# Neural Underpinnings of Learning in Dementia Populations: A Review of Motor Learning Studies Combined with Neuroimaging

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## Abstract

■ The intent of this review article is to serve as an overview of current research regarding the neural characteristics of motor learning in Alzheimer disease (AD) as well as prodromal phases of AD: at-risk populations, and mild cognitive impairment. This review seeks to provide a cognitive framework to compare various motor tasks. We will highlight the neural characteristics related to cognitive domains that, through imaging, display functional or structural changes because of AD progression. In turn, this motivates the use of motor learning paradigms as possible screening techniques for AD and will build upon our current understanding of learning abilities in AD populations. ■

## 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, Acar, & Daffner, 2018). Alzheimer 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, Isaacson, Knox, Sabbagh, & Rubino, 2021; Soria Lopez, González, & Léger, 2019). Mild cognitive impairment (MCI) is objective cognitive impairment in at least one memory (amnestic) or nonmemory (non-amnestic) cognitive domain that is less severe than what is observed in AD. Although 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 (Liss et al., 2021; Dubois et al., 2010). 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 cognitive changes. 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; Scheltens et al., 2016; Dubois et al., 2010).

Although 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, Korecka, Clark, Lee, & Trojanowski, 2007). In addition, the diagnostic process and screening of these biomarkers often does not start until severe changes in behavior and cognition, particularly memory loss, are noticeable by the patient or an informant (Alberdi, Aztiria, & Basarab, 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

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

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environmental change. A more in-depth review of these motor learning domains, their classifications, and their analyses can be found in Krakauer and colleagues (Krakauer, Hadjiosif, Xu, Wong, & Haith, 2019).

Motor actions in healthy populations have well-studied functional network substrates involving structures such as the cerebellum (Sakai, Hikosaka, & Nakamura, 2004; Llinás & Welsh, 1993), 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 Rosch & Mostofsky, 2019; Schmahmann, 2019; Opitz, 2014; Funahashi & Andreau, 2013, 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, Wu, Chan, & Yan, 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 participant may be instructed to complete a task "as quickly and accurately as possible," and their RT 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 participant's execution or suppression of goal-directed movement (Mirabella, Casanova, & Lebedev, 2014). As the participant 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 participant repeats the movement, they will have to remember what sequence of actions resulted in successful task completion.

Cognitive faculties typically decline in healthy aging (Yang, Wang, Hou, & Li, 2023; Zhao, Li, Shi, & Li, 2023; Salthouse, 2019). 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., RT, 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 with 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 article.

## 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 (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: EEG, magnetic resonance imaging (MRI), and magnetoencephalography (MEG). This section summarizes imaging information that is directly relevant to the studies analyzed in this review article, and is not a holistic overview of neural recording techniques.

MRI is a popular choice in motor learning studies because of 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 (WM) volume, the physical size of specific structures, the integrity of WM fiber tracts, or measurements of WM hyperintensities (lesions in WM that suggest neuronal demyelination). Brain activity can also be measured with MRI through functional imaging (fMRI). This technique records the 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, nonferrous 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 are correlated with behavioral performance measures and used to indicate a "prediction" of task performance. Although rs-fMRI is a well-studied technique, it is still to be determined if resting-state imaging is sufficient at predicting behavior outcomes (Ikeda, Kawano, Watanabe, Yamashita, & Kawahara, 2022; Tavor et al., 2016; Zou et al., 2013), or if this is better done through task-based

imaging (Zhao, Makowski et al., 2023; Gal, Coldham, Tik, Bernstein-Eliav, & Tavor, 2022).

