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Classification of Mild Cognitive Impairment and Alzheimer's Disease Using Manual Motor Measures

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Keywords
Manual dexterity · Alzheimer's disease · Biomarkers · Motor function · Machine learning

Abstract
Introduction: Manual motor problems have been reported in mild cognitive impairment (MCI) and Alzheimer's disease (AD), but the specific aspects that are affected, their neuropathology, and potential value for classification modeling is unknown. The current study examined if multiple measures of motor strength, dexterity, and speed are affected in MCI and AD, related to AD biomarkers, and are able to classify MCI or AD. ***Methods:*** Fifty-three cognitively normal (CN), 33 amnestic MCI, and 28 AD subjects completed five manual motor measures: grip force, Trail Making Test A, spiral tracing, finger tapping, and a simulated feeding task. Analyses included (1) group differences in manual performance; (2) associations between manual function and AD biomarkers (PET amyloid β, hippocampal volume, and APOE ε4 alleles); and (3) group classification accuracy of manual motor function using machine learning. ***Results:*** Amnestic MCI and AD subjects exhibited slower psychomotor speed and AD subjects had weaker dominant hand grip strength than CN subjects. Performance on these measures was related to amyloid β deposition (both) and hippocampal volume (psychomotor speed only). Support vector classification well-discriminated control and AD subjects (area under the curve of 0.73 and 0.77, respectively) but poorly discriminated MCI from controls or AD. ***Conclusion:*** Grip strength and spiral tracing appear preserved, while psychomotor speed is affected in amnestic MCI and AD. The

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association of motor performance with amyloid β deposition and atrophy could indicate that this is due to amyloid deposition in and atrophy of motor brain regions, which generally occurs later in the disease process. The promising discriminatory abilities of manual motor measures for AD emphasize their value alongside other cognitive and motor assessment outcomes in classification and prediction models, as well as potential enrichment of outcome variables in AD clinical trials.

Introduction

Although Alzheimer's disease (AD) is known for its hallmark memory problems, it has also been associated with impairments that spread far beyond the cognitive domain. For example, sensory deficits, such as visual problems (e.g., acuity [1] and contrast sensitivity [2]), hearing loss [3, 4], olfactory dysfunction [5, 6], and tactile deficits (e.g., angle discrimination [7]), are risk factors for AD and are already present prior to frank dementia, during the prodromal mild cognitive impairment (MCI) stage ([8, 9]). Furthermore, motor problems spanning different domains have been reported consistently in MCI and AD [10]. These include but are not limited to deficits in gait [11–13], balance [14, 15], upper and lower extremity muscle strength [16–18], dexterity (e.g., finger tapping [19], placing pegs in a board [20], drawing [21], handwriting [22, 23]), motor adaptation [24] (although motor sequence learning seems to remain intact in AD [25]), and motor-cognitive dual-tasking [26].

The above described body of studies linking motor dysfunction to MCI and AD highlight the potential value of implementing motor assessments in their diagnostic process, especially combining multiple motor measures into a single model that might substantially increase classification accuracy [27, 28]. Clinical-neurological exams generally do include a motor evaluation comprising gait, balance, bradykinesia, tremor, and rigidity [29]. Although such motor measures are found to be affected in a subset of AD patients [30], the qualitative nature of the typical neurological motor exam does not lend it for combination models that can leverage the non-correlated variance of multiple input variables [31]. While clinical neuropsychological test batteries do yield quantitative outcomes, they usually do not include motor measures beyond psychomotor speed and dexterity [32]. As such, there is a need for identifying a set of variables that can be used in a clinical setting that can aid the refinement of dementia diagnostics [33]. Furthermore, characterizing motor dysfunction in AD during the preclinical phase can help with identifying behavioral functions that are potential candidates for intervention with disease-modifying therapy [10, 34, 35].

In the current, group differences between cognitively intact individuals ("healthy controls" [HC]) and those with amnestic MCI or AD in a variety of manual motor measures were evaluated. Manual motor measures comprise all behavioral assessments that quantify hand function. These motor measures may be ideal for implementation into clinical practice because they are quick and easy to administer in a limited physical space, are cost-efficient, require minimal resources, and yield quantitative measures. In a first step, the three groups were compared on the manual measures were made, and the motor measures were linked to three established biomarkers for AD: amyloid β deposition obtained from PET imaging, hippocampal volume from structural MRI scans, and number of APOE ε4 alleles obtained from blood samples. Associating motor measures back to these established AD biomarkers may provide insight into the neuropathology underlying motor deficits in amnestic MCI and AD. This information is of crucial importance, as it is still poorly understood if motor deficits in AD are more strongly related to general atrophy or amyloidosis, or both [36]. In addition, if motor measures show high agreement with existing biomarkers, they will be able to serve as surrogate markers in clinical trials and clinical practice. It is hypothesized that amnestic MCI, and to a stronger extent AD, present with manual motor deficits, and that those measures that are most different in comparison with HC are also the ones most strongly related to the three established biomarkers under study. In a second step, supervised machine learning was used to build a classification using all available manual motor measures. We hypothesized that the machine learning model will yield good classification accuracy for distinguishing AD from HC but may perform less well with differentiating amnestic MCI from HC and AD, given that amnestic MCI represents an intermediate stage between HC and AD.

