functional integrity in cerebro-cerebellar networks in dementia. *Frontiers in Neuroscience*, *8*, 223. https://doi.org/10.3389/fnins.2014.00223
Cespón, J., Galdo-Álvarez, S., & Díaz, F. (2013). Electrophysiological correlates of amnestic mild cognitive impairment in a simon task. *PLoS ONE*, *8*(12), e81506. https://doi.org/10.1371/journal.pone.0081506
Cespón, J., Hommel, B., Korsch, M., & Galashan, D. (2020). The neurocognitive underpinnings of the Simon effect: An integrative review of current research. *Cognitive, Affective and Behavioral Neuroscience*, *20*(6), 1133–1172. https://doi.org/10.3758/s13415-020-00836-y

Cha, J., Hwang, J.-M., Jo, H. J., Seo, S. W., Na, D. L., & Lee, J.-M. (2015). Assessment of Functional Characteristics of Amnestic Mild Cognitive Impairment and Alzheimer's Disease Using Various Methods of Resting-State FMRI Analysis. *BioMed Research International*, *2015*, 907464. https://doi.org/10.1155/2015/907464

Chan, M. Y., Han, L., & Wig, G. S. (2026). *Systematic fMRI signal differences across cohorts alter lifespan connectome trajectories* (p. 2026.01.15.699580). bioRxiv. https://doi.org/10.64898/2026.01.15.699580

Chandra, A., Dervenoulas, G., Politis, M., & for the Alzheimer's Disease Neuroimaging Initiative. (2019). Magnetic resonance imaging in Alzheimer's disease and mild cognitive impairment. *Journal of Neurology*, *266*(6), 1293–1302. https://doi.org/10.1007/s00415-018-9016-3

Chang, C., Cunningham, J. P., & Glover, G. H. (2009). Influence of heart rate on the BOLD signal: The cardiac response function. *NeuroImage*, *44*(3), 857–869. https://doi.org/10.1016/j.neuroimage.2008.09.029

Chen, J. J., & Gauthier, C. J. (2021). The Role of Cerebrovascular-Reactivity Mapping in Functional MRI: Calibrated fMRI and Resting-State fMRI. *Frontiers in Physiology*, *12*. https://doi.org/10.3389/fphys.2021.657362

Cho, H., Kim, J.-H., Kim, C., Ye, B. S., Kim, H. J., Yoon, C. W., Noh, Y., Kim, G. H., Kim, Y. J., Kim, J.-H., Kim, C.-H., Kang, S. J., Chin, J., Kim, S. T., Lee, K.-H., Na, D. L., Seong, J.-K., & Seo, S. W. (2014). Shape changes of the basal ganglia and thalamus in Alzheimer's disease: A three-year longitudinal study. *Journal of Alzheimer's Disease: JAD*, *40*(2), 285–295. https://doi.org/10.3233/JAD-132072

Christou, A. I., Miall, R. C., McNab, F., & Galea, J. M. (2016). Individual differences in explicit and implicit visuomotor learning and working memory capacity. *Scientific Reports*, *6*(1), 36633. https://doi.org/10.1038/srep36633

Christou, E. A. (2011). Aging and Variability of Voluntary Contractions. *Exercise and Sport Sciences Reviews*, *39*(2), 77–84. https://doi.org/10.1097/JES.0b013e31820b85ab

Christova, P., & Georgopoulos, A. P. (2023). Differential reduction of gray matter volume with age in 35 cortical areas in men (more) and women (less). *Journal of Neurophysiology*, *129*(4), 894–899. https://doi.org/10.1152/jn.00066.2023

Churchill, J. D., Stanis, J. J., Press, C., Kushelev, M., & Greenough, W. T. (2003). Is procedural memory relatively spared from age effects? *Neurobiology of Aging*, *24*(6), 883–892. https://doi.org/10.1016/S0197-4580(02)00194-X

Cisek, P., & Kalaska, J. F. (2005). Neural correlates of reaching decisions in dorsal premotor cortex: Specification of multiple direction choices and final selection of action. *Neuron*, *45*(5), 801–814. https://doi.org/10.1016/j.neuron.2005.01.027

Cisneros, E., Karny, S., Ivry, R. B., & Tsay, J. S. (2026). A systematic investigation reveals dissociable effects of ageing on implicit and explicit components of sensorimotor learning. *Nature Human Behaviour*, 1–21. https://doi.org/10.1038/s41562-026-02468-7

Clark, G. M., Lum, J. A. G., & Ullman, M. T. (2014). A Meta-Analysis and Meta-regression of Serial Reaction Time Task Performance in Parkinson's Disease. *American Psychological Association*, *28*(6), 945–958. https://doi.org/10.1037/neu0000121.supp

Clayton, H. A., Abbas, S., T Hart, B. M., & Henriques, D. Y. P. (2024). Visuomotor adaptation across the lifespan. *PloS One*, *19*(7), e0306276. https://doi.org/10.1371/journal.pone.0306276

Cohen, D. A., Pascual-Leone, A., Press, D. Z., & Robertson, E. M. (2005). Off-line learning of motor skill memory: A double dissociation of goal and movement. *Proceedings of the National Academy of Sciences*, *102*(50), 18237–18241. https://doi.org/10.1073/pnas.0506072102

Cohen, J. R., & D'Esposito, M. (2016). The Segregation and Integration of Distinct Brain Networks and Their Relationship to Cognition. *Journal of Neuroscience*, *36*(48), 12083–12094. https://doi.org/10.1523/JNEUROSCI.2965-15.2016

Cole, M. W., Bassett, D. S., Power, J. D., Braver, T. S., & Petersen, S. E. (2014). Intrinsic and Task-Evoked Network Architectures of the Human Brain. *Neuron*, *83*(1), 238–251. https://doi.org/10.1016/j.neuron.2014.05.014

Contreras-Vidal, J. L., Teulings, H. L., & Stelmach, G. E. (1998). *Elderly subjects are impaired in spatial coordination in fine motor control*. *100*, 25–35.

Cristea, M., Noja, G. G., Stefea, P., & Sala, A. L. (2020). The Impact of Population Aging and Public Health Support on EU Labor Markets. *International Journal of Environmental Research and Public Health*, *17*(4), 1439. https://doi.org/10.3390/ijerph17041439

Cui, D., Zhang, L., Zheng, F., Wang, H., Meng, Q., Lu, W., Liu, Z., Yin, T., & Qiu, J. (2020). Volumetric reduction of cerebellar lobules associated with memory decline across the adult lifespan. *Quantitative Imaging in Medicine and Surgery*, *10*(1), 148–159. https://doi.org/10.21037/qims.2019.10.19

Curtis, C. E., & D'Esposito, M. (2003). Persistent activity in the prefrontal cortex during working memory. *Trends in Cognitive Sciences*, *7*(9), 415–423. https://doi.org/10.1016/S1364-6613(03)00197-9

Dahms, C., Brodoehl, S., Witte, O. W., & Klingner, C. M. (2020). The importance of different learning stages for motor sequence learning after stroke. *Human Brain Mapping*, *41*(1), 270–286. https://doi.org/10.1002/hbm.24793

Damoiseaux, J. S. (2017). Effects of aging on functional and structural brain connectivity. *NeuroImage, Functional Architecture of the Brain*, *160*, 32–40. https://doi.org/10.1016/j.neuroimage.2017.01.077

D'Angelo, E., Solinas, S., Garrido, J., Casellato, C., Pedrocchi, A., Mapelli, J., Gandolfi, D., & Prestori, F. (2013). Realistic modeling of neurons and networks: Towards brain simulation. *Functional Neurology*, *28*(3), 153–166.

Davis, S. W., Dennis, N. A., Buchler, N. G., White, L. E., Madden, D. J., & Cabeza, R. (2009). Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *NeuroImage*, *46*(2), 530–541. https://doi.org/10.1016/j.neuroimage.2009.01.068

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cerebral Cortex (New York, N.Y.: 1991)*, *18*(5), 1201–1209. https://doi.org/10.1093/cercor/bhm155

de Flores, R., La Joie, R., & Chételat, G. (2015). Structural imaging of hippocampal subfields in healthy aging and Alzheimer's disease. In *Neuroscience* (Vol. 309, pp. 29–50). Neuroscience. https://doi.org/10.1016/j.neuroscience.2015.08.033

de Miquel, M. A. (2021). Posterior Fossa Venous Drainage. *Frontiers in Neurology*, *12*, 680515. https://doi.org/10.3389/fneur.2021.680515

De Vis, J. B., Bhogal, A. A., Hendrikse, J., Petersen, E. T., & Siero, J. C. W. (2018). Effect sizes of BOLD CVR, resting-state signal fluctuations and time delay measures for the assessment of hemodynamic impairment in carotid occlusion patients. *NeuroImage*, *179*, 530–539. https://doi.org/10.1016/j.neuroimage.2018.06.017

de Vries, N. M., van Ravensberg, C. D., Hobbelen, J. S. M., Olde Rikkert, M. G. M., Staal, J. B., & Nijhuis-van der Sanden, M. W. G. (2012). Effects of physical exercise therapy on mobility, physical functioning, physical activity and quality of life in community-dwelling older adults with impaired mobility, physical disability and/or multi-morbidity: A meta-analysis. *Ageing Research Reviews*, *11*(1), 136–149. https://doi.org/10.1016/j.arr.2011.11.002

Debas, K., Carrier, J., Orban, P., Barakat, M., Lungu, O., Vandewalle, G., Tahar, A. H., Bellec, P., Karni, A., Ungerleider, L. G., Benali, H., & Doyon, J. (2010). Brain plasticity related to the consolidation of motor sequence learning and motor adaptation. *Proceedings of the National Academy of Sciences*, *107*(41), 17839–17844. https://doi.org/10.1073/pnas.1013176107

Deery, H. A., Di Paolo, R., Moran, C., Egan, G. F., & Jamadar, S. D. (2023). The older adult brain is less modular, more integrated, and less efficient at rest: A systematic review of large-scale resting-state functional brain networks in aging. *Psychophysiology*, *60*(1), e14159. https://doi.org/10.1111/psyp.14159

Delbuck, X., Van der Linden, M., & Collette, F. (2003). Alzheimer's Disease as a Disconnection Syndrome? In *Neuropsychology Review* (Vol. 13, Issue 2, pp. 79–92). https://doi.org/10.1007/s11065-010-9128-8

Della-Maggiore, V., Landi, S. M., & Villalta, J. I. (2015). Sensorimotor Adaptation: Multiple Forms of Plasticity in Motor Circuits. *The Neuroscientist*, *21*(2), 109–125. https://doi.org/10.1177/1073858414545228

DeTure, M. A., & Dickson, D. W. (2019). The neuropathological diagnosis of Alzheimer's disease. *Molecular Neurodegeneration*, *14*, 32. https://doi.org/10.1186/s13024-019-0333-5

Di, X., Kannurpatti, S. S., Rypma, B., & Biswal, B. B. (2013). Calibrating BOLD fMRI Activations with Neurovascular and Anatomical Constraints. *Cerebral Cortex*, *23*(2), 255–263. https://doi.org/10.1093/cercor/bhs001

Di, X., Kim, E. H., Huang, C.-C., Lin, C.-P., & Biswal, B. B. (2013). The Influence of the Amplitude of Low-Frequency Fluctuations on Resting-State Functional Connectivity. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00118

Diamond, A. (2013). Executive Functions. *Annual Review of Psychology*, *64*(1), 135–168. https://doi.org/10.1146/annurev-psych-113011-143750
Diedrichsen, J. (2006). A spatially unbiased atlas template of the human cerebellum. *NeuroImage*, *33*(1), 127–138. https://doi.org/10.1016/j.neuroimage.2006.05.056
Diedrichsen, J., Balsters, J. H., Flavell, J., Cussans, E., & Ramnani, N. (2009). A probabilistic MR atlas of the human cerebellum. *NeuroImage*, *46*(1), 39–46. https://doi.org/10.1016/j.neuroimage.2009.01.045
Diedrichsen, J., Verstynen, T., Schlerf, J., & Wiestler, T. (2010). Advances in functional imaging of the human cerebellum. *Current Opinion in Neurology*, *23*(4), 382. https://doi.org/10.1097/WCO.0b013e32833be837
Diedrichsen, J., & Zotow, E. (2015). Surface-Based Display of Volume-Averaged Cerebellar Imaging Data. *PLOS ONE*, *10*(7), e0133402. https://doi.org/10.1371/journal.pone.0133402
Doesburg, S. M., Bedo, N., & Ward, L. M. (2016). Top-down alpha oscillatory network interactions during visuospatial attention orienting. *NeuroImage*, *132*, 512–519. https://doi.org/10.1016/j.neuroimage.2016.02.076
Donchin, O., Rabe, K., Diedrichsen, J., Lally, N., Schoch, B., Gizewski, E. R., & Timmann, D. (2012). Cerebellar regions involved in adaptation to force field and visuomotor perturbation. *Journal of Neurophysiology*, *107*(1), 134–147. https://doi.org/10.1152/jn.00007.2011
Dubois, B., Feldman, H. H., Jacova, C., Cummings, J. L., DeKosky, S. T., Barberger-Gateau, P., Delacourte, A., Frisoni, G., Fox, N. C., Galasko, D., Gauthier, S., Hampel, H., Jicha, G. A., Meguro, K., O'Brien, J., Pasquier, F., Robert, P., Rossor, M., Salloway, S., … Scheltens, P. (2010). Revising the definition of Alzheimer's disease: A new lexicon. *The Lancet Neurology*, *9*(11), 1118–1127. https://doi.org/10.1016/S1474-4422(10)70223-4
Egorova, N., Veldsman, M., Cumming, T., & Brodtmann, A. (2017). Fractional amplitude of low-frequency fluctuations (fALFF) in post-stroke depression. *NeuroImage : Clinical*, *16*, 116–124. https://doi.org/10.1016/j.nicl.2017.07.014
Eimer, M. (1996). The N2pc component as an indicator of attentional selectivity. *Electroencephalography and Clinical Neurophysiology*, *99*(3), 225–234. https://doi.org/10.1016/0013-4694(96)95711-9
Eldridge, L. L., Masterman, D., & Knowlton, B. J. (2002). Intact implicit habit learning in Alzheimer's disease. *Behavioral Neuroscience*, *116*(4), 722–726. https://doi.org/10.1037/0735-7044.116.4.722
Eslinger, P. J., & Damasio, A. R. (1986). Preserved motor learning in Alzheimer's disease: Implications for anatomy and behavior. *Journal of Neuroscience*, *6*(10), 3006–3009. https://doi.org/10.1523/jneurosci.06-10-03006.1986
Esteves, I., Fouto, A. R., Ruiz-Tagle, A., Caetano, G., & Figueiredo, P. (2025). Using ECG-derived respiration for explaining BOLD-fMRI fluctuations during rest and respiratory modulations. *Scientific Reports*, *15*(1), 39420. https://doi.org/10.1038/s41598-025-23131-7
Fan, J., Juttukonda, M. R., Goodale, S. E., Wang, S., Orbán, C., Varadarajan, D., Polimeni, J. R., Chang, C., Salat, D. H., & Chen, J. E. (2025). Functional MRI signatures of autonomic physiology in aging. *Communications Biology*, *8*(1), 1287. https://doi.org/10.1038/s42003-025-08703-7
Fan, L., Hu, J., Ma, W., Wang, D., Yao, Q., & Shi, J. (2019). Altered baseline activity and connectivity associated with cognitive impairment following acute cerebellar infarction: A resting-state fMRI study. *Neuroscience Letters*, *692*, 199–203. https://doi.org/10.1016/j.neulet.2018.11.007
Fernandez-Duque, D., & Black, S. E. (2006). Attentional networks in normal aging and Alzheimer's disease. *Neuropsychology*, *20*(2), 133–143. https://doi.org/10.1037/0894-4105.20.2.133
Fernández-Ruiz, J., Hall, C., Vergara, P., & Dı´az, R. (2000). Prism adaptation in normal aging: Slower adaptation rate and larger aftereffect. *Cognitive Brain Research*, *9*(3), 223–226. https://doi.org/10.1016/S0926-6410(99)00057-9
Filip, P., Gallea, C., Lehéricy, S., Lungu, O., & Bareš, M. (2019). Neural Scaffolding as the Foundation for Stable Performance of Aging Cerebellum. *Cerebellum*, *18*(3), 500–510. https://doi.org/10.1007/S12311-019-01015-7/TABLES/2
Floyer-Lea, A., & Matthews, P. M. (2004). Changing Brain Networks for Visuomotor Control With Increased Movement Automaticity. *Journal of Neurophysiology*, *92*(4), 2405–2412. https://doi.org/10.1152/jn.01092.2003
Flück, D., Beaudin, A. E., Steinback, C. D., Kumarpillai, G., Shobha, N., McCreary, C. R., Peca, S., Smith, E. E., & Poulin, M. J. (2014). Effects of aging on the association between cerebrovascular