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 with 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, Kolb, & Mohajerani, 2020). Activity can be quantified through measurement of local field potentials, 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 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 because of 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, which are analogous to local field potentials. MEG is similar to MRI 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 WM volumes throughout the brain naturally atrophy, with the most prominent degradation occurring in frontal areas and in the hippocampus (MacDonald & Pike, 2021; Burke & Barnes, 2006). 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, Dervenoulas, Politis, & for the Alzheimer's Disease Neuroimaging Initiative, 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 (Aslan et al., 2021; Ansai et al., 2018; Wu, Chan, & Yan, 2016; Montero-Odasso et al., 2014). 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, but are employed after a diagnosis has been established (Robert et al., 2010). Other behaviors such as speech and gait have been explored as quantitative behavioral markers of disease progression (Petti, Baker, & Korhonen, 2020; Belghali, Chastan, Cignetti, Davenne, & Decker, 2017), 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. In addition, 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 whereas others maintain largely normal cognitive function.

The aim of this article 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.

## 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 1.

### 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 participants or at-risk AD participants 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, Scherder, & Hulstijn, 2007), and readers are encouraged to reference these articles for additional motor learning AD articles that were not produced from our search terms.

## RESULTS

### Participant Screening Criteria

All studies were case–control studies of Level III evidence (Burns, Rohrich, & Chung, 2011). Except for Mollica and colleagues (2017) and Eslinger and Damasio (1986), studies in this review utilized either the Mini-Mental State Exam (MMSE) or Montreal Cognitive Assessment (MoCA)