Method

Subjects

Subjects were sampled from a recently completed study (R01AG055428 [37–39]) of brain imaging and neuropsychological testing across the dementia spectrum. Motor measures were added in the framework of an ongoing study (K01AG073578). HC subjects were recruited from the community. The majority of amnestic MCI (single or multi-domain) and AD subjects were

recruited from the University of Utah cognitive disorders' clinic [40]. Their diagnosis was based on a neurological visit, neuropsychological evaluation, and brain imaging. A minority of amnestic MCI subjects (~24%) came from the community sample who met criteria after cognitive evaluation. Confirmation of group assignment was made with the Alzheimer's Disease Neuroimaging Initiative [41] classification battery, which comprises the mini mental state examination [42], the Clinical Dementia Rating Scale [43], and the Wechsler Memory Scale-Revised [44] Logical Memory II Paragraph A. The final sample included 53 subjects who were classified as cognitively intact, 33 with amnestic MCI (single or multi-domain), and 28 with mild or moderate AD. This study was performed in accordance with the Declaration of Helsinki and was approved by the University of Utah Institutional Review Board (#00106377). Control subjects and MCI subjects provided written informed consent. Individuals with AD provided assent while a legally authorized representative provided consent on their behalf.

Inclusion criteria were (a) age 65 years or older and (b) availability of a knowledgeable collateral source to comment on their cognition and daily functioning. Exclusion criteria comprised (a) medical comorbidities likely to affect cognition (i.e., neurological conditions, current severe depression, substance abuse, and major psychiatric conditions); (b) inability to complete magnetic resonance imaging (MRI) or positron emission tomography (PET) imaging; (c) inability to complete cognitive assessments due to inadequate vision, hearing, or manual dexterity; (d) being enrolled in a clinical drug trial related to anti-amyloid agents; (e) elevated depression as indicated by a score of greater than 5 on the 15-item Geriatric Depression Scale; and (f) severe dementia as indicated by a Clinical Dementia Rating score of 2 or greater or a mini mental state examination score of less than 20.

Demographic and clinical information of the 114 subjects is presented in Table 1. The overall group mean age was 74.6 ± 5.9 years. Of all subjects in the sample, 55.3% were female, and 97.4% were Caucasian or white. Mean premorbid intellectual functioning, as measured by the reading subtest of the 4th edition of the Wide Range Achievement Test [45], was in the normal range for all three groups. Symptoms of depression, which were assessed using the Geriatric Depression Scale [46], were minimal and below the cut-off score for clinical depression. An overview of performance on a range of cognitive domains by group can be found in online supplementary Table 1 (for all online suppl. material, see https://doi.org/10.1159/000539800).

Motor Assessment and Motor Data Pre-processing

An overview describing all outcome measures can be found in online supplementary Table 2. Study data were collected and managed using REDCap electronic data capture tools [47, 48].

Grip Force Strength

Grip strength was measured in pounds using a hydraulic Jamar Smart Hand Digital Dynamometer [49]. The assessment protocol has been described previously [50]. Subjects were positioned in a chair with legs, back support, and fixed arms. When the start sign was given, subjects were encouraged to squeeze as long and as tightly as possible for 5 s. Assessments were completed for the left and right hand three times each, in alternating fashion, starting with the left hand.

Grip strength data were collected for 114 subjects. The trial average for the subjects' dominant and non-dominant hand was calculated, based on their handedness obtained using the Dutch Handedness Questionnaire [51].

Archimedes Spiral Test

Archimedes spiral tracing performance was assessed using an in-house developed computerized test consisting of a spiral template that was printed on a piece of paper attached to an electronic drawing board (Wacom Intuos Wireless Pen Tablet, model CTL4100) connected to a 2017 13" MacBook laptop running MATLAB R2017b for recording. Subjects were instructed to place the pen in the center of the spiral template before the tracing started. While tracing, they were not allowed to lean on the drawing board with their hand or arm. Subjects were asked to trace the spiral as accurately and as fast as possible using their dominant hand.

Pen position was recorded at a rate of 60 Hz. Subjects' drawings were evaluated visually to ensure proper data collection, resulting in analyzable data for 107 subjects. The main reason for missing data was because subjects did not start tracing the spiral at the center of the template. Automatic quantitative analyses were performed using custom-made software written in MATLAB R2013a. This yielded the following outcome measures: movement time (seconds), defined as the time it took the subject to trace the spiral; length of drawing (cm), defined as the length of the drawn spiral; average speed, defined as the ratio of drawing length and movement time; speed variability (cm/s), defined as the standard deviation (SD) of the instantaneous speed; deviation from template (in pixels), defined as the area between the template and the drawn spiral; number of crossings, defined as the number of times the drawn spiral crossed the template, and return movements, defined as the absence or presence of one or more return movements. A qualitative overview of spiral tracings is presented in online supplementary Figure 1.

Although "return movements" and "number of crossings" are count variables, taking their median over trials resulted in fractional numbers, as there were several subjects who did not complete three valid trials. As such, these outcomes were treated as continuous variables. Note that the number of subjects with one or two invalid trials did not differ between groups ($\chi^2(\text{df} = 4, N = 107) = 3.84, p = 0.43$).

Trail Making Test A

The Trail Making Test A (TMT-A) performance relies on both motor (psychomotor speed [52, 53]) and cognitive functions (i.e., attention, visual search and scanning, sequencing [52]). Here the paper and pencil version of TMT-A that consist of a letter sized paper with the numbers 1–25 printed in circles randomly distributed across the sheet was used. Subjects were instructed to connect the circles in numeric order using a pencil as fast as possible. Completion time was recorded as the outcome measure. TMT-A data were available for 114 subjects. For statistical analysis, one outlier ($z = 4.73$) was removed.