responses to visual stimulation, hypercapnia and arterial stiffness. *Frontiers in Physiology*, *5*, 49. https://doi.org/10.3389/fphys.2014.00049
Fradet, L., Lee, G., & Dounskaia, N. (2008). Origins of submovements in movements of elderly adults. *Journal of NeuroEngineering and Rehabilitation*, *5*(1), 28. https://doi.org/10.1186/1743-0003-5-28
Frens, M. A., & Donchin, O. (2009). Forward Models and State Estimation in Compensatory Eye Movements. *Frontiers in Cellular Neuroscience*, *3*, 13. https://doi.org/10.3389/neuro.03.013.2009
Fresco, N., Tzelgov, J., & Shmuelof, L. (2023). How can caching explain automaticity? *Psychonomic Bulletin & Review*, *30*(2), 407–420. https://doi.org/10.3758/s13423-022-02191-0
Fukutani, Y., Cairns, N. J., Rossor, M. N., & Lantos, P. L. (1996). Purkinje cell loss and astrocytosis in the cerebellum in familial and sporadic Alzheimer's disease. *Neuroscience Letters*, *214*(1), 33–36. https://doi.org/10.1016/0304-3940(96)12875-5
Funahashi, S., & Andreau, J. M. (2013). Prefrontal cortex and neural mechanisms of executive function. *Journal of Physiology, Paris*, *107*(6), 471–482. https://doi.org/10.1016/j.jphysparis.2013.05.001
Gal, S., Coldham, Y., Tik, N., Bernstein-Eliav, M., & Tavor, I. (2022). Act natural: Functional connectivity from naturalistic stimuli fMRI outperforms resting-state in predicting brain activity. *NeuroImage*, *258*, 119359. https://doi.org/10.1016/j.neuroimage.2022.119359
Gale, S. A., Acar, D., & Daffner, K. R. (2018). Dementia. *The American Journal of Medicine*, *131*(10), 1161–1169. https://doi.org/10.1016/j.amjmed.2018.01.022
Galea, J. M., Vazquez, A., Pasricha, N., Orban de Xivry, J.-J., & Celnik, P. (2011). Dissociating the Roles of the Cerebellum and Motor Cortex during Adaptive Learning: The Motor Cortex Retains What the Cerebellum Learns. *Cerebral Cortex*, *21*(8), 1761–1770. https://doi.org/10.1093/cercor/bhq246
Gao, J.-H., & Liu, H.-L. (2012). Inflow effects on functional MRI. *NeuroImage, 20 YEARS OF fMRI*, *62*(2), 1035–1039. https://doi.org/10.1016/j.neuroimage.2011.09.088
Gao, J.-H., Miller, I., Lai, S., Xiong, J., & Fox, P. T. (1996). Quantitative assessment of blood inflow effects in functional MRI signals. *Magnetic Resonance in Medicine*, *36*(2), 314–319. https://doi.org/10.1002/mrm.1910360219
Gao, Y., Xu, L., Schilling, K. G., Choi, S., Chen, R., Li, Y., Li, M., Zu, Z., Ding, Z., Anderson, A. W., & Gore, J. C. (2025). Myelination selectively modulates BOLD signal in white matter. *Research Square*, rs.3.rs-6597153. https://doi.org/10.21203/rs.3.rs-6597153/v1
Garrett, D. D., Kovacevic, N., McIntosh, A. R., & Grady, C. L. (2010). Blood Oxygen Level-Dependent Signal Variability Is More than Just Noise. *Journal of Neuroscience*, *30*(14), 4914–4921. https://doi.org/10.1523/JNEUROSCI.5166-09.2010
Garrett, D. D., Kovacevic, N., McIntosh, A. R., & Grady, C. L. (2013). The Modulation of BOLD Variability between Cognitive States Varies by Age and Processing Speed. *Cerebral Cortex*, *23*(3), 684–693. https://doi.org/10.1093/cercor/bhs055
Garrett, D. D., Lindenberger, U., Hoge, R. D., & Gauthier, C. J. (2017). Age differences in brain signal variability are robust to multiple vascular controls. *Scientific Reports*, *7*(1), 10149. https://doi.org/10.1038/s41598-017-09752-7
Gellersen, H. M., Guell, X., & Sami, S. (2021). Differential vulnerability of the cerebellum in healthy ageing and Alzheimer's disease. *NeuroImage: Clinical*, *30*, 102605. https://doi.org/10.1016/j.nicl.2021.102605
Gentili, R. J., Bradberry, T. J., Oh, H., Hatfield, B. D., & Contreras Vidal, J. L. (2011). Cerebral cortical dynamics during visuomotor transformation: Adaptation to a cognitive-motor executive challenge. *Psychophysiology*, *48*(6), 813–824. https://doi.org/10.1111/j.1469-8986.2010.01143.x
Ghilardi, M. F., Alberoni, M., Rossi, M., Franceschi, M., Mariani, C., & Fazio, F. (2000). Visual feedback has differential effects on reaching movements in Parkinson's and Alzheimer's disease. *Brain Research*, *876*(1–2), 112–123. https://doi.org/10.1016/S0006-8993(00)02635-4
Ghilardi, M.-F., Ghez, C., Dhawan, V., Moeller, J., Mentis, M., Nakamura, T., Antonini, A., & Eidelberg, D. (2000). Patterns of regional brain activation associated with different forms of motor learning. *Brain Research*, *871*(1), 127–145. https://doi.org/10.1016/S0006-8993(00)02365-9
Giannelli, M., Diciotti, S., Tessa, C., & Mascalchi, M. (2010). Characterization of Nyquist ghost in EPI-fMRI acquisition sequences implemented on two clinical 1.5 T MR scanner systems: Effect of readout bandwidth and echo spacing. *Journal of Applied Clinical Medical Physics*, *11*(4), 170–180. https://doi.org/10.1120/jacmp.v11i4.3237

Glasser, M. F., Smith, S. M., Marcus, D. S., Andersson, J. L. R., Auerbach, E. J., Behrens, T. E. J., Coalson, T. S., Harms, M. P., Jenkinson, M., Moeller, S., Robinson, E. C., Sotiropoulos, S. N., Xu, J., Yacoub, E., Ugurbil, K., & Van Essen, D. C. (2016). The Human Connectome Project's neuroimaging approach. *Nature Neuroscience*, *19*(9), 1175–1187. https://doi.org/10.1038/nn.4361

Glasser, M. F., Sotiropoulos, S. N., Wilson, J. A., Coalson, T. S., Fischl, B., Andersson, J. L., Xu, J., Jbabdi, S., Webster, M., Polimeni, J. R., Van Essen, D. C., Jenkinson, M., & WU-Minn HCP Consortium. (2013). The minimal preprocessing pipelines for the Human Connectome Project. *NeuroImage*, *80*, 105–124. https://doi.org/10.1016/j.neuroimage.2013.04.127

Glover, G. H., Li, T. Q., & Ress, D. (2000). Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. *Magnetic Resonance in Medicine*, *44*(1), 162–167. https://doi.org/10.1002/1522-2594(200007)44:1%3C162::aid-mrm23%3E3.0.co;2-e

Goense, J., Bohraus, Y., & Logothetis, N. K. (2016). fMRI at High Spatial Resolution: Implications for BOLD-Models. *Frontiers in Computational Neuroscience*, *10*, 66. https://doi.org/10.3389/fncom.2016.00066

Golestani, A. M., Kwinta, J. B., Khatamian, Y. B., & Chen, J. J. (2017). The Effect of Low-Frequency Physiological Correction on the Reproducibility and Specificity of Resting-State fMRI Metrics: Functional Connectivity, ALFF, and ReHo. *Frontiers in Neuroscience*, *11*. https://www.frontiersin.org/articles/10.3389/fnins.2017.00546

Gonzalez-Castillo, J., Roopchansingh, V., Bandettini, P. A., & Bodurka, J. (2011). Physiological Noise Effects on the Flip Angle Selection in BOLD fMRI. *NeuroImage*, *54*(4), 2764–2778. https://doi.org/10.1016/j.neuroimage.2010.11.020

Greene, A. S., Gao, S., Scheinost, D., & Constable, R. T. (2018). Task-induced brain state manipulation improves prediction of individual traits. *Nature Communications*, *9*(1), 2807. https://doi.org/10.1038/s41467-018-04920-3

Groh, J., & Simons, M. (2025). White matter aging and its impact on brain function. *Neuron*, *113*(1), 127–139. https://doi.org/10.1016/j.neuron.2024.10.019

Hadjiosif, A. M., Gibo, T. L., & Smith, M. A. (2024). The cerebellum acts as the analog to the medial temporal lobe for sensorimotor memory. *Proceedings of the National Academy of Sciences*, *121*(42), e2411459121. https://doi.org/10.1073/pnas.2411459121

Harms, M. P., Somerville, L. H., Ances, B. M., Andersson, J., Barch, D. M., Bastiani, M., Bookheimer, S. Y., Brown, T. B., Buckner, R. L., Burgess, G. C., Coalson, T. S., Chappell, M. A., Dapretto, M., Douaud, G., Fischl, B., Glasser, M. F., Greve, D. N., Hodge, C., Jamison, K. W., … Yacoub, E. (2018). Extending the Human Connectome Project across ages: Imaging protocols for the Lifespan Development and Aging projects. *NeuroImage*, *183*, 972–984. https://doi.org/10.1016/j.neuroimage.2018.09.060

Harvey, P. D. (2019). Domains of cognition and their assessment. *Dialogues in Clinical Neuroscience*, *21*(3), 227–237. https://doi.org/10.31887/DCNS.2019.21.3/pharvey

Hausman, H. K., Jackson, T. B., Goen, J. R. M., & Bernard, J. A. (2020). From Synchrony to Asynchrony: Cerebellar–Basal Ganglia Functional Circuits in Young and Older Adults. *Cerebral Cortex*, *30*(2), 718–729. https://doi.org/10.1093/cercor/bhz121

Hawkins, K. M., & Sergio, L. E. (2014). Visuomotor impairments in older adults at increased Alzheimer's disease risk. *Journal of Alzheimer's Disease*, *42*(2), 607–621. https://doi.org/10.3233/JAD-140051

Hawkins, K. M., & Sergio, L. E. (2016). Adults at Increased Alzheimer's Disease Risk Display Cognitive-Motor Integration Impairment Associated with Changes in Resting-State Functional Connectivity: A Preliminary Study. *Journal of Alzheimer's Disease*, *53*(3), 1161–1172. https://doi.org/10.3233/JAD-151137

Heitger, M. H., Ronsse, R., Dhollander, T., Dupont, P., Caeyenberghs, K., & Swinnen, S. P. (2012). Motor learning-induced changes in functional brain connectivity as revealed by means of graph-theoretical network analysis. *NeuroImage*, *61*(3), 633–650. https://doi.org/10.1016/j.neuroimage.2012.03.067

Henson, R. N., Olszowy, W., Tsvetanov, K. A., Yadav, P. S., Cam-CAN, & Zeidman, P. (2024). Evaluating Models of the Ageing BOLD Response. *Human Brain Mapping*, *45*(15), e70043. https://doi.org/10.1002/hbm.70043