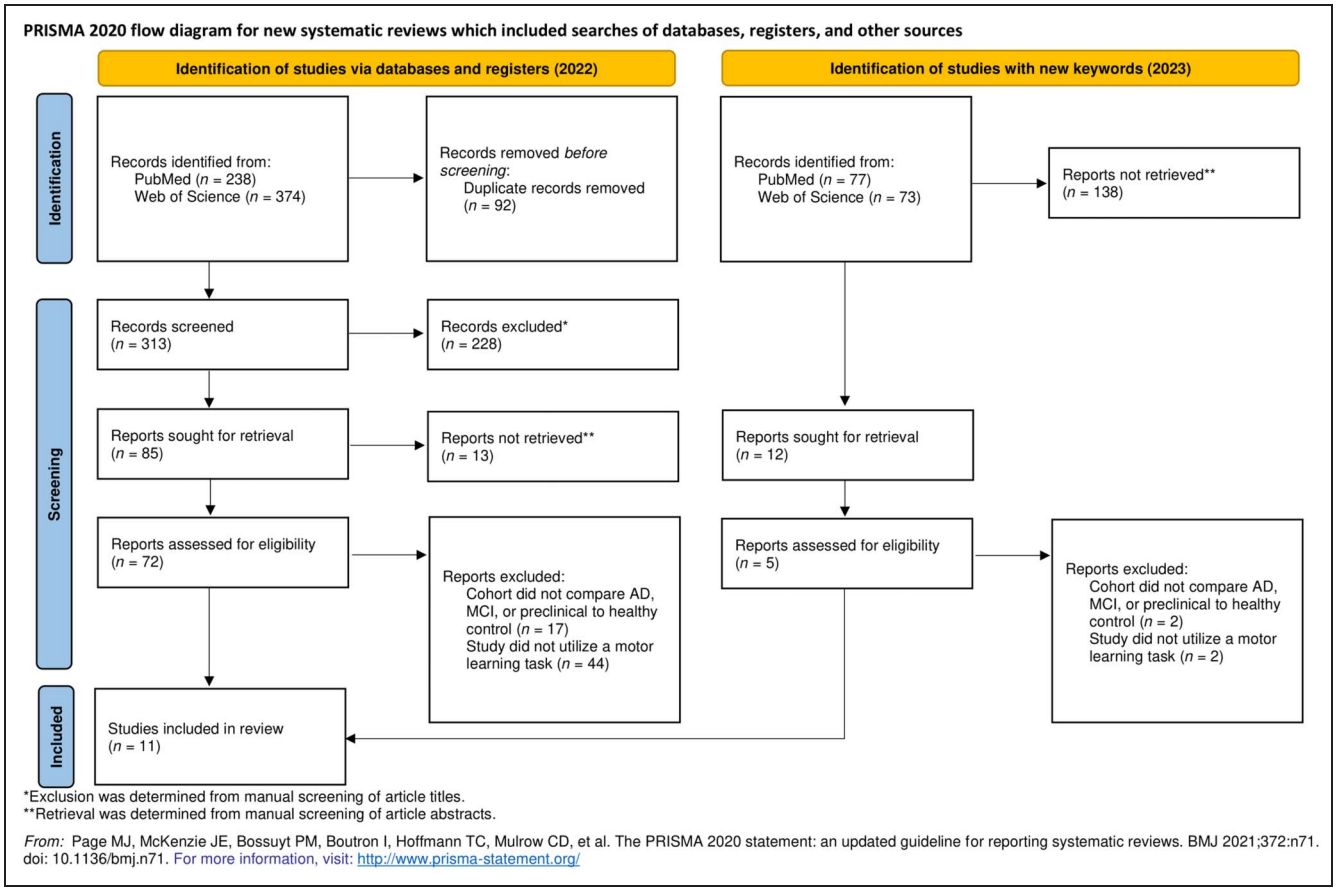


**Figure 1.** PRISMA flow diagram.

**Table 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 et al. (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 mda-MCI (7F, 6M, mean age: 71) | - MMSE<br>- California Verbal Learning Test<br>- Cambridge examination for mental disorders in elderly (CAMDEX-r)<br>- Questionnaire on subjective memory complaints<br>- IADL<br>- GDS<br>- Questionnaire with socio-demographic and clinical data | Speed of attentional shifts to target stimuli is not affected in either type of MCI, but the reduced amplitude of ERPs within temporal and parieto-occipital regions for mda-MCI patients suggests a reduced allocation of attentional resources. |
| Hawkins and Sergio (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 participants were female. | - MoCA<br>- High-risk: reporting either a maternal, multiple, or early-onset family history of AD, no cognitive impairment<br>- Low-risk: age-matched with high-risk participants, no family history, no abnormal memory complaints<br>- Saliva samples for APOE-e4 carriers | Participants with increased AD risk demonstrated more age-related WM integrity decline, with a significant association between WM compromise and cognitive motor performance. |

| | | | | | |
|---|---|---|---|---|---|
| Hawkins and Sergio (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 participants were female. | - MoCA<br>- High-risk: reporting either a maternal, multiple, or early-onset family history of AD, no cognitive impairment<br>- Low-risk: age-matched with high-risk participants, no family history, no abnormal memory complaints<br>- 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 et al. (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<br>- High-risk: reporting either a maternal, multiple, or early-onset family history of AD, no cognitive impairment<br>- Low-risk: age-matched with high-risk participants, no family history, no abnormal memory complaints<br>- Saliva samples for APOE-e4 carriers | High-risk participants 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 participants also demonstrated poorer performance in the non-standard task with lower gray matter in temporal regions. |
| Schaefer et al. (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<br>- Clinical status was confirmed with the ADNI classification battery<br>- Clinical Dementia Rating Scale<br>- 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 et al. (2018) | Sensory Motor Learning (SmoL) task of visual rotation paradigm | Resting-state functional EEG | 86 participants: 22 normal (mean age: 68.3), 47 aMCI (mean age: 72.8), 17 AD (mean age: 70.1) | - MMSE<br>- Diagnosis was based on National Institute on Aging-Alzheimer's Association workgroups | Significant differences between healthy elderly, MCI and AD patients were demonstrated by showing that physiological brain aging shows |

**Table 1.** (*continued*)

| *Author* | *Motor Task/Motor Learning Category* | *Neuromonitoring Technique* | *Population Size* | *Screening Methods* | *General Findings* |
|---|---|---|---|---|---|
| | / Motor adaptation | | | - DSM-IV-TR criteria<br>- Neuropsychological testing to assess memory, attention, executive function, visuospatial construction abilities | characteristic small world EEG rhythms, i.e., being lower in alpha bands. |
| Wiesman et al. (2021) | Visuospatial discrimination task / De novo motor task | Task-based MEG | 35 participants: 20 healthy controls (12F, 8M, mean age: 72.7), 17 aMCI (mean age: 69.3), 21 probable AD (mean age: 69.3) | - MMSE & MoCA<br>- IADL, FAQ<br>- PET scan to identify amyloid-positive groups<br>- Battery of cognitive tests to assess verbal memory, language, processing speed, learning, attention, and executive function | Participants 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. |

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; FAQ = Functional Activities Questionnaire; GDS = Geriatric Depression Scale; IADL = instrumental activities of daily living.