Finger Tapping

Finger tapping data were available for 110 subjects. Assessment of finger tapping has been described previously [19]. In short, a computerized finger tapping test that was developed in-house using version 3 of the PsychoPy software suite [54–56] was used to measure unimanual and bimanual finger tapping performance. The task can be downloaded from: https://github.com/vnckppl/FingerTappingTask [57]. The task has four conditions

Table 1. Demographics

Variable	Metric	Controls	MCI		AD		Total
				p value		*p* value	
Sample size	*n*	**53**	**33**		**28**		**114**
Age, years	m (SD)	73.9 (5.6)	74.7 (6.1)	0.58	75.7 (6.4)	0.19	74.6 (5.9)
Sex (female)	*n* (%)	33 (66.3)	13 (39.4)	0.09	17 (60.7)	0.09	63 (55.3)
Right handed	*n* (%)	49 (92.5)	32 (97.0)	0.59	27 (96.4)	0.59	108 (94.7)
Education	m (SD)	16.6 (2.3)	16.2 (2.7)	0.36	15.1 (2.3)	**0.008**	16.1 (2.5)
WRAT	m (SD)	113 (8.3)	109.5 (9.2)	0.07	108 (8.7)	**0.016**	110.7 (8.8)
GDS	m (SD)	1.1 (1.3)	1.6 (1.3)	0.07	1.6 (1.5)	0.11	1.4 (1.4)
MMSE	m (SD)	29.0 (1.2)	26.3 (1.9)	<**0.001**	22.9 (2.6)	<**0.001**	26.7 (3.0)
Caucasian	*n* (%)	52 (98.1)	32 (97.0).58	0.89	27 (96.4)	0.89	111 (97.4)
AD biomarkers							
SUVR	m (SD)	0.51 (0.11)	0.72 (0.15)	<**0.001**	0.78 (0.16)	<**0.001**	0.6 (0.2)
Hippocampal volume	m (SD)	4.29 (0.48)	3.66 (0.81)	<**0.001**	3.19 (0.85)	<**0.001**	3.8 (0.8)
Number of APOE e4 alleles				<**0.001**		<**0.001**	
0	*n* (%)	40 (75.5)	8 (25.0)		9 (32.1)		57 (50.4)
1	*n* (%)	12 (22.6)	17 (53.1)		12 (42.9)		41 (36.3)
2	*n* (%)	1 (1.9)	7 (21.9)		7 (25.0)		15 (13.3)
Time since MRI[1]	m (SD)	−318.7 (292.4)	−87.1 (204.3)	<**0.001**	−135.9 (266.7)	**0.004**	−206.8 (281.9)
Time since PET[1]	m (SD)	−291.5 (300.0)	−35.2 (236.3)	<**0.001**	−82.8 (295.1)	**0.002**	−167.2 (303.8)

m, mean; SD, standard deviation; *n*, number; *p*, *p* value compared to the control group. Linear regression analysis was used for continuous variables and χ^2 tests to compare proportions; Education = years of education completed; WRAT= normative, age corrected standard score of the wide range achievement test-4 reading subtest; GDS = total score on the geriatric depression scale; MMSE = mini mental state examination; Caucasian = self-reported Caucasian or white race; SUVR = ^{18}F-Flutemetamol PET scan global composite standardized uptake value ratio; Hippocampal volume = bilateral hippocampal volume expressed as per-thousand of the estimated total intracranial volume. [1]Number of days between neuroimaging (MRI or PET) assessment and completion of motor assessments. A negative number indicates that neuroimaging assessment preceded the motor assessment.

(left index finger tapping, right index finger tapping, simultaneous index finger tapping, and alternate finger tapping) each consisting of three 10-s trials. Finger taps were registered by left and right finger presses on the corresponding shift keys on the keyboard. For single finger tapping, subjects were instructed to press as fast as possible. For dual finger tapping, subjects were instructed to press simultaneously with their left and right index fingers as fast as possible with the goal to complete as many pairs within 10 s. For the alternate tapping test, subjects were instructed to tap using one index finger after the other, as fast as possible, starting with either side.

Left and right handed performance was converted to dominant and non-dominant hand performance for analysis. Presence of tapping gaps, defined as periods where subjects paused tapping for 1 s or more were extracted from the raw data for all conditions. Each outcome measure was collected 3 times. The subject's median score was selected for each of these outcome measures to yield scores robust against outliers at the subject level. Finger tapping performance for this sample has been described separately [19]. Here, results of the group analyses of finger tapping performance or their relationship with AD biomarkers are not repeated, but finger tapping outcome measures were included in the machine learning classification model. An overview of group differences in tapping performance for the current sample is included as online supplementary Table 3.

Simulated Feeding Task

The simulated feeding task (SFT) is a manual motor task in which subjects are asked to move beans between cups using a spoon, which has been validated against activities of daily living outcomes in amnestic MCI patients [58]. A visual demonstration of the task is available via the Open Science Framework (https://osf.io/phs57/wiki/Functional_reaching_task/). Methods of this task have been described previously [59, 60]. In short, subjects use a standard plastic spoon to scoop two raw kidney beans at a time from a central cup (all cups were 9.5 cm in diameter and 5.8 cm deep) to one of three distal cups arranged at a radius of 16 cm at −40°, 0°, and 40° relative to the central cup. Subjects were instructed to use their non-dominant hand (to avoid ceiling effects) to move two beans at a time from the central cup to the cup ipsilateral (same side) to the hand used, then from the central cup to the middle cup, and lastly from the central cup to the contralateral cup. They were requested to repeat this sequence four more times for a total of 15 out-and-back movements. After the subject completed the task once with their dominant hand, six trials of this task were completed with the non-dominant hand. Trial completion time in seconds was recorded for all trials.

Time to complete the dominant hand trial, time to complete the first non-dominant hand trial, average time over the 6 non-dominant hand trials, non-dominant hand variability scores over the 6 trials (calculated with a proprietary algorithm), and the

non-standardized and standardized (i.e., divided by the intercept) linear regression beta-coefficient over the 6 trials were calculated and used as input for the classification model. SFT performance for this sample has been described separately [59–61]. Here, results of the SFT group analyses or their relationship with AD biomarkers are not repeated, but SFT outcome measures are included in the machine learning classification model. An overview of group differences in SFT performance for the current sample is included as online supplementary Table 3.