Heuer, H., & Hegele, M. (2008). Adaptation to visuomotor rotations in younger and older adults. *Psychology and Aging*, *23*(1), 190–202. https://doi.org/10.1037/0882-7974.23.1.190
Hicks, T. H., Magalhães, T. N. C., Jackson, T. B., Ballard, H. K., Herrejon, I. A., & Bernard, J. A. (2024). Functional and structural cerebellar-behavior relationships in aging. *Brain Structure and Function*, *230*(1), 10. https://doi.org/10.1007/s00429-024-02862-9
Hoch, M. J., & Shepherd, T. M. (2022). MRI-Visible Anatomy of the Basal Ganglia and Thalamus. *Neuroimaging Clinics of North America, Neuroimaging Anatomy, Part 1: Brain and Skull*, *32*(3), 529–541. https://doi.org/10.1016/j.nic.2022.05.003
Hogan, M. J., Staff, R. T., Bunting, B. P., Murray, A. D., Ahearn, T. S., Deary, I. J., & Whalley, L. J. (2011). Cerebellar brain volume accounts for variance in cognitive performance in older adults. *Cortex*, *47*(4), 441–450. https://doi.org/10.1016/j.cortex.2010.01.001
Hong, Y., Alvarado, R. L., Jog, A., Greve, D. N., & Salat, D. H. (2020). Serial Reaction Time Task Performance in Older Adults with Neuropsychologically Defined Mild Cognitive Impairment. *Journal of Alzheimer's Disease*, *74*(2), 491–500. https://doi.org/10.3233/JAD-191323
Hrybouski, S., Das, S. R., Xie, L., Brown, C. A., Flamporis, M., Lane, J., Nasrallah, I. M., Detre, J. A., Yushkevich, P. A., & Wolk, D. A. (2025). BOLD Amplitude Correlates of Preclinical Alzheimer's Disease. *Neurobiology of Aging*. https://doi.org/10.1016/j.neurobiolaging.2025.03.007
Huang, C.-C., Hsieh, W.-J., Lee, P.-L., Peng, L.-N., Liu, L.-K., Lee, W.-J., Huang, J.-K., Chen, L.-K., & Lin, C.-P. (2015). Age-related changes in resting-state networks of a large sample size of healthy elderly. *CNS Neuroscience & Therapeutics*, *21*(10), 817–825. https://doi.org/10.1111/cns.12396
Huang, J., Gegenfurtner, K. R., Schütz, A. C., & Billino, J. (2017). Age effects on saccadic adaptation: Evidence from different paradigms reveals specific vulnerabilities. *Journal of Vision*, *17*(6). https://doi.org/10.1167/17.6.9
Huang, V. S., Haith, A., Mazzoni, P., & Krakauer, J. W. (2011). Rethinking motor learning and savings in adaptation paradigms: Model-free memory for successful actions combines with internal models. *Neuron*, *70*(4), 787–801. https://doi.org/10.1016/j.neuron.2011.04.012
Huck, J., Jäger, A.-T., Schneider, U., Grahl, S., Fan, A. P., Tardif, C., Villringer, A., Bazin, P.-L., Steele, C. J., & Gauthier, C. J. (2023). Modeling venous bias in resting state functional MRI metrics. *Human Brain Mapping*, *44*(14), 4938–4955. https://doi.org/10.1002/hbm.26431
Huck, J., Wanner, Y., Fan, A. P., Jäger, A.-T., Grahl, S., Schneider, U., Villringer, A., Steele, C. J., Tardif, C. L., Bazin, P.-L., & Gauthier, C. J. (2019). High resolution atlas of the venous brain vasculature from 7 T quantitative susceptibility maps. *Brain Structure and Function*, *224*(7), 2467–2485. https://doi.org/10.1007/s00429-019-01919-4
Ikeda, S., Kawano, K., Watanabe, S., Yamashita, O., & Kawahara, Y. (2022). Predicting behavior through dynamic modes in resting-state fMRI data. *NeuroImage*, *247*, 118801. https://doi.org/10.1016/j.neuroimage.2021.118801
Ikkai, A., & Curtis, C. E. (2011). Common neural mechanisms supporting spatial working memory, attention and motor intention. *Neuropsychologia*, *49*(6), 1428–1434. https://doi.org/10.1016/j.neuropsychologia.2010.12.020
Imamizu, H., Miyauchi, S., Tamada, T., Sasaki, Y., Takino, R., Pütz, B., Yoshioka, T., & Kawato, M. (2000). Human cerebellar activity reflecting an acquired internal model of a new tool. *Nature*, *403*(6766), Article 6766. https://doi.org/10.1038/35003194
Ito, H., Kanno, I., Ibaraki, M., & Hatazawa, J. (2002). Effect of aging on cerebral vascular response to Paco2 changes in humans as measured by positron emission tomography. *Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism*, *22*(8), 997–1003. https://doi.org/10.1097/00004647-200208000-00011
Ito, M. (2008). Control of mental activities by internal models in the cerebellum. *Nature Reviews Neuroscience*, *9*(4), 304–313. https://doi.org/10.1038/nrn2332
Jacobs, H. I. L., Gronenschild, H. B. M., Evers, E. A. T., Ramakers, I. H. G. B., Hofman, P. A. M., Backes, W. H., Jolles, J., Verhey, F. R. J., & Van Boxtel, M. P. J. (2015). Visuospatial processing in early Alzheimer's disease: Amultimodal neuroimaging study. *Cortex*, *64*, 394–406. https://doi.org/10.1016/j.cortex.2012.01.005
Jacobs, H. I. L., Hopkins, D. A., Mayrhofer, H. C., Bruner, E., van Leeuwen, F. W., Raaijmakers, W., & Schmahmann, J. D. (2018). The cerebellum in Alzheimer's disease: Evaluating its role in cognitive decline. *Brain*, *141*(1), 37–47. https://doi.org/10.1093/brain/awx194

Jafari, Z., Kolb, B. E., & Mohajerani, M. H. (2020). Neural oscillations and brain stimulation in Alzheimer's disease. *Progress in Neurobiology*, *194*, 101878. https://doi.org/10.1016/j.pneurobio.2020.101878
Jezzard, P., & Balaban, R. S. (1995). Correction for geometric distortion in echo planar images from B0 field variations. *Magnetic Resonance in Medicine*, *34*(1), 65–73. https://doi.org/10.1002/mrm.1910340111
Jin, W., Qin, H., Zhang, K., & Chen, X. (2020). Spatial Navigation. *Advances in Experimental Medicine and Biology*, *1284*, 63–90. https://doi.org/10.1007/978-981-15-7086-5_7
Johari, K., den Ouden, D.-B., & Behroozmand, R. (2018). Effects of Aging on Temporal Predictive Mechanisms of Speech and Hand Motor Reaction Time. *Aging Clinical and Experimental Research*, *30*(10), 1195–1202. https://doi.org/10.1007/s40520-018-0902-4
Jones, D. T., Machulda, M. M., Vemuri, P., McDade, E. M., Zeng, G., Senjem, M. L., Gunter, J. L., Przybelski, S. A., Avula, R. T., Knopman, D. S., Boeve, B. F., Petersen, R. C., & Jack, C. R. (2011a). Age-related changes in the default mode network are more advanced in Alzheimer disease. *Neurology*, *77*(16), 1524–1531. https://doi.org/10.1212/WNL.0b013e318233b33d
Jones, D. T., Machulda, M. M., Vemuri, P., McDade, E. M., Zeng, G., Senjem, M. L., Gunter, J. L., Przybelski, S. A., Avula, R. T., Knopman, D. S., Boeve, B. F., Petersen, R. C., & Jack, C. R. (2011b). Age-related changes in the default mode network are more advanced in Alzheimer disease. *Neurology*, *77*(16), 1524–1531. https://doi.org/10.1212/WNL.0b013e318233b33d
Kafri, M., & Atun-Einy, O. (2019). From Motor Learning Theory to Practice: A Scoping Review of Conceptual Frameworks for Applying Knowledge in Motor Learning to Physical Therapist Practice. *Physical Therapy*, *99*(12), 1628–1643. https://doi.org/10.1093/ptj/pzz118
Kannurpatti, S. S., & Biswal, B. B. (2008). Detection and scaling of task-induced fMRI-BOLD response using resting state fluctuations. *NeuroImage*, *40*(4), 1567–1574. https://doi.org/10.1016/j.neuroimage.2007.09.040
Karinkanta, S., Piirtola, M., Sievänen, H., Uusi-Rasi, K., & Kannus, P. (2010). Physical therapy approaches to reduce fall and fracture risk among older adults. *Nature Reviews Endocrinology*, *6*(7), 396–407. https://doi.org/10.1038/nrendo.2010.70
Kassinopoulos, M., & Mitsis, G. D. (2021). Physiological noise modeling in fMRI based on the pulsatile component of photoplethysmograph. *NeuroImage*, *242*, 118467. https://doi.org/10.1016/j.neuroimage.2021.118467
Keilholz, S. D., Pan, W.-J., Billings, J., Nezafati, M., & Shakil, S. (2017). Noise and non-neuronal contributions to the BOLD signal: Applications to and insights from animal studies. *NeuroImage*, *154*, 267–281. https://doi.org/10.1016/j.neuroimage.2016.12.019
Ketcham, C. J., & Stelmach, G. E. (2004). Movement Control in the Older Adult. In *Technology for Adaptive Aging*. National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK97342/
Khan, M. A., & Franks, I. M. (2003). Online Versus Offline Processing of Visual Feedback in the Production of Component Submovements. *Journal of Motor Behavior*, *35*(3), 285–295. https://doi.org/10.1080/00222890309602141
King, B. R., Fogel, S. M., Albouy, G., & Doyon, J. (2013). Neural correlates of the age-related changes in motor sequence learning and motor adaptation in older adults. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00142
King, M., Hernandez-Castillo, C. R., Poldrack, R. A., Ivry, R. B., & Diedrichsen, J. (2019). Functional boundaries in the human cerebellum revealed by a multi-domain task battery. *Nature Neuroscience*, *22*(8), 1371–1378. https://doi.org/10.1038/s41593-019-0436-x
King, M., Shahshahani, L., Ivry, R. B., & Diedrichsen, J. (2023). A task-general connectivity model reveals variation in convergence of cortical inputs to functional regions of the cerebellum. *eLife*, *12*, e81511. https://doi.org/10.7554/eLife.81511
Klimesch, W. (1997). EEG-alpha rhythms and memory processes. *International Journal of Psychophysiology*, *26*(1–3), 319–340. https://doi.org/10.1016/S0167-8760(97)00773-3
Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews*, *29*(2–3), 169–195. https://doi.org/10.1016/S0165-0173(98)00056-3
Knopman, D. S., & Nissen, M. J. (1987). Implicit learning in patients with probable Alzheimer's disease. *Neurology*, *37*(5), 784–788. https://doi.org/10.1212/wnl.37.5.784

Koen, J. D., & Rugg, M. D. (2019). Neural Dedifferentiation in the Aging Brain. *Trends in Cognitive Sciences*, *23*(7), 547–559. https://doi.org/10.1016/j.tics.2019.04.012
Koralek, A. C., Jin, X., Long, J. D., Costa, R. M., & Carmena, J. M. (2012). CORTICOSTRIATAL PLASTICITY IS NECESSARY FOR LEARNING INTENTIONAL NEUROPROSTHETIC SKILLS. *Nature*, *483*(7389), 331–335. https://doi.org/10.1038/nature10845
Korte, J. A., Steele, C. J., Joiner, W. M., & Fan, A. P. (2026). Age-Related Low Frequency Amplitude Differences in Resting-State Blood Oxygenation Level-Dependent Signal in the Cerebellum. *Human Brain Mapping*, *47*(7), e70541. https://doi.org/10.1002/hbm.70541
Kosslyn, S. M., Digirolamo, G. J., Thompson, W. L., & Alpert, N. M. (1998). Mental rotation of objects versus hands: Neural mechanisms revealed by positron emission tomography. *Psychophysiology*, *35*(2), 151–161. https://doi.org/10.1111/1469-8986.3520151
Koziol, L. F., Budding, D., Andreasen, N., D'Arrigo, S., Bulgheroni, S., Imamizu, H., Ito, M., Manto, M., Marvel, C., Parker, K., Pezzulo, G., Ramnani, N., Riva, D., Schmahmann, J., Vandervert, L., & Yamazaki, T. (2014). Consensus Paper: The Cerebellum's Role in Movement and Cognition. *Cerebellum (London, England)*, *13*(1), 151–177. https://doi.org/10.1007/s12311-013-0511-x
Krakauer, J. W., Ghez, C., & Ghilardi, M. F. (2005). Adaptation to Visuomotor Transformations: Consolidation, Interference, and Forgetting. *The Journal of Neuroscience*, *25*(2), 473–478. https://doi.org/10.1523/JNEUROSCI.4218-04.2005
Krakauer, J. W., Hadjiosif, A. M., Xu, J., Wong, A. L., & Haith, A. M. (2019). Motor learning. *Comprehensive Physiology*, *9*(2), 613–663. https://doi.org/10.1002/cphy.c170043
Krakauer, J. W., & Mazzoni, P. (2011). Human sensorimotor learning: Adaptation, skill, and beyond. *Current Opinion in Neurobiology, Sensory and Motor Systems*, *21*(4), 636–644. https://doi.org/10.1016/j.conb.2011.06.012
Krakauer, J. W., & Shadmehr, R. (2006). Consolidation of motor memory. *Trends in Neurosciences*, *29*(1), 58–64. https://doi.org/10.1016/j.tins.2005.10.003
Krienen, F. M., & Buckner, R. L. (2009). Segregated Fronto-Cerebellar Circuits Revealed by Intrinsic Functional Connectivity. *Cerebral Cortex (New York, NY)*, *19*(10), 2485–2497. https://doi.org/10.1093/cercor/bhp135
Küblböck, M., Woletz, M., Höflich, A., Sladky, R., Kranz, G. S., Hoffmann, A., Lanzenberger, R., & Windischberger, C. (2014). Stability of low-frequency fluctuation amplitudes in prolonged resting-state fMRI. *NeuroImage*, *103*, 249–257. https://doi.org/10.1016/j.neuroimage.2014.09.038
Kwak, Y., Peltier, S., Bohnen, N., Müller, M., Dayalu, P., & Seidler, R. D. (2010). Altered Resting State Cortico-Striatal Connectivity in Mild to Moderate Stage Parkinson's Disease. *Frontiers in Systems Neuroscience*, *4*. https://doi.org/10.3389/fnsys.2010.00143
Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., Kennedy, D. N., Hoppel, B. E., Cohen, M. S., & Turner, R. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences of the United States of America*, *89*(12), 5675–5679. https://doi.org/10.1073/pnas.89.12.5675
Latora, V., & Marchiori, M. (2001). Efficient behavior of small-world networks. *Physical Review Letters*, *87*(19), 198701-1-198701–198704. https://doi.org/10.1103/PhysRevLett.87.198701
Lee, Q. N., Chen, J. E., Wheeler, G. J., & Fan, A. P. (2023). Characterizing systemic physiological effects on the blood oxygen level dependent signal of resting-state fMRI in time-frequency space using wavelets. *Human Brain Mapping*, *44*(18), 6537–6551. https://doi.org/10.1002/hbm.26533
Lee, V., Ross, B., & Tracy, B. (2001). Functional Assessment of Older Adults in an Emergency Department. *Canadian Journal of Occupational Therapy*, *68*(2), 121–129. https://doi.org/10.1177/000841740106800208
Lee, Y.-Y., Winstein, C. J., & Fisher, B. E. (2016). Role of the dorsolateral prefrontal cortex in context-dependent motor performance. *The European Journal of Neuroscience*, *43*(7), 954–960. https://doi.org/10.1111/ejn.13178
Lei, Y., & Wang, J. (2018). The effect of proprioceptive acuity variability on motor adaptation in older adults. *Experimental Brain Research*, *236*(2), 599–608. https://doi.org/10.1007/s00221-017-5150-x
Lerner, G., Albert, S., Caffaro, P. A., Villalta, J. I., Jacobacci, F., Shadmehr, R., & Della-Maggiore, V. (2020). The Origins of Anterograde Interference in Visuomotor Adaptation. *Cerebral Cortex (New York, NY)*, *30*(7), 4000–4010. https://doi.org/10.1093/cercor/bhaa016

Lesage, E., Hansen, P. C., & Miall, R. C. (2017). Right Lateral Cerebellum Represents Linguistic Predictability. *The Journal of Neuroscience*, *37*(26), 6231–6241. https://doi.org/10.1523/JNEUROSCI.3203-16.2017

Liss, J. L., Seleri Assunção, S., Cummings, J., Atri, A., Geldmacher, D. S., Candela, S. F., Devanand, D. P., Fillit, H. M., Susman, J., Mintzer, J., Bittner, T., Brunton, S. A., Kerwin, D. R., Jackson, W. C., Small, G. W., Grossberg, G. T., Clevenger, C. K., Cotter, V., Stefanacci, R., … Sabbagh, M. N. (2021). Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: A review and synthesis. *Journal of Internal Medicine*, *290*(2), 310–334. https://doi.org/10.1111/joim.13244

Liu, T. T., Nalci, A., & Falahpour, M. (2017). The Global Signal in fMRI: Nuisance or Information? *NeuroImage*, *150*, 213–229. https://doi.org/10.1016/j.neuroimage.2017.02.036

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the basis of the fMRI signal. *Nature*, *412*(6843), 150–157. https://doi.org/10.1038/35084005

Long, J., Feng, Y., Liao, H. P., Zhou, Q., & Urbin, M. A. (2018). Motor sequence learning is associated with hippocampal subfield volume in humans with medial temporal lobe epilepsy. *Frontiers in Human Neuroscience*, *12*, 367. https://doi.org/10.3389/fnhum.2018.00367

Lopes da Silva, F. (2013). EEG and MEG: Relevance to neuroscience. *Neuron*, *80*(5), 1112–1128. https://doi.org/10.1016/j.neuron.2013.10.017

Luo, N., Sui, J., Abrol, A., Lin, D., Chen, J., Vergara, V. M., Fu, Z., Du, Y., Damaraju, E., Xu, Y., Turner, J. A., & Calhoun, V. D. (2019). Age-related structural and functional variations in 5,967 individuals across the adult lifespan. *Human Brain Mapping*, *41*(7), 1725–1737. https://doi.org/10.1002/hbm.24905