**Table 2.** Preclinical/MCI/AD Studies of Motor Learning without Neuromonitoring

| *Author* | *Motor Task/Motor Learning Category* | *Participants* | *Screening Methods* | *Summary of Findings* |
|---|---|---|---|---|
| Eslinger and Damasio (1986) | Angular rotary pursuit task/ motor adaptation | 16 participants: 8 healthy controls (mean age: 70.8); 8 AD participants (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 et al. (2020) | Serial Reaction Time Task (SRTT) / sequence learning | 42 participants: 22 controls (8M, 14F, mean age: 67.6); 20 MCI (13M, 7F, mean age: 66.7) | - MMSE<br>- Neuropsychological tests to assess global cognitive function, premorbid intelligence, four specific cognitive domains | MCI participants performed poorer than healthy controls in RT, commission errors, and omission errors in the SRTT. However, learning slopes in randomized blocks were similar between healthy and MCI participants, pointing to retained implicit memory. |
| Mollica et al. (2017) | VMC task / De novo motor task | 81 participants: 47 controls (mean age: 65.4); 19 "preclinical" (mean age: 67.4); 15 AD (mean age: 68.1) | - CSF p-tau, tau testing<br>- Depression and anxiety assessments<br>- Self-rated subjective cognitive decline questionnaires<br>- Neuropsychological tests to assess recall, total recall, learning, total learning, semantic fluency, visual object and space perception battery | RT was longer than controls in preclinical AD, and even longer in AD. This was the only behavioral measurement that was significantly different when compared with the control group. Visuomotor dysfunction occurs at earlier stages of AD and may be associated with cerebrospinal fluid Aβ42 protein deposition. |
| Yan and Dick (2006) | Novel motor reaching task / Motor acuity | 88 participants: 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<br>- Functional deficits: BADLS, FAQ, NPI<br>- No history of chronic alcoholism, psychiatric illness, or other neurological disorders<br>- CDR scale<br>- Hachiniski Ischemic Scale<br>- Tested for Vitamin B-12 deficiency, thyroid-stimulating hormone<br>- 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 participants only improved movement time. |

ADRDA = Alzheimer's Disease and Related Disorders Association; BADLS = Bristol Activities of Daily Living Scale; CDR = clinical dementia rating; CSF = cerebrospinal fluid; P-tau = phosphorylated tau; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke; NPI = Neuro-Psychiatric Inventory; SPECT = single-photon emission computed tomography.

to identify the cognitive status of all the participants. In general, a participant 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 and multidomain amnestic MCI scored 1.5 *SD*s below healthy age- and education-matched peers on the MMSE (these healthy scores were between 24 and 30), whereas 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 (Part A and/or Part B) and/or the Wechsler Adult Intelligence Scale was used in Schaefer, Mollica, Hong, 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.

The overall age of participants in these studies ranged between 60 and 80 years for controls, MCI, and AD. Participants in these studies were also closely balanced in sex, apart from Hawkins and Sergio (2014, 2016), where all participants were female, and in Mollica and Eslinger, where participant sex was not reported or clearly delineated within cognitive groups. Regarding participant demographics, only Schaefer and colleagues 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 and colleagues, with 86 total participants. The smallest participant group was in Vidoni and colleagues, with 19 total participants 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 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.