AD Biomarkers

The well-established AD biomarkers [62] that were cross-correlated with manual motor performance were whole brain amyloid β deposition, hippocampal volume, and APOE ε4 allele status.

Amyloid β Deposition

^{18}F-Flutemetamol, a radioactive diagnostic agent indicated for PET imaging of the brain, was used to estimate β-amyloid neuritic plaque density (deposition). The ligand was produced under PET cGMP standards and conducted under an approved FDA Investigational New Drug (IND) application. Imaging was performed on A GE Discovery PET/CT 710 (GE Healthcare), which has a full width at half-maximum spatial resolution of 5.0 mm and excellent performance characteristics [63, 64]. Emission imaging took 20 min and was performed 90 min after the injection of approximately 185 mBq (5 mCi) of ^{18}F-Flutemetamol. A regional semi-quantitative technique described by Vandenberghe et al. [65] and refined by Thurfjell et al. [66] was used to analyze the ^{18}F-Flutemetamol binding. The CortexID Suite software (GE Healthcare) was used to automatically obtained a composite standardized uptake value ratio in the cerebral cortex which was normalized to the pons [67]. PET imaging was collected on average 23.9 ± 43.4 weeks prior to the motor assessments.

Hippocampal Volume

MRI images were acquired on a 3.0 T S Prisma scanner with a 64-channel head coil. T1-weighted data were acquired using a sagittal MP2RAGE sequence (TR = 5,000 ms, TE = 2.93 ms, flip angles = 4° and 5°, respectively, acquisition matrix = 256 × 256, field of view = 256 × 256 mm, slice thickness 1 mm, resolution = 1 × 1 × 1 mm, acquisition time = ~7 min). All scans were examined for the presence of common artifacts, including motion, susceptibility, and distortion, and were determined to be of sufficient quality for quantitative analysis. All data were processed on the same workstation using FreeSurfer image analysis suite v6.0 (http://surfer.nmr.mgh.harvard.edu/) to estimate total intracranial and hippocampal volumes. Technical details have been described previously [68–70]. Hippocampal volumes were expressed as proportion of the estimated total intracranial volume to account for differences in head size [71]. MRI scans were collected on average 29.5 ± 40.3 weeks prior to the motor assessments.

APOE Genotyping

Polymerase chain reaction and fluorescence monitoring using hybridization probes for APOE genotyping was conducted using whole blood samples. Subjects were classified into three groups of having 0, 1, or 2 APOE ε4 alleles.

Statistical Analysis

Group Differences and Associations with Biomarkers

Group differences in demographics and motor performance and correlations with biomarkers were computed in R version 4.3.1. The significance level of 0.05 was used for all hypothesis tests, and false discovery rate (FDR) correction was applied to adjust for multiple comparisons. Group differences for potentially confounding variables were examined using linear regression models for continuous variables and using χ^2 tests for categorical variables via the MASS R package (7.3–60). Group differences in motor performance measures and associations between continuous biomarkers (i.e., Amyloid β deposition and hippocampal volume) and motor performance measures were assessed using linear regression analysis. Associations between count (i.e., number of APOE ε4 alleles) biomarkers and motor performance measures were tested using Poisson regression analysis. All models were adjusted for age and sex.

To identify how motor function differed between preclinical and clinical AD versus cognitively intact individuals, differences between (a) control subjects and amnestic MCI subjects; and (b) control subjects and AD subjects were tested.

The η^2 value for the group factor, i.e., the proportion of variance in the model explained by group, is reported as a measure of effect size for the group comparisons. The η^2 value for the motor outcome measure is reported as a measure of effect size for the motor-biomarker association analyses for continuous biomarkers. Incidence rate ratios were reported as measure of effect size for the motor-biomarker association analyses for count biomarkers.

For group comparisons, multiple comparison correction was applied by running FDR correction on the total, single array of p values for both the comparisons of controls versus amnestic MCI subjects and controls versus AD subjects. For motor-biomarker associations, multiple comparison correction was applied by running FDR correction on the total, single array of p values of all three biomarker and motor variable combinations.

Substantial non-normality of the residuals of the outcome measure in a linear regression can violate the assumptions for this method. In order to mitigate potential effects of non-normality of the data on the reported results, a three-step approach was taken: (1) outliers, defined as values smaller or larger than 2.5 standard deviations from the total sample mean, were set to the mean ± 2.5 standard deviation; (2) variables with a skewness ≥1 were log-transformed; (3) non-parametric permutation regression analysis (https://github.com/mtorchiano/lmPerm) was used for the analysis of group difference of motor measures and analysis of associations between motor measures and AD biomarkers. Because this approach did not result in significantly different outcomes, only the results from the analysis of non-transformed data using conventional linear regression were reported for greater interpretability.

Classification Modeling

Support Vector Classification (SVC) from the Scikit Learn (1.3.0) package implemented in Python 3.11.3 was used for classification. In total, 2 grip strength variables, 10 Archimedes spiral variables, 2 TMT-A variables, 24 finger tapping variables, and 7 simulated feedings task variables were entered as motor predictors. Note that for the previous group difference analysis only raw TMT-A performance was considered, while here both

raw and scaled-scores (scores adjusted for age and sex) are incorporated. This was done to reduce the number of multiple comparisons for the group analysis, while also trying to build the most optimal classification model. Age and sex were also entered into the classification model, as a way of controlling for any imbalance in these variables between groups. An overview of all motor outcome measures that were selected for the machine learning model is presented in online supplementary Table 2.