Ma, Q., Pu, M., Haihambo, N., Baetens, K., Heleven, E., Deroost, N., Baeken, C., & Van Overwalle, F. (2023). Effective cerebello–cerebral connectivity during implicit and explicit social belief sequence learning using dynamic causal modeling. *Social Cognitive and Affective Neuroscience*, *18*(1), nsac044. https://doi.org/10.1093/scan/nsac044

MacDonald, M. E., & Pike, G. B. (2021a). MRI of healthy brain aging: A review. *NMR in Biomedicine*, *34*(9), e4564. https://doi.org/10.1002/nbm.4564

MacDonald, M. E., & Pike, G. B. (2021b). MRI of healthy brain aging: A review. *NMR in Biomedicine*, *34*(9), e4564. https://doi.org/10.1002/nbm.4564

Malagurski, B., Deschwanden, P. F., Jäncke, L., & Mérillat, S. (2022). Longitudinal functional connectivity patterns of the default mode network in healthy older adults. *NeuroImage*, *259*, 119414. https://doi.org/10.1016/j.neuroimage.2022.119414

Marcus, D., Harwell, J., Olsen, T., Hodge, M., Glasser, M., Prior, F., Jenkinson, M., Laumann, T., Curtiss, S., & Van Essen, D. (2011). Informatics and Data Mining Tools and Strategies for the Human Connectome Project. *Frontiers in Neuroinformatics*, *5*. https://doi.org/10.3389/fninf.2011.00004

Maresch, J., Mudrik, L., & Donchin, O. (2021). Measures of explicit and implicit in motor learning: What we know and what we don't. *Neuroscience & Biobehavioral Reviews*, *128*, 558–568. https://doi.org/10.1016/j.neubiorev.2021.06.037

Mariscal, D. M., Sombric, C. J., & Torres-Oviedo, G. (2025). Age and self-selected walking speed impact the generalization of locomotor memories across contexts. *Journal of Neurophysiology*, *133*(5), 1410–1421. https://doi.org/10.1152/jn.00432.2023

Mascali, D., DiNuzzo, M., Gili, T., Moraschi, M., Fratini, M., Maraviglia, B., Serra, L., Bozzali, M., & Giove, F. (2015). Intrinsic Patterns of Coupling between Correlation and Amplitude of Low-Frequency fMRI Fluctuations Are Disrupted in Degenerative Dementia Mainly due to Functional Disconnection. *PLOS ONE*, *10*(4), e0120988. https://doi.org/10.1371/journal.pone.0120988

Mccarthy, P., Benuskova, L., & Franz, E. A. (2014). The age-related posterior-anterior shift as revealed by voxelwise analysis of functional brain networks. *Frontiers in Aging Neuroscience*, *6*. https://doi.org/10.3389/fnagi.2014.00301

McDougle, S. D., Bond, K. M., & Taylor, J. A. (2015). Explicit and Implicit Processes Constitute the Fast and Slow Processes of Sensorimotor Learning. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *35*(26), 9568–9579. https://doi.org/10.1523/JNEUROSCI.5061-14.2015

McDougle, S. D., Bond, K. M., & Taylor, J. A. (2017). Implications of plan-based generalization in sensorimotor adaptation. *Journal of Neurophysiology*, *118*(1), 383–393. https://doi.org/10.1152/jn.00974.2016
McDougle, S. D., & Taylor, J. A. (2019a). Dissociable cognitive strategies for sensorimotor learning. *Nature Communications*, *10*(1), 40. https://doi.org/10.1038/s41467-018-07941-0
McDougle, S. D., & Taylor, J. A. (2019b). Dissociable cognitive strategies for sensorimotor learning. *Nature Communications*, *10*(1), 40. https://doi.org/10.1038/s41467-018-07941-0
McDougle, S. D., Wilterson, S. A., Turk-Browne, N. B., & Taylor, J. A. (2022). Revisiting the Role of the Medial Temporal Lobe in Motor Learning. *Journal of Cognitive Neuroscience*, *34*(3), 532. https://doi.org/10.1162/jocn_a_01809
McElroy, C. L., Wang, B., Zhang, H., & Jin, K. (2024). Cerebellum and Aging: Update and Challenges. *Aging and Disease*, *15*(6), 2345–2360. https://doi.org/10.14336/AD.2024.0220
McKenna, E., Bray, L. C. J., Zhou, W., & Joiner, W. M. (2017). The absence or temporal offset of visual feedback does not influence adaptation to novel movement dynamics. *Journal of Neurophysiology*, *118*(4), 2483–2498. https://doi.org/10.1152/jn.00636.2016
Medaglia, J. D., Lynall, M.-E., & Bassett, D. S. (2015). Cognitive Network Neuroscience. *Journal of Cognitive Neuroscience*, *27*(8), 1471–1491. https://doi.org/10.1162/jocn_a_00810
Messier, J., & Kalaska, J. F. (1997). Differential effect of task conditions on errors of direction and extent of reaching movements. *Experimental Brain Research 1997 115:3*, *115*(3), 469–478. https://doi.org/10.1007/PL00005716
Mevel, K., Chételat, G., Eustache, F., & Desgranges, B. (2011). The Default Mode Network in Healthy Aging and Alzheimer's Disease. *International Journal of Alzheimer's Disease*, *2011*, 535816. https://doi.org/10.4061/2011/535816
Miall, R. C., & Robertson, E. M. (2006). Functional Imaging: Is the Resting Brain Resting? *Current Biology*, *16*(23), R998–R1000. https://doi.org/10.1016/j.cub.2006.10.041
Millar, P. R., Petersen, S. E., Ances, B. M., Gordon, B. A., Benzinger, T. L. S., Morris, J. C., & Balota, D. A. (2020). Evaluating the Sensitivity of Resting-State BOLD Variability to Age and Cognition after Controlling for Motion and Cardiovascular Influences: A Network-Based Approach. *Cerebral Cortex*, *30*(11), 5686–5701. https://doi.org/10.1093/cercor/bhaa138
Mirabella, G., Casanova, M., & Lebedev, M. (2014). Should I stay or should I go? Conceptual underpinnings of goal-directed actions. *Frontiers in Systems Neuroscience*, *8*, 206. https://doi.org/10.3389/fnsys.2014.00206
Mitchell, D. B. (1989). How many memory systems? Evidence from aging. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, *15*(1), 31–49. https://doi.org/10.1037/0278-7393.15.1.31
Mitoma, H., Kakei, S., Tanaka, H., & Manto, M. (2023). Morphological and Functional Principles Governing the Plasticity Reserve in the Cerebellum: The Cortico-Deep Cerebellar Nuclei Loop Model. *Biology*, *12*(11), Article 11. https://doi.org/10.3390/biology12111435
Mitoma, H., Kakei, S., Yamaguchi, K., & Manto, M. (2021). Physiology of Cerebellar Reserve: Redundancy and Plasticity of a Modular Machine. *International Journal of Molecular Sciences*, *22*(9), 4777. https://doi.org/10.3390/ijms22094777
Moisello, C., Crupi, D., Tunik, E., Quartarone, A., Bove, M., Tononi, G., & Ghilardi, M. F. (2009). The serial reaction time task revisited: A study on motor sequence learning with an arm-reaching task. *Experimental Brain Research*, *194*(1), 143–155. https://doi.org/10.1007/s00221-008-1681-5
Mollica, M. A., Navarra, J., Fernández-Prieto, I., Olives, J., Tort, A., Valech, N., Coll-Padrós, N., Molinuevo, J. L., & Rami, L. (2017). Subtle visuomotor difficulties in preclinical Alzheimer's disease. *Journal of Neuropsychology*, *11*(1), 56–73. https://doi.org/10.1111/jnp.12079
Montero-Odasso, M., Oteng-Amoako, A., Speechley, M., Gopaul, K., Beauchet, O., Annweiler, C., & Muir-Hunter, S. W. (2014). The Motor Signature of Mild Cognitive Impairment: Results From the Gait and Brain Study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, *69*(11), 1415–1421. https://doi.org/10.1093/gerona/glu155
Morcom, A. M., & Johnson, W. (2015). Neural Reorganization and Compensation in Aging. *Journal of Cognitive Neuroscience*, *27*(7), 1275–1285. https://doi.org/10.1162/jocn_a_00783
Mordkoff, J. T., & Gianaros, P. J. (2000). Detecting the onset of the lateralized readiness potential: A comparison of available methods and procedures. *Psychophysiology*, *37*(3), 347–360. https://doi.org/10.1017/S0048577200982039

Morehead, J. R., Qasim, S. E., Crossley, M. J., & Ivry, R. (2015). Savings upon Re-Aiming in Visuomotor Adaptation. *The Journal of Neuroscience*, *35*(42), 14386–14396. https://doi.org/10.1523/JNEUROSCI.1046-15.2015

Morehead, J. R., Taylor, J. A., Parvin, D. E., & Ivry, R. B. (2017). Characteristics of Implicit Sensorimotor Adaptation Revealed by Task-irrelevant Clamped Feedback. *Journal of Cognitive Neuroscience*, *29*(6), 1061–1074. https://doi.org/10.1162/jocn_a_01108

Muellbacher, W., Ziemann, U., Wissel, J., Dang, N., Kofler, M., Facchini, S., Boroojerdi, B., Poewe, W., & Hallett, M. (2002). Early consolidation in human primary motor cortex. *Nature*, *415*(6872), 640–644. https://doi.org/10.1038/nature712

Mungas, D., Beckett, L., Harvey, D., Farias, S. T., Reed, B., Carmichael, O., Olichney, J., Miller, J., & DeCarli, C. (2010). Heterogeneity of Cognitive Trajectories in Diverse Older Person. *Psychology and Aging*, *25*(3), 606–619. https://doi.org/10.1037/a0019502

Murray, A., & Prashad, S. (2025). *A Review of the Differential Effects of Age on Online and Offline Learning of Implicit Motor Sequences*. https://doi.org/10.1123/jmld.2024-0072

Nemeth, D., & Janacsek, K. (2011). The Dynamics of Implicit Skill Consolidation in Young and Elderly Adults. *The Journals of Gerontology: Series B*, *66B*(1), 15–22. https://doi.org/10.1093/geronb/gbq063

Nettekoven, C., Zhi, D., Shahshahani, L., Pinho, A. L., Saadon-Grosman, N., Buckner, R. L., & Diedrichsen, J. (2024). A hierarchical atlas of the human cerebellum for functional precision mapping. *Nature Communications*, *15*(1), 8376. https://doi.org/10.1038/s41467-024-52371-w

Newell, K. M., Mayer-Kress, G., & Liu, Y.-T. (2009). Aging, time scales, and sensorimotor variability. *Psychology and Aging*, *24*(4), 809–818. https://doi.org/10.1037/a0017911

Nguyen, K. P., Zhou, W., McKenna, E., Colucci-Chang, K., Bray, L. C. J., Hosseini, E. A., Alhussein, L., Rezazad, M., & Joiner, W. M. (2019). The 24-h savings of adaptation to novel movement dynamics initially reflects the recall of previous performance. *Journal of Neurophysiology*, *122*(3), 933–946. https://doi.org/10.1152/jn.00569.2018

Niccoli, T., & Partridge, L. (2012). Ageing as a Risk Factor for Disease. *Current Biology*, *22*(17), R741–R752. https://doi.org/10.1016/j.cub.2012.07.024

Nichols, W. W., O'Rourke, M. F., & Vlachopoulos. (2011). *McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles*.

Nieto-Castanon, A. (2020). FMRI minimal preprocessing pipeline. In *Handbook of functional connectivity Magnetic Resonance Imaging methods in CONN* (pp. 3–16). Hilbert Press. https://doi.org/10.56441/hilbertpress.2207.6598

Nieto-Castanon, A., & Whitfield-Gabrieli, S. (2020). *CONN functional connectivity toolbox: RRID SCR_009550, release 20*. https://doi.org/10.56441/hilbertpress.2048.3738

Okamoto, T., Shirao, T., Shutoh, F., Suzuki, T., & Nagao, S. (2011). Post-training cerebellar cortical activity plays an important role for consolidation of memory of cerebellum-dependent motor learning. *Neuroscience Letters*, *504*(1), 53–56. https://doi.org/10.1016/j.neulet.2011.08.056

Oki, M., Matsumoto, M., Yoshikawa, Y., Fukushima, M., Nagasawa, A., Takakura, T., & Suzuki, Y. (2021). Risk Factors for Falls in Patients with Alzheimer Disease: A Retrospective Study of Balance, Cognition, and Visuospatial Ability. *Dementia and Geriatric Cognitive Disorders Extra*, *11*(1), 58–63. https://doi.org/10.1159/000514285

Olson, M., Lockhart, T. E., & Lieberman, A. (2019). Motor Learning Deficits in Parkinson's Disease (PD) and Their Effect on Training Response in Gait and Balance: A Narrative Review. *Frontiers in Neurology*, *10*. https://doi.org/10.3389/fneur.2019.00062

Onuki, Y., Van Someren, E. J. W., De Zeeuw, C. I., & Van der Werf, Y. D. (2015). Hippocampal-cerebellar interaction during spatio-temporal prediction. *Cerebral Cortex*, *25*(2), 313–321. https://doi.org/10.1093/cercor/bht221

Opitz, B. (2014). *Memory Function and the Hippocampus*. https://doi.org/10.1159/000356422

O'Reilly, J. X., Beckmann, C. F., Tomassini, V., Ramnani, N., & Johansen-Berg, H. (2010). Distinct and Overlapping Functional Zones in the Cerebellum Defined by Resting State Functional Connectivity. *Cerebral Cortex (New York, NY)*, *20*(4), 953–965. https://doi.org/10.1093/cercor/bhp157

Osoba, M. Y., Rao, A. K., Agrawal, S. K., & Lalwani, A. K. (2019). Balance and gait in the elderly: A contemporary review. *Laryngoscope Investigative Otolaryngology*, *4*(1), 143–153. https://doi.org/10.1002/lio2.252

Parizkova, M., Lerch, O., Moffat, S. D., Andel, R., Mazancova, A. F., Nedelska, Z., Vyhnalek, M., Hort, J., & Laczó, J. (2018). The effect of Alzheimer's disease on spatial navigation strategies. *Neurobiology of Aging*, *64*, 107–115. https://doi.org/10.1016/j.neurobiolaging.2017.12.019

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proceedings of the National Academy of Sciences*, *101*(35), 13091–13095. https://doi.org/10.1073/pnas.0405148101

Park, D. C., & Reuter-Lorenz, P. (2009). The Adaptive Brain: Aging and Neurocognitive Scaffolding. *Annual Review of Psychology*, *60*(Volume 60, 2009), 173–196. https://doi.org/10.1146/annurev.psych.59.103006.093656

Penny, W. D., Friston, K. J., Ashburner, S. J., & Kiebel, T. E. N. (Eds.). (2006). *Statistical Parametric Mapping: The Analysis of Functional Brain Images* (1st ed.). Elsevier.