## 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) because of practice.

### *Task Descriptions*

Yan and Dick (2006) required participants to move a stylus on a tablet from a centered starting position away from

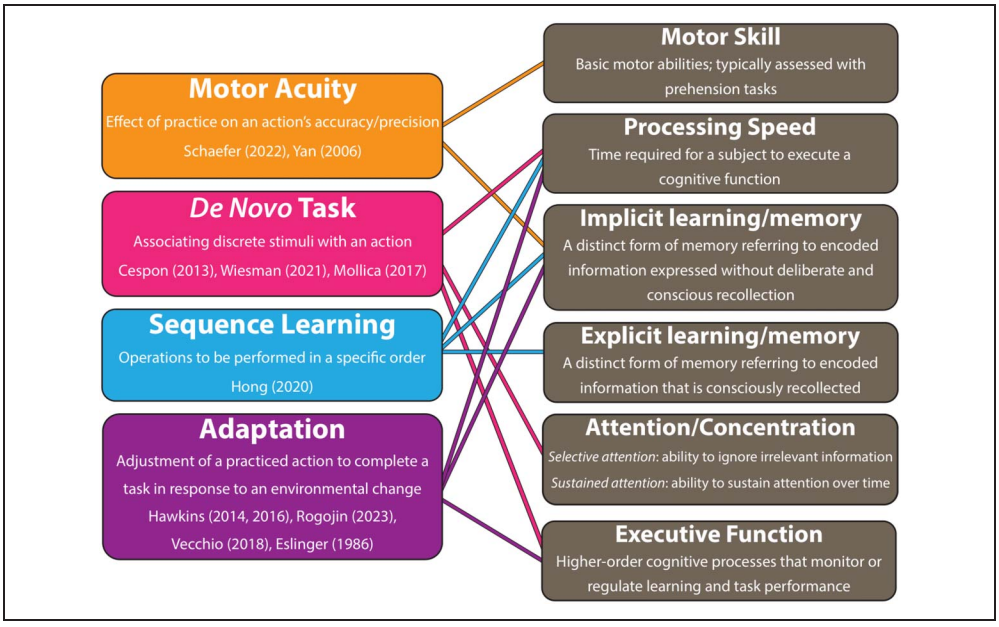


**Figure 2.** Cognitive domains assessed by each motor task. Figure adapted from Krakauer (Krakauer et al., 2019). Each motor task can assess multiple cognitive domains listed. Definitions obtained from Harvey (2019), Zucchella and colleagues (2018), and Baggetta and Alexander (2016).

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, Malek-Ahmadi, Hooyman, King, and Duff (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 (Long, Feng, Liao, Zhou, & Urbin, 2018; Albouy et al., 2008) and movement execution (Burman, 2019) combined with well-established patterns of atrophy in the hippocampus in AD (de Flores, La Joie, & Chételat, 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 nondominant 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 participants 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 before visual feedback (Fradet, Lee, & Dounskaia, 2008). As a result, an increase in primary submovement after repeated attempts is a measure of retention of motor experience (Thomas, Yan, & Stelmach, 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 (Yan & Zhou, 2009; Ghilardi et al., 2000).

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 intraparticipant 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 (VMC) is relatively understudied, but previous studies have demonstrated recruitment of the hippocampus and other temporal regions for VMC (Onuki, Van Someren, De Zeeuw, & Van der Werf, 2015; Tankus & Fried, 2012). Combined with known deficits in AD participants' learning ability because of 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, Peterson, Manning, & Brashear, 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 (Jin, Qin, Zhang, & Chen, 2020; Allison et al., 2019; Parizkova et al., 2018; Allison, Fagan, Morris, & Head, 2016).

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.

## Sequence Learning

Learning the sequences of actions is an important aspect in daily functioning and is a major component of Instrumental 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 utility of sequence learning studies in assessing AD (i.e., recalling the sequence of actions to complete a functional goal in ADL assessments; Alberdi et al., 2016; Robert et al., 2010; Benke, 1993), our search did not produce any articles in which neural imaging was conducted on AD participants in conjunction with a motor sequence task. Consequently, proposed mechanisms will be summarized, and we will provide a brief overview of overall findings.

### *Task Description*

Hong (Hong, Alvarado, Jog, Greve, & Salat, 2020) employed a well-studied behavioral paradigm, the serial reaction time task (SRTT), to study learning deficits in MCI populations compared with 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, with patterned blocks comprised of a 12-button pattern repeated six times. Both the random and sequenced portions of the paradigm were designed to have an "equal probability of button pressing". The authors made these modifications to the SRTT to parse out motor skill contributions from implicit cognitive learning. The subsequent models of learning were controlled for motor skill learning, allowing for analysis representative of implicit learning between MCI and healthy groups.