Data were split into a training set (70% of the data) and a testing set (30% of the data). The Pipeline and GridSearchCV methods from Scikit Learn with 5-fold cross-validation were used to identify the optimal model based on the training data. Parameter tuning for all pre-processing steps described below were carried out as part of a single pipeline. Data were scaled using a robust scaler, which removes the median from the data and subsequently scales them according to the quantile range. Scaling is necessary to prevent variables recorded on a larger numeric scale receiving larger weights in the support vector classification. Balanced iterative logistic regression-based recursive feature elimination with a step size of 1 and with the Limited-Memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) as the optimization algorithm, was used to determine features to retain. The optimal number of features was determined by iterating over the range starting at 1 to the total number of features. Nine out of the 47 input variables were retained: dominant finger tapping speed, number of trials without gaps or onset delays for non-dominant hand tapping, TMT-A raw and scaled score, simulated feeding task non-dominant hand average, simulated feeding task variability scores (2), simulated feeding task dominant hand completion time, and sex.

Synthetic oversampling of all classes but the majority class was applied to reduce the effect of imbalances in the number of subjects per group. GridSearchCV selected Adaptive Synthetic (ADASYN [72]) oversampling over Support Vector Machine-Synthetic Minority Over-Sampling Technique (SVM-SMOTE [73, 74]; both from the imblearn-learn package 0.11.0) or no oversampling. SVM-SMOTE synthetically generates extra samples of the minority class along directions from existing minority class samples residing near the decision boundary derived using SVM. ADASYN synthetically generates extra samples of the minority class along directions from existing minority class samples across the entire feature space, but it generates different numbers of samples depending on an estimate of the local distribution of the minority class.

The SVC was run as part of GridSearchCV to identify optimal model parameters. It was identified that a radial basis function (as compared to a linear function), a regularization parameter of 1 (selected from: 0.1, 1, 10, 100, 1,000) and a gamma parameter of 0.01 (selected from: 1, 0.1, 0.01, 0.001, 0.0001) yielded optimal predictive results given the training sample. The overall classification accuracy of the training model was 70%. Bootstrapping with replacement of the test data set with 500 iterations was used to obtain median and 95% confidence intervals for model accuracy [75].

Permutation feature importance analysis was used to identify the contribution of individual predictor variables to the prediction model. For each of the 9 selected variables, the model was rerun 200 times, each time randomly shuffling the values of all subjects for that variable to render it meaningless on average. The difference in overall model accuracy using the original (true) data compared to the data with reshuffled values is a measure of how much the particular variable contributes to the overall accuracy of the model.

Results

On average, HC subjects had completed an additional 1.5 years of education and had a premorbid intelligence quotient that was 5 points higher than AD subjects (see Table 1). Both the amnestic MCI and AD group had a lower MMSE score than control subjects. Mean age, the distribution of sex, handedness, the amount of depression symptoms, and race did not differ significantly between groups (all ps ≥ 0.09).

Group Differences in Motor Performance

An overview of unadjusted motor scores stratified by group is presented in Table 2. Both amnestic MCI and AD subjects performed slower on TMT-A. AD subjects also had weaker dominant hand grip strength than control subjects (see Table 3; Fig. 1). No group differences in spiral tracing performance were observed.

Because of the well-documented sex-differences in grip strength in the general population [76], a post hoc analysis was conducted to evaluate if the observed group difference in grip strength between HC and AD differed for males and females. To this end, a group-by-sex interaction term was added to the linear model. Because further splitting up groups reduces statistical power, the amnestic MCI and AD groups were combined into a single group. This analysis revealed that female, but not male, amnestic MCI and AD subjects had weaker non-dominant hand grip strength than HC (beta = −10.7, p = 0.04, η^2 = 0.01).

Associations between Motor Performance and AD Biomarkers

Significant associations between motor performance measures and biomarkers are displayed in Figure 2. Collapsed over all groups, an increase in completion time for the TMT-A was associated with a larger composite score of Amyloid β deposition (0.0030 ± 0.0012, p = 0.016, η^2 = 0.05). One pound decrease in dominant hand grip strength was associated with a 0.0027 (±0.0012, p = 0.035, η^2 = 0.04) larger composite score of amyloid β deposition. An increase in TMT-A completion time was also associated with smaller hippocampi (−0.0113 ± 0.0054, p = 0.037, η^2 = 0.03). These results, however, did not survive FDR correction for multiple comparisons. No other motor measures were associated with AD biomarkers ($0.09 < p < 0.96$).

Classification Modeling

The overall classification accuracy of the training data was 70%, while the overall median classification accuracy of the independent test data was 58% with a 95% confidence interval of [42%, 73%]. That is, 58% of the subjects in an

Table 2. Unadjusted group means

Variable	Controls	MCI	AD	Total	*n*
Trail Making Test A					
Time to complete[s]	30.3 (9.7)	37.2 (14.2)	47.6 (14.2)	36.5 (14.0)	113
Hand grip strength					
Dominant[lbs]	64.8 (21.1)	66.9 (22.3)	56.2 (22.8)	63.3 (22.1)	114
Non-dominant[lbs]	61.9 (20.4)	64.3 (23.7)	54.6 (21.8)	60.8 (21.9)	114
Spiral Tracing Test					
Movement time[s]	9.6 (5.7)	8.6 (4.1)	8.9 (4.8)	9.1 (5.0)	107
Trace length[p]	2,657.8 (112.5)	2,672.3 (128.8)	2,663.3 (121.7)	2,663.3 (118.6)	107
Average speed[p/s]	374.1 (192.3)	413.3 (179.5)	389.0 (186.2)	388.9 (186.3)	107
Speed variability[p/s]	2,657.8 (112.5)	2,672.3 (128.8)	2,663.3 (121.7)	2,663.3 (118.6)	107
Mean template deviation[p]	7.7 (2.0)	8.2 (1.9)	8.6 (3.0)	8.1 (2.3)	107
Template deviation variability[p]	5.2 (1.5)	5.7 (1.4)	5.4 (1.7)	5.4 (1.5)	107
Template deviation sum[p]	7,261.4 (3,594.0)	7,206.3 (2,970.3)	7,327.2 (3,488.7)	7,260.8 (3,368.6)	107
Template deviation variability by time[p/s]	1 (0.7)	1.1 (1.0)	1.1 (0.8)	1 (0.8)	107
Number of crossings	4.7 (0.9)	4.6 (1.0)	4.2 (1.5)	4.6 (1.1)	107
Number of return movements	0.3 (0.5)	0.5 (0.6)	0.3 (0.5)	0.3 (0.5)	107