Persson, J., Pudas, S., Nilsson, L.-G., & Nyberg, L. (2014). Longitudinal assessment of default-mode brain function in aging. *Neurobiology of Aging*, *35*(9), 2107–2117. https://doi.org/10.1016/j.neurobiolaging.2014.03.012

Petti, U., Baker, S., & Korhonen, A. (2020). A systematic literature review of automatic Alzheimer's disease detection from speech and language. *Journal of the American Medical Informatics Association: JAMIA*, *27*(11), 1784–1797. https://doi.org/10.1093/jamia/ocaa174

Phillips, J. S., McMillan, C. T., Smith, E. E., & Grossman, M. (2017). Category learning in Alzheimer's disease and normal cognitive aging depends on initial experience of feature variability. *Neuropsychologia*, *98*, 98–110. https://doi.org/10.1016/j.neuropsychologia.2016.07.003

Poe, M. K., & Seifert, L. S. (1997). Implicit and explicit tests: Evidence for dissociable motor skills in probable Alzheimer's dementia. *Perceptual and Motor Skills*, *85*(3 PART I), 631–634. https://doi.org/10.1177/003151259708500201

Popa, L. S., & Ebner, T. J. (2019). Cerebellum, Predictions and Errors. *Frontiers in Cellular Neuroscience*, *12*. https://doi.org/10.3389/fncel.2018.00524

Porro, C. A., Francescato, M. P., Cettolo, V., Diamond, M. E., Baraldi, P., Zuiani, C., Bazzocchi, M., & di Prampero, P. E. (1996). Primary Motor and Sensory Cortex Activation during Motor Performance and Motor Imagery: A Functional Magnetic Resonance Imaging Study. *The Journal of Neuroscience*, *16*(23), 7688–7698. https://doi.org/10.1523/JNEUROSCI.16-23-07688.1996

Porsteinsson, A. P., Isaacson, R. S., Knox, S., Sabbagh, M. N., & Rubino, I. (2021). Diagnosis of Early Alzheimer's Disease: Clinical Practice in 2021. *The Journal of Prevention of Alzheimer's Disease*, *8*(3), 371–386. https://doi.org/10.14283/jpad.2021.23

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154. https://doi.org/10.1016/j.neuroimage.2011.10.018

Power, J. D., Plitt, M., Laumann, T. O., & Martin, A. (2017). Sources and implications of whole-brain fMRI signals in humans. *NeuroImage*, *146*, 609–625. https://doi.org/10.1016/j.neuroimage.2016.09.038

Preibisch, C., Wallenhorst, T., Heidemann, R., Zanella, F. E., & Lanfermann, H. (2008). Comparison of parallel acquisition techniques generalized autocalibrating partially parallel acquisitions (GRAPPA) and modified sensitivity encoding (mSENSE) in functional MRI (fMRI) at 3T. *Journal of Magnetic Resonance Imaging*, *27*(3), 590–598. https://doi.org/10.1002/jmri.21191

Prvulovic, D., Hubl, D., Sack, A. T., Melillo, L., Maurer, K., Frölich, L., Lanfermann, H., Zanella, F. E., Goebel, R., Linden, D. E. J., & Dierks, T. (2002). Functional imaging of visuospatial processing in Alzheimer's disease. *NeuroImage*, *17*(3), 1403–1414. https://doi.org/10.1006/nimg.2002.1271

Raitamaa, L., Huotari, N., Korhonen, V., Helakari, H., Koivula, A., Kananen, J., & Kiviniemi, V. (2021). Spectral analysis of physiological brain pulsations affecting the BOLD signal. *Human Brain Mapping*, *42*(13), 4298–4313. https://doi.org/10.1002/hbm.25547

Ramnani, N. (2006). The primate cortico-cerebellar system: Anatomy and function. *Nature Reviews Neuroscience*, *7*(7), Article 7. https://doi.org/10.1038/nrn1953

Ranganathan, R., Costa, S., Mengote, A. M., Thomas, M., & Ved, R. (2026). Identifying motor learning deficits in neurological conditions: A critical analysis of a perennial problem. *Experimental Brain Research*, *244*(3), 43. https://doi.org/10.1007/s00221-026-07237-6

Ren, J., Wu, Y. D., Chan, J. S., & Yan, J. H. (2013). Cognitive aging affects motor performance and learning. *Geriatrics & Gerontology International*, *13*(1), 19–27. https://doi.org/10.1111/j.1447-0594.2012.00914.x

Reuter, E.-M., Pearcey, G. E. P., & Carroll, T. J. (2018). Greater neural responses to trajectory errors are associated with superior force field adaptation in older adults. *Experimental Gerontology*, *110*, 105–117. https://doi.org/10.1016/j.exger.2018.05.020

Reuter-Lorenz, P. A., & Cappell, K. A. (2008). *Neurocognitive Aging and the Compensation Hypothesis*. https://journals.sagepub.com/doi/full/10.1111/j.1467-8721.2008.00570.x?casa_token=d_h39paSxDsAAAAA%3Ai-Jt-yfgmcVJWh7bduvDyW1LsqDg9-A9t9VkSinJL0alT9XH4BeRTeRwm3u0L4urj0bsMmonCLvI

Reuter-Lorenz, P. A., & Mikels, J. A. (2005). A split-brain model of Alzheimer's disease?: Behavioral evidence for comparable intra and interhemispheric decline. *Neuropsychologia*, *43*(9), 1307–1317. https://doi.org/10.1016/J.NEUROPSYCHOLOGIA.2004.12.007

Reuter-Lorenz, P. A., Stanczak, L., & Miller, A. C. (1999). Neural recruitment and cognitive aging: Two hemispheres are better than one, especially as you age. *Psychological Science*, *10*(6), 494–500. https://doi.org/10.1111/1467-9280.00195

Ries, J. D. (2018). Rehabilitation for Individuals with Dementia: Facilitating Success. *Current Geriatrics Reports*, *7*(1), 59–70. https://doi.org/10.1007/s13670-018-0237-1

Risso, G., Bieri, M., Bertoni, T., Martinelli, I., Mastria, G., Catinari, L., Allet, L., Serino, A., & Bassolino, M. (2025). Proprioception impacts body perception in healthy aging – Insights from a psychophysical and computational approach. *iScience*, *28*(10), 113481. https://doi.org/10.1016/j.isci.2025.113481

Robert, P., Ferris, S., Gauthier, S., Ihl, R., Winblad, B., & Tennigkeit, F. (2010). Review of Alzheimer's disease scales: Is there a need for a new multi-domain scale for therapy evaluation in medical practice? *Alzheimer's Research & Therapy*, *2*(4), 24. https://doi.org/10.1186/alzrt48

Rogojin, A., Gorbet, D. J., Hawkins, K. M., & Sergio, L. E. (2023). Differences in structural MRI and diffusion tensor imaging underlie visuomotor performance declines in older adults with an increased risk for Alzheimer's disease. *Frontiers in Aging Neuroscience*, *14*. https://www.frontiersin.org/articles/10.3389/fnagi.2022.1054516

Rohn, T. T., Catlin, L. W., & Poon, W. W. (2012). Caspase-cleaved glial fibrillary acidic protein within cerebellar white matter of the Alzheimer's disease brain. *International Journal of Clinical and Experimental Pathology*, *6*(1), 41–48.

Roig, M., Ritterband-Rosenbaum, A., Lundbye-Jensen, J., & Nielsen, J. B. (2014). Aging increases the susceptibility to motor memory interference and reduces off-line gains in motor skill learning. *Neurobiology of Aging*, *35*(8), 1892–1900. https://doi.org/10.1016/j.neurobiolaging.2014.02.022

Romero, J. E., Coupe, P., Lanuza, E., Catheline, G., & Manjón, J. V. (2021a). Toward a unified analysis of cerebellum maturation and aging across the entire lifespan: A MRI analysis. *Human Brain Mapping*, *42*(5), 1287–1303. https://doi.org/10.1002/hbm.25293

Romero, J. E., Coupe, P., Lanuza, E., Catheline, G., & Manjón, J. V. (2021b). Toward a unified analysis of cerebellum maturation and aging across the entire lifespan: A MRI analysis. *Human Brain Mapping*, *42*(5), 1287–1303. https://doi.org/10.1002/hbm.25293

Rosch, K. S., & Mostofsky, S. (2019). Chapter 19—Development of the frontal lobe. In M. D'Esposito & J. H. Grafman (Eds.), *Handbook of Clinical Neurology* (Vol. 163, pp. 351–367). Elsevier. https://doi.org/10.1016/B978-0-12-804281-6.00019-7

Ruitenberg, M. F. L., Koppelmans, V., De Dios, Y. E., Gadd, N. E., Wood, S. J., Reuter-Lorenz, P. A., Kofman, I., Bloomberg, J. J., Mulavara, A. P., & Seidler, R. D. (2018). Neural correlates of multi-day learning and savings in sensorimotor adaptation. *Scientific Reports*, *8*(1), 14286. https://doi.org/10.1038/s41598-018-32689-4

Saenen, L., Verheyden, G., & Orban de Xivry, J.-J. (2023). The differential effect of age on upper limb sensory processing, proprioception, and motor function. *Journal of Neurophysiology*, *130*(5), 1183–1193. https://doi.org/10.1152/jn.00364.2022

Sala-Llonch, R., Bartrés-Faz, D., & Junqué, C. (2015). Reorganization of brain networks in aging: A review of functional connectivity studies. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.00663

Salimi, S., Irish, M., Foxe, D., Hodges, J. R., Piguet, O., & Burrell, J. R. (2019). Visuospatial dysfunction in Alzheimer's disease and behavioural variant frontotemporal dementia. *Journal of the Neurological Sciences*, *402*, 74–80. https://doi.org/10.1016/j.jns.2019.04.019

Salthouse, T. A. (2019). Trajectories of normal cognitive aging. *Psychology and Aging*, *34*(1), 17–24. https://doi.org/10.1037/pag0000288

Salthouse, T. A., & Ferrer-Caja, E. (2003). What needs to be explained to account for age-related effects on multiple cognitive variables? *Psychology and Aging*, *18*(1), 91–110. https://doi.org/10.1037/0882-7974.18.1.91
Sambataro, F., Murty, V. P., Callicott, J. H., Tan, H.-Y., Das, S., Weinberger, D. R., & Mattay, V. S. (2010). Age-related alterations in default mode network: Impact on working memory performance. *Neurobiology of Aging*, *31*(5), 839–852. https://doi.org/10.1016/j.neurobiolaging.2008.05.022
Sarazin, M., Deweer, B., Merkl, A., Von Poser, N., Pillon, B., & Dubois, B. (2002). Procedural learning and striatofrontal dysfunction in Parkinson's disease. *Movement Disorders*, *17*(2), 265–273. https://doi.org/10.1002/mds.10018
Schaefer, S. Y., Malek-Ahmadi, M., Hooyman, A., King, J. B., & Duff, K. (2022). Association between Motor Task Performance and Hippocampal Atrophy Across Cognitively Unimpaired, Amnestic Mild Cognitive Impairment, and Alzheimer's Disease Individuals. *Journal of Alzheimer's Disease*, *85*(4), 1411–1417. https://doi.org/10.3233/JAD-210665
Scheltens, P., Blennow, K., Breteler, M. M. B., de Strooper, B., Frisoni, G. B., Salloway, S., & Van der Flier, W. M. (2016). Alzheimer's disease. *The Lancet*, *388*(10043), 505–517. https://doi.org/10.1016/S0140-6736(15)01124-1
Schlerf, J., Ivry, R. B., & Diedrichsen, J. (2012). Encoding of Sensory Prediction Errors in the Human Cerebellum. *Journal of Neuroscience*, *32*(14), 4913–4922. https://doi.org/10.1523/JNEUROSCI.4504-11.2012
Schmahmann, J. D. (2016). Cerebellum in Alzheimer's disease and frontotemporal dementia: Not a silent bystander. *Brain: A Journal of Neurology*, *139*(Pt 5), 1314–1318. https://doi.org/10.1093/brain/aww064
Schmahmann, J. D. (2019). The cerebellum and cognition. *Neuroscience Letters, The Cerebellum in Health and Disease*, *688*, 62–75. https://doi.org/10.1016/j.neulet.2018.07.005
Schmidt, R. A. (1991). *Motor learning & performance: From principles to practice* (pp. ix, 310). Human Kinetics Books.
Schroeter, M. L., Schmiedel, O., & von Cramon, D. Y. (2004). Spontaneous Low-Frequency Oscillations Decline in the Aging Brain. *Journal of Cerebral Blood Flow & Metabolism*, *24*(10), 1183–1191. https://doi.org/10.1097/01.WCB.0000135231.90164.40
Seidler, R. D. (2007). Aging affects motor learning but not savings at transfer of learning. *Learning & Memory (Cold Spring Harbor, N.Y.)*, *14*(1–2), 17–21. https://doi.org/10.1101/lm.394707
Seidler, R. D., Bo, J., & Anguera, J. A. (2012). Neurocognitive contributions to motor skill learning: The role of working memory. *Journal of Motor Behavior*, *44*(6), 445–453. https://doi.org/10.1080/00222895.2012.672348
Seidler, R. D., Gluskin, B. S., & Greeley, B. (2017). Right prefrontal cortex transcranial direct current stimulation enhances multi-day savings in sensorimotor adaptation. *Journal of Neurophysiology*, *117*(1), 429–435. https://doi.org/10.1152/jn.00563.2016
Serrien, D. J., Swinnen, S. P., & Stelmach, G. E. (2000). Age-Related Deterioration of Coordinated Interlimb Behavior. *The Journals of Gerontology: Series B*, *55*(5), P295–P303. https://doi.org/10.1093/geronb/55.5.P295
Shadmehr, R., & Brashers-Krug, T. (1997). Functional Stages in the Formation of Human Long-Term Motor Memory. *Journal of Neuroscience*, *17*(1), 409–419. https://doi.org/10.1523/JNEUROSCI.17-01-00409.1997
Shaw, L. M., Korecka, M., Clark, C. M., Lee, V. M.-Y., & Trojanowski, J. Q. (2007). Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nature Reviews Drug Discovery*, *6*(4), Article 4. https://doi.org/10.1038/nrd2176
Shen, H. H. (2015). Resting-state connectivity. *Proceedings of the National Academy of Sciences*, *112*(46), 14115–14116. https://doi.org/10.1073/pnas.1518785112
Shen, Q., Ren, H., & Duong, T. Q. (2008). CBF, BOLD, CBV, and CMRO2 fMRI Signal Temporal Dynamics at 500-msec Resolution. *Journal of Magnetic Resonance Imaging : JMRI*, *27*(3), 599–606. https://doi.org/10.1002/jmri.21203
Shin, W., Horowitz, S., Ragin, A., Chen, Y., Walker, M., & Carroll, T. J. (2007). Quantitative cerebral perfusion using dynamic susceptibility contrast MRI: Evaluation of reproducibility and age- and gender-dependence with fully automatic image postprocessing algorithm. *Magnetic Resonance in Medicine*, *58*(6), 1232–1241. https://doi.org/10.1002/mrm.21420
Shrout, P. E., & Fleiss, J. L. (1979). Intraclass correlations: Uses in assessing rater reliability. *Psychological Bulletin*, *86*(2), 420–428. https://doi.org/10.1037/0033-2909.86.2.420