### *Processing Speed*

Regardless of the block type, MCI participants had significantly slower mean RTs compared with 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 Yan and 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 participants, MCI participants demonstrated higher commission errors per block. Both groups demonstrated improved motor skill as opposed to implicit procedural learning, as indicated by greater improvement in randomized blocks than the sequenced blocks. Notably, the similarity between groups in patterned blocks points to preservation of implicit motor learning in MCI. It should be noted that explicit processes also contribute to sequenced block performance in the SRTT (Moisello et al., 2009; Robertson, 2007); however, this aspect of learning was not explored in this study.

## 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, Brower, North, Zhou, & Joiner, 2021; Taylor, Krakauer, & Ivry, 2014). However, the studies presented here did not differentiate between the two strategies. As a result, increase in performance errors are a result of task switching and have been interpreted to reflect limits in cognitive flexibility, while the measured hand or arm movement to separately 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 participants' 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. participants 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 RT, respectively) were calculated for each healthy young, low-risk AD, and high-risk AD participant 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 and Sergio (2014), Rogojin, Gorbet, Hawkins, and Sergio (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 rotary 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 diffusion tensor imaging 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 and Sergio (2016) task, this would be the ability to switch from same plane/same direction to offset plane/opposite direction tasks. The participants at high risk of AD demonstrated significantly larger error scores when the plane and direction were offset when compared with healthy controls and low-risk AD participants. 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 DMN, as identified through seed-based analysis of rs-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 and Sergio (2014) group demonstrated lower fractional anisotropy (where high fractional anisotropy 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 participants were compared with young participants, these structural changes were found to be more severe, with the WM changes also identified in the hippocampus and posterior WM tracts. The severity of WM hyperintensities in these regions correlated significantly with task performance, indicating that WM changes in normal aging occur in the anterior portions of the brain. In contrast, WM changes were more prominent in posterior regions in participants with AD, which appeared to reduce motor planning capability.

The analysis by Rogojin and colleagues (2023) demonstrated similar correlations between visuomotor performance and decreased WM integrity throughout most WM tracts, but particularly the inferior fronto-occipital fasciculus. 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 participants 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, whereas 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 before 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, Uibo, Kreegipuu, & Allik, 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.

Although Eslinger and Damasio (1986) found that AD patients demonstrated greater improvement with practice than healthy controls (similar to Schaefer et al. [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 Rogojin and colleagues (2023), Vecchio and colleagues (2018), and Hawkins and Sergio (2014, 2016), indicate that implicit learning is not preserved in AD. However, these tasks are reflective of open-loop skill learning (without direct performance feedback), whereas the rotary pursuit task in Eslinger and Damasio (1986) reflects closed-loop skill (with direct performance feedback) learning (Sarazin et al., 2002; Gabrieli, Stebbins, Singh, Willingham, & Goetz, 1997). This may contribute to the different conclusions about AD learning. Open-loop skill learning may be more sensitive to cognitive decline, as demonstrated by high-risk but asymptomatic AD participants in Hawkins' and Rogojin's tasks, but further study is required in prodromal populations to confirm this association.

## 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 participants to generate a completely new feedback controller to successfully complete the task (Yang, Cowan, & Haith, 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 and colleagues (Cespón, Galdo-Álvarez, & Díaz, 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; single domain amnestic MCI), or multidomain amnestic MCI (deficits in multiple cognitive domains including memory; multidomain amnestic MCI). Participants 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, Hommel, Korsch, & Galashan, 2020). The authors reported on the percentage of errors (percentage of incorrect button presses), RT, and "interference," the interaction effect on performance caused by the Simon effect.

In Wiesman's task (Wiesman et al., 2021), participants 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 VMC task 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 VMC, 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 RTs, errors, and omission rate for healthy, pre-AD (participants in the preclinical stage of AD), and AD participants. Differences between participants were evaluated using mean RT of correct responses.