Raw mean averages and standard deviations (in parentheses) for the three experimental groups and the total sample. s, seconds; lbs, pounds; p, pixels; p/s, pixels per second; *n*, total number of subjects with complete data.

Table 3. Group differences in motor function

Outcome measure	MCI versus controls			AD versus controls		
	beta	*p* value	η^2	beta	*p* value	η^2
Trail Making Test A						
Raw completion time, sec	7.02	**0.013**	0.04	16.76	<**0.001**	0.22
Grip strength						
Dominant hand (lbs)	−4.14	0.176	0.01	−6.67	**0.037**	0.01
Non-dominant hand (lbs)	−4.21	0.172	0.01	−5.79	0.072	0.01
Spiral tracing						
Movement time, sec	−1.01	0.397	0.01	−0.48	0.701	<0.01
Trace length (pixels)	16.95	0.541	<0.01	11.61	0.693	<0.01
Average speed, pixels/sec	41.01	0.35	0.01	10.08	0.828	<0.01
Speed variability, σ pixels/sec	7.1	0.696	<0.01	−6.64	0.73	<0.01
Mean template deviation, pixels	0.41	0.434	0.01	0.78	0.164	0.02
Template deviation variability, σ pixels	0.56	0.107	0.02	0.11	0.76	<0.01
Template deviation sum, pixels	−106.45	0.894	<0.01	26.5	0.975	<0.01
Template deviation variability by Time, σ pixels/sec	0.09	0.611	<0.01	0.07	0.71	<0.01
Number of crossings	−0.05	0.84	<0.01	−0.44	0.116	0.02
Number of return movements	0.17	0.174	0.02	−0.02	0.892	<0.01

Values printed in **bold** indicate tests that retain significance after FDR correction.

independent data set were accurately labeled by the classification model. Compared to a null model that would simply predict the most frequent class for all observations that would yield 45% accuracy (i.e., 15 controls of out 33 subjects in the test set), this is a 13% increase in accuracy.

The group-specific precision, defined as the proportion of a group that was classified correctly (i.e., "true-positive rate") was 67% for HC, 25% for amnestic MCI, and 70% for AD. The cells of the *confusion matrix* (see Fig. 3a) show the proportion of the class in the row that is

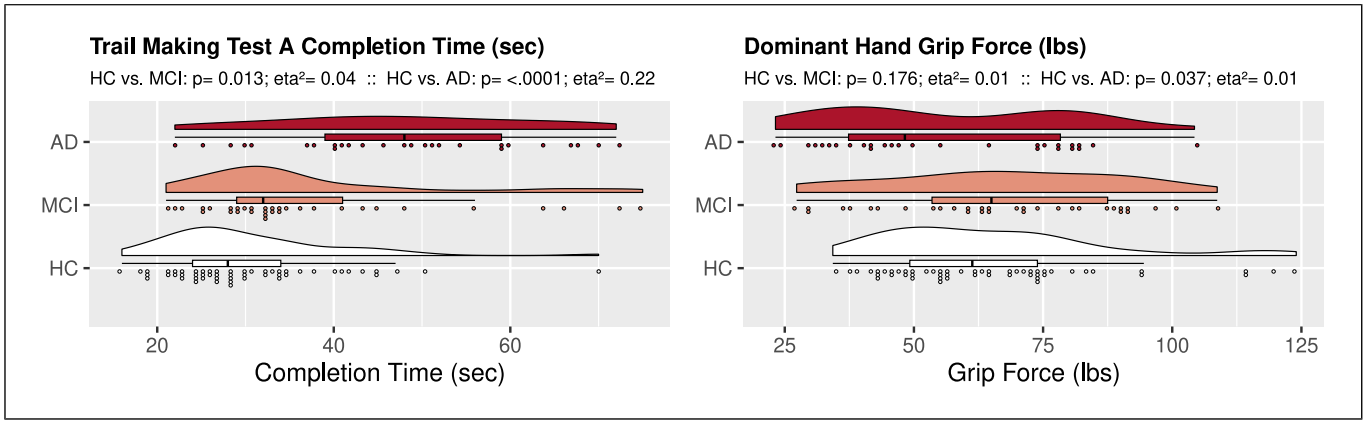

Fig. 1. Trail Making Test A and dominant hand grip strength: group comparisons. Rain cloud plots with density curves, boxplots, and individual subject scores divided over 75 bins. The top cloud (red) presents data from the AD subject group, the middle cloud (salmon colored) presents data from the amnestic MCI subject group, and the bottom cloud (white) presents data from the control group. Above each figure, *p* values and eta^2 as measures of effect size are reported (1) for the analysis comparing controls to amnestic MCI subjects ("HC vs. MCI") and (2) for the analysis comparing controls to AD subjects ("HC vs. AD"). For Trail Making Test A, both amnestic MCI and AD subjects performed slower than control subjects. AD subject had weaker Dominant Hand Grip Strength than control subjects.