Singh, S. P. (2014). Magnetoencephalography: Basic principles. *Annals of Indian Academy of Neurology*, *17*(Suppl 1), S107–S112. https://doi.org/10.4103/0972-2327.128676
Smallwood, J., Bernhardt, B. C., Leech, R., Bzdok, D., Jefferies, E., & Margulies, D. S. (2021). The default mode network in cognition: A topographical perspective. *Nature Reviews Neuroscience*, *22*(8), Article 8. https://doi.org/10.1038/s41583-021-00474-4
Smith, C. D., Walton, A., Loveland, A. D., Umberger, G. H., Kryscio, R. J., & Gash, D. M. (2005). Memories that last in old age: Motor skill learning and memory preservation. *Neurobiology of Aging*, *26*(6), 883–890. https://doi.org/10.1016/j.neurobiolaging.2004.08.014
Smith, M. A., Ghazizadeh, A., & Shadmehr, R. (2006a). Interacting adaptive processes with different timescales underlie short-term motor learning. *PLoS Biology*, *4*(6), e179. https://doi.org/10.1371/journal.pbio.0040179
Smith, M. A., Ghazizadeh, A., & Shadmehr, R. (2006b). Interacting adaptive processes with different timescales underlie short-term motor learning. *PLoS Biology*, *4*(6), e179. https://doi.org/10.1371/journal.pbio.0040179
Smitha, K., Akhil Raja, K., Arun, K., Rajesh, P., Thomas, B., Kapilamoorthy, T., & Kesavadas, C. (2017). Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. *The Neuroradiology Journal*, *30*(4), 305–317. https://doi.org/10.1177/1971400917697342
Sokolov, A. A., Miall, R. C., & Ivry, R. B. (2017). The Cerebellum: Adaptive Prediction for Movement and Cognition. *Trends in Cognitive Sciences*, *21*(5), 313–332. https://doi.org/10.1016/j.tics.2017.02.005
Song, A. W., Wolff, S. D., Balaban, R. S., & Jezzard, P. (1997). The effect of off-resonance radio frequency pulse saturation on fMRI contrast. *NMR in Biomedicine*, *10*(4–5), 208–215. https://doi.org/10.1002/(SICI)1099-1492(199706/08)10:4/5%3C208::AID-NBM467%3E3.0.CO;2-S
Soria Lopez, J. A., González, H. M., & Léger, G. C. (2019). Chapter 13—Alzheimer's disease. In S. T. Dekosky & S. Asthana (Eds.), *Handbook of Clinical Neurology* (Vol. 167, pp. 231–255). Elsevier. https://doi.org/10.1016/B978-0-12-804766-8.00013-3
Sosnik, R., Polyakov, F., & Flash, T. (2009). Motor Sequences. In *Encyclopedia of Neuroscience* (pp. 1047–1056). Elsevier. https://doi.org/10.1016/B978-008045046-9.01325-5
Sowell, E. R., Thompson, P. M., & Toga, A. W. (2004). Mapping Changes in the Human Cortex throughout the Span of Life. *The Neuroscientist*, *10*(4), 372–392. https://doi.org/10.1177/1073858404263960
Stebbins, G. T. (2007). Chapter 27—Neuropsychological Testing. In C. G. Goetz (Ed.), *Textbook of Clinical Neurology (Third Edition)* (pp. 539–557). W.B. Saunders. https://doi.org/10.1016/B978-141603618-0.10027-X
Stergiou, N., Kent, J. A., & McGrath, D. (2016). *Human Movement Variability and Aging*. https://doi.org/10.1123/kr.2015-0048
Stoodley, C. J. (2012). The Cerebellum and Cognition: Evidence from Functional Imaging Studies. *The Cerebellum*, *11*(2), 352–365. https://doi.org/10.1007/s12311-011-0260-7
Stoodley, C. J., & Schmahmann, J. D. (2009). Functional topography in the human cerebellum: A meta-analysis of neuroimaging studies. *NeuroImage*, *44*(2), 489–501. https://doi.org/10.1016/j.neuroimage.2008.08.039
Sullivan, G. M., & Feinn, R. (2012). Using Effect Size—Or Why the P Value Is Not Enough. *Journal of Graduate Medical Education*, *4*(3), 279–282. https://doi.org/10.4300/JGME-D-12-00156.1
't Hart, B. M., Taqvi, U., Gastrock, R. Q., Ruttle, J. E., Modchalingam, S., & Henriques, D. Y. P. (2024). Measures of Implicit and Explicit Adaptation Do Not Linearly Add. *eNeuro*, *11*(8), ENEURO.0021-23.2024. https://doi.org/10.1523/ENEURO.0021-23.2024
Tanaka, H., Ishikawa, T., Lee, J., & Kakei, S. (2020). The Cerebro-Cerebellum as a Locus of Forward Model: A Review. *Frontiers in Systems Neuroscience*, *14*. https://doi.org/10.3389/fnsys.2020.00019
Tankus, A., & Fried, I. (2012). Visuomotor coordination and motor representation by human temporal lobe neurons. *Journal of Cognitive Neuroscience*, *24*(3), 600–610. https://doi.org/10.1162/jocn_a_00160
Tarantini, S., Tran, C. H. T., Gordon, G. R., Ungvari, Z., & Csiszar, A. (2017). Impaired neurovascular coupling in aging and Alzheimer's disease: Contribution of astrocyte dysfunction and endothelial

impairment to cognitive decline. *Experimental Gerontology*, *94*, 52–58. https://doi.org/10.1016/j.exger.2016.11.004
Tarumi, T., & Zhang, R. (2018). Cerebral Blood Flow in Normal Aging Adults: Cardiovascular Determinants, Clinical Implications, and Aerobic Fitness. *Journal of Neurochemistry*, *144*(5), 595–608. https://doi.org/10.1111/jnc.14234
Tavor, I., Jones, O. P., Mars, R. B., Smith, S. M., Behrens, T. E., & Jbabdi, S. (2016). Task-free MRI predicts individual differences in brain activity during task performance. *Science*, *352*(6282), 216–220. https://doi.org/10.1126/science.aad8127
Taylor, J. A., Klemfuss, N. M., & Ivry, R. B. (2010). An explicit strategy prevails when the cerebellum fails to compute movement errors. *Cerebellum (London, England)*, *9*(4), 580–586. https://doi.org/10.1007/s12311-010-0201-x
Taylor, J. A., Krakauer, J. W., & Ivry, R. B. (2014a). Explicit and Implicit Contributions to Learning in a Sensorimotor Adaptation Task. *Journal of Neuroscience*, *34*(8), 3023–3032. https://doi.org/10.1523/JNEUROSCI.3619-13.2014
Taylor, J. A., Krakauer, J. W., & Ivry, R. B. (2014b). Explicit and Implicit Contributions to Learning in a Sensorimotor Adaptation Task. *Journal of Neuroscience*, *34*(8), 3023–3032. https://doi.org/10.1523/JNEUROSCI.3619-13.2014
Therrien, A. S., & Wong, A. L. (2022). Mechanisms of Human Motor Learning Do Not Function Independently. *Frontiers in Human Neuroscience*, *15*, 785992. https://doi.org/10.3389/fnhum.2021.785992
Thomas, J. R., Yan, J. H., & Stelmach, G. E. (2000). Movement Substructures Change as a Function of Practice in Children and Adults. *Journal of Experimental Child Psychology*, *75*(3), 228–244. https://doi.org/10.1006/jecp.1999.2535
Thomas Yeo, B. T., Krienen, F. M., Eickhoff, S. B., Yaakub, S. N., Fox, P. T., Buckner, R. L., Asplund, C. L., & Chee, M. W. L. (2015). Functional specialization and flexibility in human association cortex. *Cerebral Cortex*, *25*(10), 3654–3672. https://doi.org/10.1093/cercor/bhu217
Thomas Yeo, B. T., Krienen, F. M., Sepulcre, J., Sabuncu, M. R., Lashkari, D., Hollinshead, M., Roffman, J. L., Smoller, J. W., Zöllei, L., Polimeni, J. R., Fischl, B., Liu, H., & Buckner, R. L. (2011). The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *Journal of Neurophysiology*, *106*(3), 1125–1165. https://doi.org/10.1152/jn.00338.2011
Tian, Q., Chastan, N., Bair, W.-N., Resnick, S. M., Ferrucci, L., & Studenski, S. A. (2017). The brain map of gait variability in aging, cognitive impairment and dementia—A systematic review. *Neuroscience & Biobehavioral Reviews*, *74*, 149–162. https://doi.org/10.1016/j.neubiorev.2017.01.020
Todorov, D. I., Capps, R. A., Barnett, W. H., Latash, E. M., Kim, T., Hamade, K. C., Markin, S. N., Rybak, I. A., & Molkov, Y. I. (2019). The interplay between cerebellum and basal ganglia in motor adaptation: A modeling study. *PLoS ONE*, *14*(4), e0214926. https://doi.org/10.1371/journal.pone.0214926
Tomasi, D., & Volkow, N. D. (2012a). Aging and Functional Brain Networks. *Molecular Psychiatry*, *17*(5), 471–558. https://doi.org/10.1038/mp.2011.81
Tomasi, D., & Volkow, N. D. (2012b). Aging and functional brain networks. *Molecular Psychiatry*, *17*(5), 549–558. https://doi.org/10.1038/mp.2011.81
Tommasin, S., Mascali, D., Gili, T., Eid Assan, I., Moraschi, M., Fratini, M., Wise, R. G., Macaluso, E., Mangia, S., & Giove, F. (2017). Task-Related Modulations of BOLD Low-Frequency Fluctuations within the Default Mode Network. *Frontiers in Physics*, *5*. https://doi.org/10.3389/fphy.2017.00031
Tong, Y., Hocke, L. M., Licata, S. C., & Frederick, B. deB. (2012). Low-frequency oscillations measured in the periphery with near-infrared spectroscopy are strongly correlated with blood oxygen level-dependent functional magnetic resonance imaging signals. *Journal of Biomedical Optics*, *17*(10), 106004. https://doi.org/10.1117/1.JBO.17.10.106004
Toniolo, S., Serra, L., Olivito, G., Caltagirone, C., Mercuri, N. B., Marra, C., Cercignani, M., & Bozzali, M. (2020). Cerebellar White Matter Disruption in Alzheimer's Disease Patients: A Diffusion Tensor Imaging Study. *Journal of Alzheimer's Disease*, *74*(2), 615–624. https://doi.org/10.3233/JAD-191125
Trewartha, K. M., Garcia, A., Wolpert, D. M., & Flanagan, J. R. (2014). Fast But Fleeting: Adaptive Motor Learning Processes Associated with Aging and Cognitive Decline. *Journal of Neuroscience*, *34*(40), 13411–13421. https://doi.org/10.1523/JNEUROSCI.1489-14.2014

Tsay, J. S., Kim, H. E., McDougle, S. D., Taylor, J. A., Haith, A., Avraham, G., Krakauer, J. W., Collins, A. G., & Ivry, R. B. (2024). Fundamental processes in sensorimotor learning: Reasoning, refinement, and retrieval. *eLife*, *13*, e91839. https://doi.org/10.7554/eLife.91839

Tseng, Y., Diedrichsen, J., Krakauer, J. W., Shadmehr, R., & Bastian, A. J. (2007). Sensory Prediction Errors Drive Cerebellum-Dependent Adaptation of Reaching. *Journal of Neurophysiology*, *98*(1), 54–62. https://doi.org/10.1152/jn.00266.2007

Tsvetanov, K. A., Henson, R. N. A., Jones, P. S., Mutsaerts, H., Fuhrmann, D., Tyler, L. K., Cam-CAN, & Rowe, J. B. (2021). The effects of age on resting-state BOLD signal variability is explained by cardiovascular and cerebrovascular factors. *Psychophysiology*, *58*(7), e13714. https://doi.org/10.1111/psyp.13714

Tsvetanov, K. A., Henson, R. N. A., & Rowe, J. B. (2021). Separating vascular and neuronal effects of age on fMRI BOLD signals. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *376*(1815), 20190631. https://doi.org/10.1098/rstb.2019.0631

Tsvetanov, K. A., Henson, R. N. A., Tyler, L. K., Davis, S. W., Shafto, M. A., Taylor, J. R., Williams, N., Cam-CAN, & Rowe, J. B. (2015). The effect of ageing on fMRI: Correction for the confounding effects of vascular reactivity evaluated by joint fMRI and MEG in 335 adults. *Human Brain Mapping*, *36*(6), 2248–2269. https://doi.org/10.1002/hbm.22768

Tzvi, E., Loens, S., & Donchin, O. (2022). Mini-review: The Role of the Cerebellum in Visuomotor Adaptation. *Cerebellum (London, England)*, *21*(2), 306–313. https://doi.org/10.1007/s12311-021-01281-4

Uddin, L. Q., & Garavan, H. (2026). Task and Resting-State Functional Magnetic Resonance Imaging Modeling of Brain-Behavior Relationships in Developmental Cohorts. *Biological Psychiatry, The Promise and Challenges of Mapping Brain-Behavior Associations in Psychiatry*, *99*(10), 830–839. https://doi.org/10.1016/j.biopsych.2025.09.012

United Nations. (n.d.). *Population*. United Nations. Retrieved June 9, 2026, from https://www.un.org/en/global-issues/population

Uusberg, A., Uibo, H., Kreegipuu, K., & Allik, J. (2013). EEG alpha and cortical inhibition in affective attention. *International Journal of Psychophysiology*, *89*(1), 26–36. https://doi.org/10.1016/j.ijpsycho.2013.04.020

Uwisengeyimana, J. de D., Nguchu, B. A., Wang, Y., Zhang, D., Liu, Y., Qiu, B., & Wang, X. (2020). Cognitive function and cerebellar morphometric changes relate to abnormal intra-cerebellar and cerebro-cerebellum functional connectivity in old adults. *Experimental Gerontology*, *140*, 111060. https://doi.org/10.1016/j.exger.2020.111060

Vachon, C. M., Modchalingam, S., Hart, B. M. 't, & Henriques, D. Y. P. (2020). The effect of age on visuomotor learning processes. *PLOS ONE*, *15*(9), e0239032. https://doi.org/10.1371/journal.pone.0239032

van der Zwaag, W., Jorge, J., Butticaz, D., & Gruetter, R. (2015). Physiological noise in human cerebellar fMRI. *Magnetic Resonance Materials in Physics, Biology and Medicine*, *28*(5), 485–492. https://doi.org/10.1007/s10334-015-0483-6

Van Dijk, K. R. A., Sabuncu, M. R., & Buckner, R. L. (2012). The Influence of Head Motion on Intrinsic Functional Connectivity MRI. *NeuroImage*, *59*(1), 431–438. https://doi.org/10.1016/j.neuroimage.2011.07.044

Van Essen, D. C., Ugurbil, K., Auerbach, E., Barch, D., Behrens, T. E. J., Bucholz, R., Chang, A., Chen, L., Corbetta, M., Curtiss, S. W., Della Penna, S., Feinberg, D., Glasser, M. F., Harel, N., Heath, A. C., Larson-Prior, L., Marcus, D., Michalareas, G., Moeller, S., … WU-Minn HCP Consortium. (2012). The Human Connectome Project: A data acquisition perspective. *NeuroImage*, *62*(4), 2222–2231. https://doi.org/10.1016/j.neuroimage.2012.02.018

Van Halteren-Van Tilborg, I. A. D. A., Scherder, E. J. A., & Hulstijn, W. (2007). Motor-Skill learning in Alzheimer's disease: A review with an eye to the clinical practice. *Neuropsychology Review*, *17*(3), 203–212. https://doi.org/10.1007/s11065-007-9030-1

Van Tilborg, I. A. D. A., Kessels, R. P. C., & Hulstijn, W. (2011). Learning by observation and guidance in patients with Alzheimer's dementia. *NeuroRehabilitation*, *29*(3), 295–304. https://doi.org/10.3233/NRE-2011-0705