### *Processing Speed*

In Mollica and colleagues, mean RT in AD patients were significantly slower than pre-AD and control participants. Correlations between cerebrospinal fluid Aβ42 levels, an amino acid that is a biomarker of AD, and RTs were shown across all participants. However, Cespón and Wiesman did not find RTs nor movement latency to be affected by diagnosis. Although the differences in findings may be because of inherent motor skill deficits across the AD spectrum (it is unclear if Cespón evaluated

visuomotor ability, whereas 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 multiple-domain amnestic MCI (mda-MCI) 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 mda-MCI participants 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 single-domain amnestic MCI or mda-MCI populations (Cespón et al., 2020). In addition, the authors found that diagnosis was associated with response-locked lateralized readiness potential: 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 nonrelevant stimuli (Bacigalupo & Luck, 2019; Doesburg, Bedo, & Ward, 2016). When compared with healthy controls, participants 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 participants on the AD spectrum demonstrate differences in functional selection of visual information and decreased ability to represent stimulus information in visuospatial processing.

Mollica and colleagues designed the VMC to limit the contribution of executive functions, yet 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.

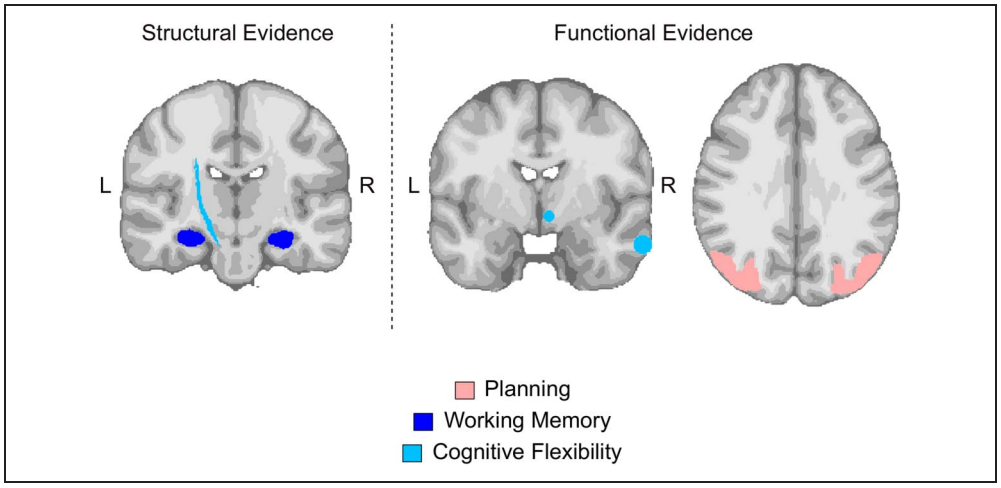


**Figure 3.** Brain regions that correlate with participant diagnosis. Tasks that evaluated planning produced decreased amplitude within posterior regions (P07 and P08 electrode pair) as noted through EEG (Cespón et al., 2013). Behavioral output measuring working memory correlated with hippocampal size (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.

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).

## 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 articles 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. In addition, despite the use of motor learning tasks, only four studies specifically assessed visuomotor abilities through the Trail-Making Test or through subtests of the Wechsler Adult Intelligence Scale–Fourth Edition. 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 and Sergio (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. 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" (Reuter-Lorenz & Mikels, 2005; Delbuck, Van der Linden, & Collette, 2003). Vecchio and colleagues (2018) found differences in neural activity within posterior regions between healthy, MCI, and AD participants that corresponded with implicit learning ability. Hawkins and Sergio (2014) noted structural changes in anterior regions for healthy aging participants, whereas the degeneration moved more to more posterior regions in at-risk AD participants. Such changes were tied to deficits in cognitive flexibility. Moreover, Wiesman and colleagues (2021) and Cespón and colleagues (2013) found a lack of inhibitory LRPs and oscillatory activity in posterior regions near the visual cortex.

Although 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. Although the temporal lobe is known to contribute to spatial navigation (Howard, Fotedar, Datey, & Hasselmo, 2005; Ekstrom et al., 2003), this region has also been tied to VMC ability (Tankus & Fried, 2012; Vann, Aggleton, & Maguire, 2009). Because navigational tasks are challenging in AD and tied to deterioration of the hippocampus (Vlček & Laczó, 2014; Gazova et al., 2013), this may be another neural change that underlies motor learning differences, even if the task is not a spatial navigation task. 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

et al. [2017] points to the posterior parietal cortex, Hong et al. [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. In addition, questions regarding generalization, adaptation processes, temporal stability, forward and inverse models, and sensory prediction errors are probed in typical motor learning settings (Zhou, Kruse, Brower, North, & Joiner, 2022; Bindra et al., 2021; Alhussein, Hosseini, Nguyen, Smith, & Joiner, 2019; Nguyen et al., 2019; McKenna, Bray, Zhou, & Joiner, 2017; Zhou, Fitzgerald, Colucci-Chang, Murthy, & Joiner, 2017; Wagner & Smith, 2008; Smith, Ghazizadeh, & Shadmehr, 2006) 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, Lum, & Ullman, 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 nonmotor studies (Phillips, McMillan, Smith, & Grossman, 2017; Eldridge, Masterman, & Knowlton, 2002; 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 (Lojkowska et al., 2013; Santos et al., 2011; Venneri et al., 2011; Thomann et al., 2008), decreased cerebellar WM integrity (Toniolo et al., 2020; Rohn, Catlin, & Poon, 2012; Fukutani, Cairns, Rossor, & Lantos, 1996), and lower cerebellar functional activity (Cha et al., 2015; Castellazzi et al., 2014; Binnewijzend et al., 2012) and decreased gray and WM volume in the basal ganglia (Wurst et al., 2023; Cho et al., 2014) correlate with AD diagnosis and MMSE scores. These subcortical regions are understudied in AD investigations because of the belief that amyloid and tau do not affect these areas (Jacobs et al., 2018) combined with the difficulty in imaging such structures (Hoch & Shepherd, 2022; Diedrichsen, Verstynen, Schlerf, & Wiestler, 2010). Discrepancies in implicit learning maintenance in MCI/AD patients as revealed by the variable performance in Schaefer and colleagues (2022), or the lack of improvement in Vecchio and colleagues (2018), may be explained by activity changes in the aforementioned subcortical regions (Bernard 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 (Van Tilborg, Kessels, & Hulstijn, 2011; Knopman & Nissen, 1987).

### Conclusion

The cognitive demand from motor learning tasks is especially high in MCI/AD populations. This results in quantitative behavioral measures that reflect the combination of multiple cognitive processes. 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 are 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.

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### Author Contributions

Jessica A. Korte: Conceptualization; Formal analysis; Investigation; Visualization; Writing—Original draft; Writing—Review & editing. Alyssa M. Weakley: Writing—Review & editing. Kareelynn Donjuan Fernandez: Formal analysis; Investigation; Visualization; Writing—Original draft. Wilsaan Joiner: Conceptualization; Supervision; Writing—Review & editing. Audrey P. Fan: Conceptualization; Supervision; Writing—Review & editing.

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## Diversity in Citation Practices

Retrospective analysis of the citations in every article published in this journal from 2010 to 2021 reveals a persistent pattern of gender imbalance: Although the proportions of authorship teams (categorized by estimated gender identification of first author/last author) publishing in the *Journal of Cognitive Neuroscience* (*JoCN*) during this period were M(an)/M = .407, W(oman)/M = .32, M/W = .115, and W/W = .159, the comparable proportions for the articles that these authorship teams cited were M/M = .549, W/M = .257, M/W = .109, and W/W = .085 (Postle and Fulvio, *JoCN*, 34:1, pp. 1–3). Consequently, *JoCN* encourages all authors to consider gender balance explicitly when selecting which articles to cite and gives them the opportunity to report their article's gender citation balance.

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