Vandevoorde, K., & Orban de Xivry, J.-J. (2019). Internal model recalibration does not deteriorate with age while motor adaptation does. *Neurobiology of Aging*, *80*, 138–153. https://doi.org/10.1016/j.neurobiolaging.2019.03.020

Vandevoorde, K., & Orban de Xivry, J.-J. (2020). Why is the explicit component of motor adaptation limited in elderly adults? *Journal of Neurophysiology*, *124*(1), 152–167. https://doi.org/10.1152/jn.00659.2019
Varangis, E., Habeck, C. G., Razlighi, Q. R., & Stern, Y. (2019). The Effect of Aging on Resting State Connectivity of Predefined Networks in the Brain. *Frontiers in Aging Neuroscience*, *11*. https://doi.org/10.3389/fnagi.2019.00234
Vecchio, F., Miraglia, F., Quaranta, D., Lacidogna, G., Marra, C., & Rossini, P. M. (2018). Learning processes and brain connectivity in a cognitive-motor task in neurodegeneration: Evidence from EEG network analysis. *Journal of Alzheimer's Disease*, *66*(2), 471–481. https://doi.org/10.3233/JAD-180342
Venneri, A., Gorgoglione, G., Toraci, C., Nocetti, L., Panzetti, P., & Nichelli, P. (2011). Combining Neuropsychological and Structural Neuroimaging Indicators of Conversion to Alzheimer's Disease in Amnestic Mild Cognitive Impairment. *Current Alzheimer Research*, *8*(7), 789–797. https://doi.org/10.2174/156720511797633160
Verdú, E., Ceballos, D., Vilches, J. J., & Navarro, X. (2000). Influence of aging on peripheral nerve function and regeneration. *Journal of the Peripheral Nervous System: JPNS*, *5*(4), 191–208. https://doi.org/10.1046/j.1529-8027.2000.00026.x
Verstynen, T., & Sabes, P. N. (2011). How Each Movement Changes the Next: An Experimental and Theoretical Study of Fast Adaptive Priors in Reaching. *Journal of Neuroscience*, *31*(27), 10050–10059. https://doi.org/10.1523/JNEUROSCI.6525-10.2011
Vidal-Piñeiro, D., Valls-Pedret, C., Fernández-Cabello, S., Arenaza-Urquijo, E. M., Sala-Llonch, R., Solana, E., Bargalló, N., Junqué, C., Ros, E., & Bartrés-Faz, D. (2014). Decreased Default Mode Network connectivity correlates with age-associated structural and cognitive changes. *Frontiers in Aging Neuroscience*, *6*. https://doi.org/10.3389/fnagi.2014.00256
Viessmann, O., Möller, H. E., & Jezzard, P. (2019). Dual regression physiological modeling of resting-state EPI power spectra: Effects of healthy aging. *NeuroImage, Physiological and Quantitative MRI*, *187*, 68–76. https://doi.org/10.1016/j.neuroimage.2018.01.011
Viswanathan, A., & Sudarsky, L. (2012). Chapter 45—Balance and gait problems in the elderly. In S. H. Subramony & A. Dürr (Eds.), *Ataxic Disorders* (Vol. 103, pp. 623–634). Elsevier. https://doi.org/10.1016/B978-0-444-51892-7.00045-0
Wagner, M. J., & Smith, M. A. (2008). Shared internal models for feedforward and feedback control. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *28*(42), 10663–10673. https://doi.org/10.1523/JNEUROSCI.5479-07.2008
Wali, M. (2020). Role of the somatosensory cortex in motor memory consolidation. *Journal of Neurophysiology*, *124*(3), 648–651. https://doi.org/10.1152/jn.00770.2019
Walløe, S., Pakkenberg, B., & Fabricius, K. (2014). Stereological estimation of total cell numbers in the human cerebral and cerebellar cortex. *Frontiers in Human Neuroscience*, *8*. https://doi.org/10.3389/fnhum.2014.00508
Wang, S., Rao, B., Chen, L., Chen, Z., Fang, P., Miao, G., Xu, H., & Liao, W. (2021). Using Fractional Amplitude of Low-Frequency Fluctuations and Functional Connectivity in Patients With Post-stroke Cognitive Impairment for a Simulated Stimulation Program. *Frontiers in Aging Neuroscience*, *13*, 724267. https://doi.org/10.3389/fnagi.2021.724267
Watts, D. J., & Strogatz, S. H. (1998). Collective dynamics of 'small-world' networks. *Nature*, *393*(6684), Article 6684. https://doi.org/10.1038/30918
Wei, K., & Koerding, K. (2010). Uncertainty of feedback and state estimation determines the speed of motor adaptation. *Frontiers in Computational Neuroscience*, *4*. https://doi.org/10.3389/fncom.2010.00011
Welvaert, M., & Rosseel, Y. (2013). On the Definition of Signal-To-Noise Ratio and Contrast-To-Noise Ratio for fMRI Data. *PLOS ONE*, *8*(11), e77089. https://doi.org/10.1371/journal.pone.0077089
Wiesman, A. I., Murman, D. L., May, P. E., Schantell, M., Wolfson, S. L., Johnson, C. M., & Wilson, T. W. (2021). Visuospatial alpha and gamma oscillations scale with the severity of cognitive dysfunction in patients on the Alzheimer's disease spectrum. *Alzheimer's Research and Therapy*, *13*(1), 1–12. https://doi.org/10.1186/s13195-021-00881-w
Willingham, D. B., Peterson, E. W., Manning, C., & Brashear, H. R. (1997). Patients with Alzheimer's disease who cannot perform some motor skills show normal learning of other motor skills. *Neuropsychology*, *11*(2), 261–271. https://doi.org/10.1037//0894-4105.11.2.261

Winstein, C., Lewthwaite, R., Blanton, S. R., Wolf, L. B., & Wishart, L. (2014). Infusing Motor Learning Research Into Neurorehabilitation Practice: A Historical Perspective With Case Exemplar From the Accelerated Skill Acquisition Program. *Journal of Neurologic Physical Therapy : JNPT*, *38*(3), 190–200. https://doi.org/10.1097/NPT.0000000000000046

Woletz, M., Hoffmann, A., Tik, M., Sladky, R., Lanzenberger, R., Robinson, S., & Windischberger, C. (2019). Beware detrending: Optimal preprocessing pipeline for low-frequency fluctuation analysis. *Human Brain Mapping*, *40*(5), 1571–1582. https://doi.org/10.1002/hbm.24468

Wolpe, N., Ingram, J. N., Tsvetanov, K. A., Henson, R. N., Wolpert, D. M., Tyler, L. K., Brayne, C., Bullmore, E. T., Calder, A. C., Cusack, R., Dalgleish, T., Duncan, J., Matthews, F. E., Marslen-Wilson, W. D., Shafto, M. A., Campbell, K., Cheung, T., Davis, S., Geerligs, L., … Rowe, J. B. (2020). Age-related reduction in motor adaptation: Brain structural correlates and the role of explicit memory. *Neurobiology of Aging*, *90*, 13–23. https://doi.org/10.1016/j.neurobiolaging.2020.02.016

Wolpert, D. M., Diedrichsen, J., & Flanagan, J. R. (2011). Principles of sensorimotor learning. *Nature Reviews Neuroscience*, *12*(12), 739–751. https://doi.org/10.1038/nrn3112

Wolpert, D. M., & Miall, R. C. (1996). Forward Models for Physiological Motor Control. *Neural Networks: The Official Journal of the International Neural Network Society*, *9*(8), 1265–1279. https://doi.org/10.1016/s0893-6080(96)00035-4

Wu, Q., Chan, J. S. Y., & Yan, J. H. (2016). Mild cognitive impairment affects motor control and skill learning. *Reviews in the Neurosciences*, *27*(2), 197–217. https://doi.org/10.1515/revneuro-2015-0020

Wurst, Z., Birčák Kuchtová, B., Křemen, J., Lahutsina, A., Ibrahim, I., Tintěra, J., Bartoš, A., Brabec, M., Rai, T., Zach, P., Musil, V., Olympiou, N., & Mrzílková, J. (2023). Basal Ganglia Compensatory White Matter Changes on DTI in Alzheimer's Disease. *Cells*, *12*(9), Article 9. https://doi.org/10.3390/cells12091220

Xi, Q., Zhao, X., Wang, P., Guo, Q., Yan, C., & He, Y. (2012). Functional MRI study of mild Alzheimer's disease using amplitude of low frequency fluctuation analysis. *Chinese Medical Journal*, *125*(5), 858–862.

Xing, L., Bao, Y., Wang, B., Shi, M., Wei, Y., Huang, X., Dai, Y., Shi, H., Gai, X., Luo, Q., Yin, Y., & Qin, D. (2023). Falls caused by balance disorders in the elderly with multiple systems involved: Pathogenic mechanisms and treatment strategies. *Frontiers in Neurology*, *14*, 1128092. https://doi.org/10.3389/fneur.2023.1128092

Xing, X.-X. (2021). Globally Aging Cortical Spontaneous Activity Revealed by Multiple Metrics and Frequency Bands Using Resting-State Functional MRI. *Frontiers in Aging Neuroscience*, *13*, 803436. https://doi.org/10.3389/fnagi.2021.803436

Yabluchanskiy, A., Nyul-Toth, A., Csiszar, A., Gulej, R., Saunders, D., Towner, R., Turner, M., Zhao, Y., Abdelkari, D., Rypma, B., & Tarantini, S. (2021). Age-related alterations in the cerebrovasculature affect neurovascular coupling and BOLD fMRI responses: Insights from animal models of aging. *Psychophysiology*, *58*(7), e13718. https://doi.org/10.1111/psyp.13718

Yamaguchi, F., Meyer, J. S., Sakai, F., & Yamamoto, M. (1979). Normal human aging and cerebral vasoconstrictive responses to hypocapnia. *Journal of the Neurological Sciences*, *44*(1), 87–94. https://doi.org/10.1016/0022-510x(79)90226-0

Yan, J., & Dick, M. (2006). Practice effects on motor control in healthy seniors and patients with mild cognitive impairment and Alzheimer's disease. *Aging, Neuropsychology, and Cognition*, *13*(3–4), 385–410. https://doi.org/10.1080/138255890969609

Yan, J. H., & Zhou, C. L. (2009). Effects of motor practice on cognitive disorders in older adults. *European Review of Aging and Physical Activity*, *6*(2), 67–74. https://doi.org/10.1007/S11556-009-0049-6/FIGURES/3

Yang, A. C., Tsai, S.-J., Lin, C.-P., Peng, C.-K., & Huang, N. E. (2018a). Frequency and amplitude modulation of resting-state fMRI signals and their functional relevance in normal aging. *Neurobiology of Aging*, *70*, 59–69. https://doi.org/10.1016/j.neurobiolaging.2018.06.007

Yang, A. C., Tsai, S.-J., Lin, C.-P., Peng, C.-K., & Huang, N. E. (2018b). Frequency and amplitude modulation of resting-state fMRI signals and their functional relevance in normal aging. *Neurobiology of Aging*, *70*, 59–69. https://doi.org/10.1016/j.neurobiolaging.2018.06.007

Yang, C. S., Cowan, N. J., & Haith, A. M. (2021). De novo learning versus adaptation of continuous control in a manual tracking task. *eLife*, *10*, e62578. https://doi.org/10.7554/eLife.62578

Yang, Y., Wang, D., Hou, W., & Li, H. (2023). Cognitive Decline Associated with Aging. In Z. Zhang (Ed.), *Cognitive Aging and Brain Health* (pp. 25–46). Springer Nature. https://doi.org/10.1007/978-981-99-1627-6_3

Yu, T., Cai, L. Y., Torrisi, S., Vu, A. T., Morgan, V. L., Goodale, S. E., Ramadass, K., Meisler, S. L., Lv, J., Warren, A. E. L., Englot, D. J., Cutting, L., Chang, C., Gore, J. C., Landman, B. A., & Schilling, K. G. (2023). Distortion correction of functional MRI without reverse phase encoding scans or field maps. *Magnetic Resonance Imaging*, *103*, 18–27. https://doi.org/10.1016/j.mri.2023.06.016

Yu-Feng, Z., Yong, H., Chao-Zhe, Z., Qing-Jiu, C., Man-Qiu, S., Meng, L., Li-Xia, T., Tian-Zi, J., & Yu-Feng, W. (2007). Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. *Brain and Development*, *29*(2), 83–91. https://doi.org/10.1016/j.braindev.2006.07.002

Zhang, H., Wang, B., Li, K., Wang, X., Li, X., Zhu, J., Zhao, Q., Yang, Y., Lv, L., Zhang, M., & Zhang, H. (2019). Altered Functional Connectivity Between the Cerebellum and the Cortico-Striato-Thalamo-Cortical Circuit in Obsessive-Compulsive Disorder. *Frontiers in Psychiatry*, *10*. https://www.frontiersin.org/articles/10.3389/fpsyt.2019.00522

Zhang, Z., Wang, H., Zhang, T., Nie, Z., & Wei, K. (2024). Perceptual error based on Bayesian cue combination drives implicit motor adaptation. *eLife*, *13*. https://doi.org/10.7554/eLife.94608.2

Zhao, S., Li, Y., Shi, Y., & Li, X. (2023). Cognitive Aging: How the Brain Ages? In Z. Zhang (Ed.), *Cognitive Aging and Brain Health* (pp. 9–21). Springer Nature. https://doi.org/10.1007/978-981-99-1627-6_2

Zhao, W., Makowski, C., Hagler, D. J., Garavan, H. P., Thompson, W. K., Greene, D. J., Jernigan, T. L., & Dale, A. M. (2023). Task fMRI paradigms may capture more behaviorally relevant information than resting-state functional connectivity. *NeuroImage*, *270*, 119946. https://doi.org/10.1016/j.neuroimage.2023.119946

Zheng, J., Yang, Q., Makris, N., Huang, K., Liang, J., Ye, C., Yu, X., Tian, M., Ma, T., Mou, T., Guo, W., Kikinis, R., & Gao, Y. (2023). Three-Dimensional Digital Reconstruction of the Cerebellar Cortex: Lobule Thickness, Surface Area Measurements, and Layer Architecture. *Cerebellum (London, England)*, *22*(2), 249–260. https://doi.org/10.1007/s12311-022-01390-8

Zhong, X. Z., & Chen, J. J. (2022). Resting-state functional magnetic resonance imaging signal variations in aging: The role of neural activity. *Human Brain Mapping*, *43*(9), 2880–2897. https://doi.org/10.1002/hbm.25823

Zhou, W., Fitzgerald, J., Colucci-Chang, K., Murthy, K. G., & Joiner, W. M. (2017). The temporal stability of visuomotor adaptation generalization. *Journal of Neurophysiology*, *118*(4), 2435–2447. https://doi.org/10.1152/jn.00822.2016

Zhou, W., Kruse, E. A., Brower, R., North, R., & Joiner, W. M. (2022). Motion state-dependent motor learning based on explicit visual feedback is quickly recalled, but is less stable than adaptation to physical perturbations. *Journal of Neurophysiology*, *128*(4), 854–871. https://doi.org/10.1152/jn.00520.2021

Zhou, Z., Li, H., Srinivasan, D., Abdulkadir, A., Nasrallah, I., Wen, J., Doshi, J., Erus, G., Mamourian, E., Bryan, N. R., Wolk, D. A., Beason-Held, L., Resnick, S. M., Satterthwaite, T. D., Davatzikos, C., Shou, H., & Fan, Y. (2023). Multiscale functional connectivity patterns of the aging brain learned from harmonized rsfMRI data of the multi-cohort iSTAGING study. *NeuroImage*, *269*, 119911. https://doi.org/10.1016/j.neuroimage.2023.119911

Zou, Q., Ross, T. J., Gu, H., Geng, X., Zuo, X.-N., Hong, L. E., Gao, J.-H., Stein, E. A., Zang, Y.-F., & Yang, Y. (2013). Intrinsic resting-state activity predicts working memory brain activation and behavioral performance. *Human Brain Mapping*, *34*(12), 3204–3215. https://doi.org/10.1002/hbm.22136

Zou, Q.-H., Zhu, C.-Z., Yang, Y., Zuo, X.-N., Long, X.-Y., Cao, Q.-J., Wang, Y.-F., & Zang, Y.-F. (2008). An improved approach to detection of amplitude of low-frequency fluctuation (ALFF) for resting-state fMRI: Fractional ALFF. *Journal of Neuroscience Methods*, *172*(1), 137–141. https://doi.org/10.1016/j.jneumeth.2008.04.012

Zuo, L., Lan, X., Zhou, Y., Liu, H., Hu, Y., Wang, Y., Liu, T., & Li, Z. (2025). Cerebellar-cerebral circuits functional connectivity in patients with cognitive impairment after basal ganglia stroke: A pilot study. *Frontiers in Aging Neuroscience*, *17*, 1478891. https://doi.org/10.3389/fnagi.2025.1478891

Zuo, X.-N., Di Martino, A., Kelly, C., Shehzad, Z. E., Gee, D. G., Klein, D. F., Castellanos, F. X., Biswal, B. B., & Milham, M. P. (2010). The oscillating brain: Complex and reliable. *NeuroImage*, *49*(2), 1432–1445. https://doi.org/10.1016/j.neuroimage.2009.09.037

Zvornik, A., Andersen, K. A., Petersen, A. D., Novén, M., Siebner, H. R., Lundbye-Jensen, J., & Karabanov, A. N. (2024). Older and younger adults differ in time course of skill acquisition but not in overall improvement in a bimanual visuomotor tracking task. *Frontiers in Aging Neuroscience*, *16*. https://doi.org/10.3389/fnagi.2024.1373252

Appendix

A. Supplementary Figures

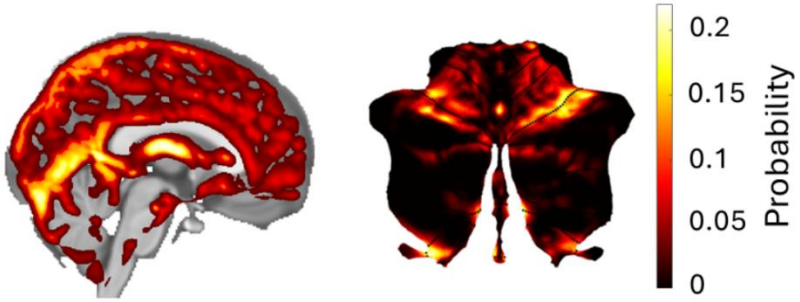


Figure A4. 1 *The Venous Probability Atlas (VENAT, left; (Huck et al., 2019)) projected on SUIT space (right).*

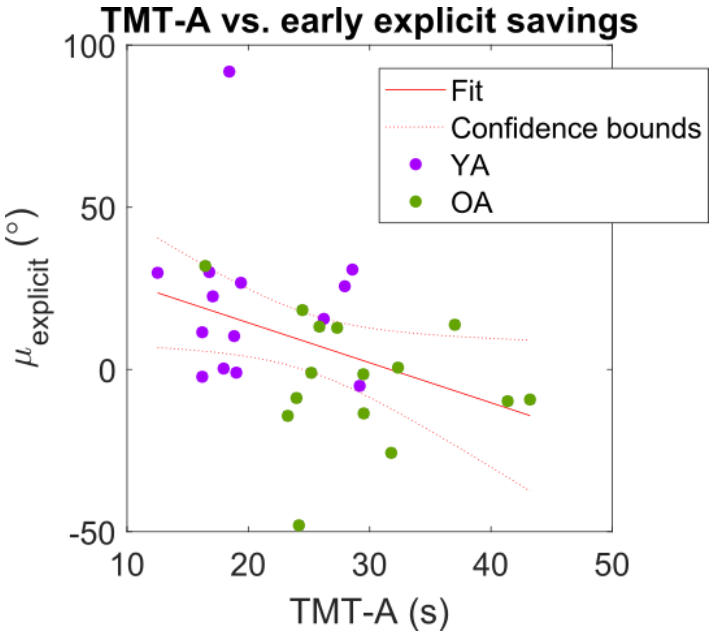


Figure A5. 1 *Correlation between TMT-A performance and savings of early explicit contributions. TMT-A was significantly correlated, p=0.0397.*

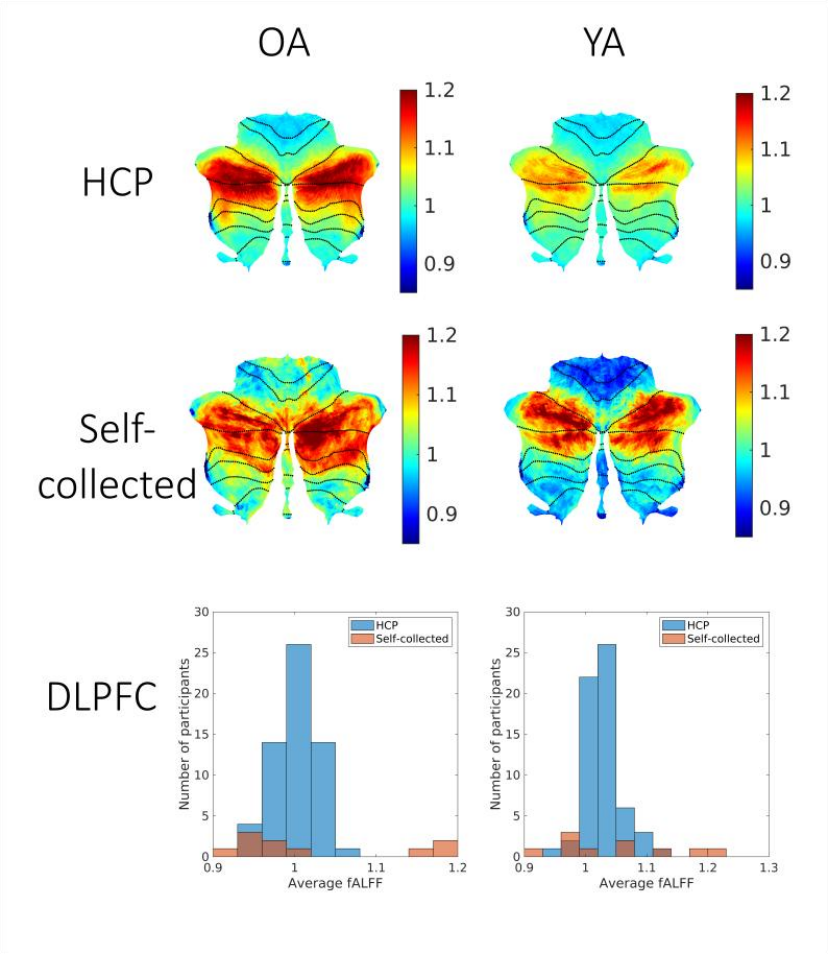


Figure A5. 2 *Comparison of self-collected fMRI data to HCP data. YA are on the left, OA on the right.* ***Top row****: tSNR from HCP dataset (similar to Figure 4.X).* ***Middle row:*** *tSNR from cerebellum from self-collected data.* ***Bottom row:*** *fALFF in the DLPFC in HCP participants (blue) and Davis/Sacramento participants (orange) in YA (left) and OA (right).*

B. Supplementary Tables

Table A4. 1 *Multi-linear mixed-effects model reporting group-level differences of FC from the cerebellar seed region, with group as a categorical variable and sex, mFD, and session as covariates for the selected cohort after controlling for random effects (N=120; YA = 61, OA = 59 after quality control). In this model, FC between the Crus II cerebellar seed and the listed ROIs are the dependent variables. Only ROIs that pass p-FDR<0.05 for the group effect are shown. The independent variables are listed below.*

Effect	β	± SE	*T*	*p*-value	*p-FDR corrected*
	Cerebellum Left VIIIb (MNI: x= -22, y= -48, z= -56) Network 3				
Group[a]	-0.395	0.129	3.064	0.0024	0.0201
mFD	0.350	1.205	0.290	0.7718	0.8898
Sex	0.121	0.113	1.072	0.2848	0.5905
Session	0.012	0.093	0.129	0.8972	0.9771
	Precentral gyrus (MNI: x= -1, y= -23, z= 62) Network 3				
Group[a]	0.473	0.158	-2.989	0.0031	0.0201
mFD	-6.060	1.473	-4.113	0.0001	0.0049**
Sex	0.154	0.139	1.108	0.2689	0.5905
Session	-0.205	0.110	-1.869	0.0629	0.5943
	Lateral occipital cortex (MNI: x= -34, y= -64, z=18) Network 5				
Group[a]	-0.527	0.164	3.209	0.0015	0.0185
mFD	0.718	1.538	0.467	0.6412	0.8232
Sex	0.012	0.144	0.086	0.9318	0.9770
Session	-0.025	0.120	-0.210	0.8340	0.9771
	Cerebellum Left IX (MNI: x= -7, y= -55, z= -49) Network 7				
Group[a]	-0.304	0.101	3.016	0.0028	0.0201
mFD	-0.698	0.929	-0.751	0.4533	0.7127
Sex	-0.069	0.089	-0.773	0.4403	0.6739
Session	0.093	0.066	1.419	0.1572	0.6541
	Cerebellum Right Crus I (MNI: x= 42, y= -49, z= -32) Network 8				
Group[a]	-0.451	0.155	2.914	0.0039	0.0234
mFD	0.576	1.405	0.410	0.6825	0.8460
Sex	-0.293	0.137	-2.139	0.0334	0.2318
Session	0.143	0.093	1.548	0.1230	0.6499
	Cerebellum Right X (MNI: x= -40, y= -52, z= -35) Network 8				
Group[a]	-0.446	0.149	2.990	0.0031	0.0201
mFD	0.166	1.341	0.124	0.9017	0.9407
Sex	-0.352	0.132	-2.662	0.0083	0.1437
Session	0.112	0.085	1.317	0.1890	0.6686
	Left middle frontal gyrus (MNI: x= -41, y= 24, z= 40) Network 13				

Group[a]	1.036	0.357	-2.903	0.0040	0.0234
mFD	-5.107	3.075	-1.661	0.0981	0.3401
Sex	0.519	0.320	1.619	0.1068	0.3612
Session	-0.029	0.169	-0.172	0.8633	0.9771
	Cerebellum Left Crus II (MNI: x= 18, y= -38, z= -45) Network 15				
Group[a]	-0.365	0.119	3.055	0.0025	0.0201
mFD	-0.909	1.119	-0.812	0.4174	0.6890
Sex	0.015	0.105	0.144	0.8857	0.9595
Session	0.098	0.088	1.120	0.2639	0.8171
	Anterior middle temporal gyrus (MNI: x= -13, y= -85, z= -40) Network 16				
Group[a]	0.820	0.260	-3.154	0.0018	0.0189
mFD	1.733	2.337	0.741	0.4592	0.7127
Sex	-0.134	0.231	-0.582	0.5609	0.7479
Session	0.113	0.147	0.770	0.4423	0.9008
	Right frontal pole (MNI: x= 61, y= -6, z= -18) Network 16				
Group[a]	1.167	0.219	-5.327	0.0000	0.0000
mFD	-4.438	2.008	-2.210	0.0280	0.1620
Sex	0.423	0.193	2.188	0.0297	0.2318
Session	0.018	0.138	0.129	0.8972	0.9771
	Right lateral occipital cortex (MNI: x= 23, y= 36, z= 43) Network 16				
Group[a]	1.104	0.229	-4.814	0.0000	0.0001
mFD	-3.569	2.104	-1.696	0.0912	0.3282
Sex	0.167	0.202	0.824	0.4110	0.6678
Session	0.073	0.146	0.503	0.6154	0.9688
	Left superior frontal gyrus (MNI: x= -21, y= 29, z = 45) Network 16				
Group[a]	0.665	0.254	-2.622	0.0093	0.0484
mFD	-7.029	2.292	-3.066	0.0024	0.0504
Sex	0.590	0.225	2.625	0.0092	0.1437
Session	0.110	0.147	0.746	0.4566	0.9008
	Right angular gyrus (MNI: x= -44, y= -68, z= 37) Network 16				
Group[a]	0.993	0.350	-2.838	0.0049	0.0270
mFD	-7.930	3.124	-2.538	0.0118	0.1022
Sex	0.522	0.311	1.676	0.0951	0.3499
Session	0.045	0.191	0.235	0.8143	0.9771
	Posterior cingulate gyrus (MNI: x= 52, y= -56, z= 28) Network 16				
Group[a]	1.519	0.280	-5.424	<0.0001	<0.0001
mFD	-2.103	2.573	-0.818	0.4145	0.6890
Sex	0.255	0.247	1.034	0.3024	0.6047
Session	0.151	0.179	0.842	0.4005	0.8723

	Medial superior frontal gyrus (MNI: x= 0, y= 50, z= 30) Network 16				
Group[a]	0.737	0.216	-3.405	0.0008	0.0115
mFD	-2.731	1.986	-1.375	0.1704	0.4192
Sex	0.255	0.191	1.336	0.1828	0.4648
Session	0.009	0.137	0.064	0.9492	0.9771
	Paracingulate gyrus (MNI: x= 0, y= 50 z= 5) Network 16				
Group[a]	0.713	0.200	-3.561	0.0004	0.0077
mFD	-5.279	1.845	-2.862	0.0046	0.0597
Sex	0.175	0.177	0.988	0.3240	0.6115
Session	-0.062	0.130	-0.481	0.6312	0.9688
	Right posterior middle temporal gyrus (MNI: x= 61, y= -25, z= -6) Network 17				
Group[a]	0.679	0.222	-3.057	0.0025	0.0201
mFD	1.315	2.081	0.632	0.5280	0.7845
Sex	0.391	0.195	2.004	0.0462	0.2529
Session	0.099	0.163	0.612	0.5414	0.9008
	Left angular gyrus (MNI: x= -52, y= -54, z= 28) Network 17				
Group[a]	1.185	0.371	-3.193	0.0016	0.0185
mFD	-8.282	3.158	-2.623	0.0093	0.0878
Sex	0.626	0.334	1.874	0.0622	0.2941
Session	-0.162	0.168	-0.964	0.3361	0.8544
	Right anterior middle temporal gyrus (MNI: x= 51, y= 4, z= -30) Network 17				
Group[a]	0.677	0.173	-3.903	0.0001	0.0028
mFD	-3.576	1.598	-2.238	0.0262	0.1600
Sex	0.361	0.153	2.358	0.0192	0.1997
Session	-0.031	0.113	-0.271	0.7867	0.9771
	Left posterior middle temporal gyrus (MNI: x= -56, y= -11, z= -19) Network 17				
Group[a]	0.748	0.193	-3.878	0.0001	0.0028
mFD	-4.327	1.737	-2.491	0.0134	0.1073
Sex	0.545	0.171	3.185	0.0016	0.1437
Session	-0.066	0.110	-0.595	0.5524	0.9008