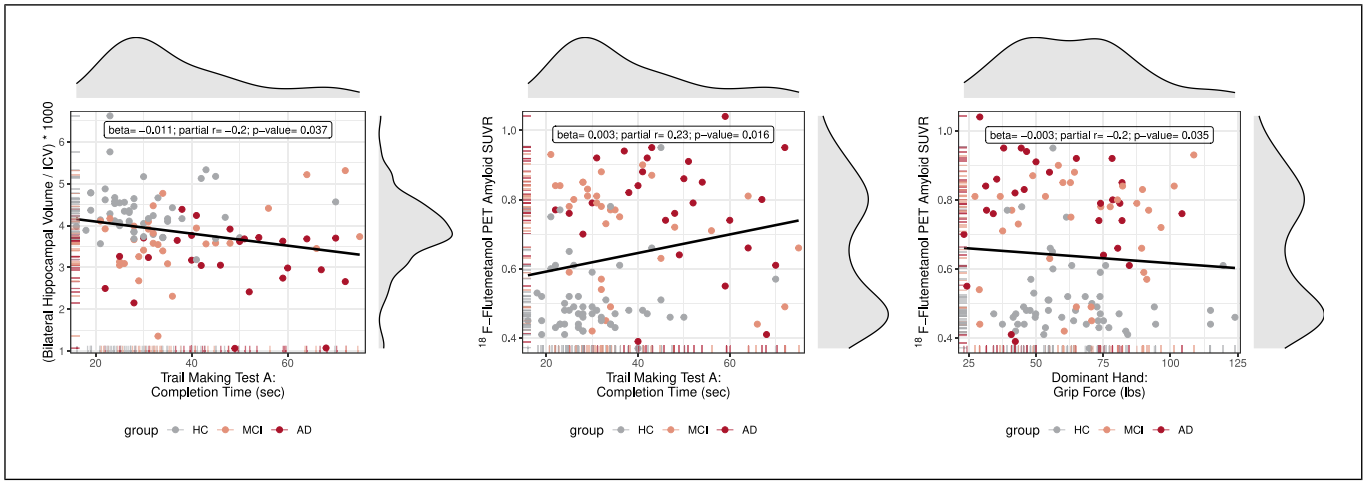

Fig. 2. Associations between AD biomarkers and motor measures. The figures display scatterplots with distribution density curves for the motor measures (top) and AD biomarker (right-hand side), as well as rug plots for the motor measures (bottom) and AD biomarker (left-hand side). Note that while individual observations are color-coded for groups, analyses were collapsed over groups. ICV, intracranial volume; SUVR, standardized uptake value ratio – whole brain relative to the pons; partial r, partial correlation coefficient adjusted for age and sex.

predicted as the class in the column. The diagonal corresponds with the group-wise "recall" of the classification model. It shows that 67% of the HC among all HC subjects and 64% of AD subjects among all AD subjects were accurately classified, while 29% of amnestic MCI subjects among all amnestic MCI subjects were correctly labeled.

In 50% of the cases, amnestic MCI subjects were classified as control subjects, and in 17% of the cases as AD subjects. Precision and recall can be combined into a single "F1" score [77], which is defined as:

$$F_1 - score = 2 \times \frac{Precision \times Recall}{Precision + Recall}$$

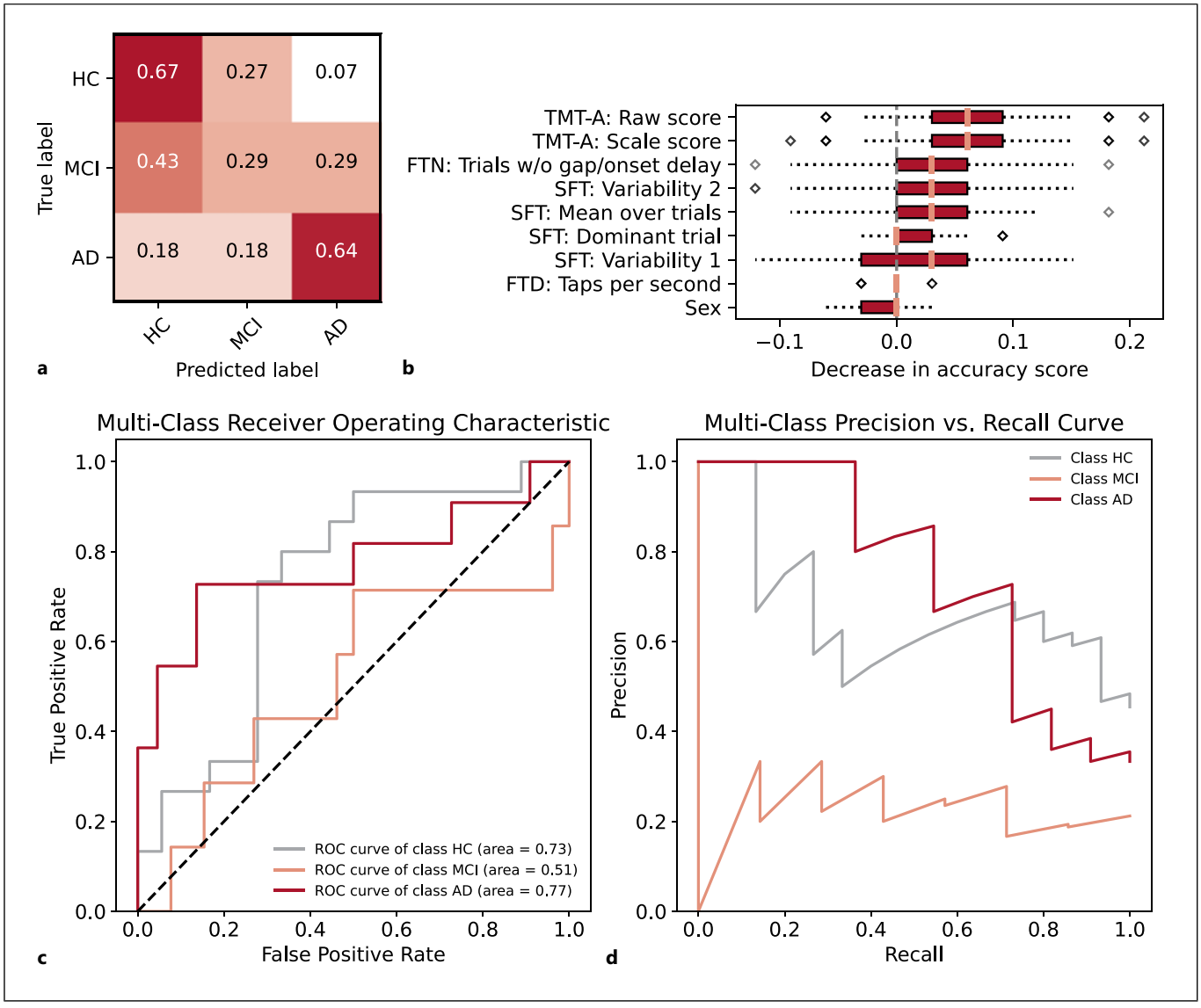

Fig. 3. Support vector classification metrics for the classification of group. **a** Normalized confusion matrix. Each square indicates the proportion of subjects in the group labeled on the y-axis that is predicted as the group labeled on the x-axis. **b** Permutation feature importance. Boxplots with 95% confidence interval; salmon-colored markers indicate the median proportional reduction of model accuracy after permuting the variable in question; TMT-A, Trail Making Test A; FTN, finger tapping non-dominant hand; SFT, simulated feeding task; FTD, finger tapping dominant hand. **c** Multiclass ROC curves: each class is compared to the 2 other classes. **d** Multiclass precision versus recall curves.

F1 is less biased against disproportional sample size of classes and ranges from 0 to 1 with higher scores indicating more specific and sensitive models. F1 scores for control, amnestic MCI, and AD subjects were 0.67, 0.27, and 0.67, respectively. The overall multiclass area under the curve (AUC) score for the classification model was 0.69. Figure 3c shows receiver-operator curves (ROC) and corresponding AUC scores for each group in comparison to the two other groups. AUC scores for the control group, amnestic MCI group, and AD group were 0.73, 0.51, and 0.77, respectively. While the AUC for the control and AD groups indicate acceptable discrimination, the AUC for the amnestic MCI group indicates poor discrimination [78].

An overview of the permutation feature importance is displayed in Figure 3b. Values indicate the decrease in model accuracy after random permutation of its values.

Larger values indicate greater feature importance. The three most important variables in the prediction model that were used for classification of the test hold-out data were (1) TMT-A raw score; (2) TMT-A scale score; and (3) number of trials with gaps or onset delays for the non-dominant hand finger tapping test.

Discussion

Manual Motor Performance in Amnestic MCI and AD

We investigated if individuals with amnestic MCI and AD perform worse on a variety of manual motor functions. In line with previous studies, MCI and AD subjects were slower in completing TMT-A than HC [79, 80]. The effect size for the group difference in TMT-A speed between HC and AD was large and was the only difference that survived multiple comparisons corrections. This may be due to the fact that TMT-A relies on both motor function (e.g., psychomotor speed, visuospatial inhibition and motor planning [52, 53]), and -perhaps even more-on cognitive functioning [52], whereas the other motor measures under study may rely less on cognitive abilities.

AD subjects, but not amnestic MCI subjects, had significantly weaker dominant hand grip strength than control subjects. These observations are in line with other work [81]. Even though muscle strength has continuously been identified as a risk factor for incident MCI [16, 82], no significant differences in grip strength between HC and amnestic MCI subjects were observed. A likely explanation for this seeming discrepancy is that, while grip strength is a risk factor for MCI, it is not in the causal pathway. Therefore, potentially only a subset of MCI subjects will present with weaker muscle strength, which may be averaged out in a group level analysis. This stresses the importance of applying clustering analysis techniques that could identify subgroups of MCI individuals with motor problems. Interestingly, a post hoc analysis showed that females, but not males, from the combined amnestic MCI and AD group had weaker dominant hand grip strength than HC. This aligns with a recent report showing that weak grip strength in females, but not in males, predicts incident MCI [83].

Contrary to the study hypothesis, no significant group differences in spiral tracing performance were observed, suggesting that this skill is generally preserved, at least up until mild to moderate AD. These results are somewhat surprising, given that prior research demonstrated that the spiral test used here is sensitive to motor deficits related to the effects of normal aging [84] and adjuvant chemotherapy for breast cancer [85]. Moreover, qualitative group comparisons imply that AD subjects, and to a lesser extent amnestic MCI subjects, are less precise in tracing the spiral than HC subjects, which do not seem to be driven by individual outliers (see online suppl. Fig. 1). Also, a preliminary analysis of this study with fewer subjects did initially reveal significant effects of AD on tracing accuracy [86]. Nevertheless, the effect sizes for all quantitative spiral tracing outcome measures for the current analysis were small, which indicates that it is unlikely that significant effects were missed due to insufficient power. Overall, the group differences in motor behavior suggest that tracing and muscle strength are relatively preserved in MCI and AD, whereas manual motor measures that rely on timing (i.e., tapping) or that may rely more on cognitive functioning (e.g., the simulated feeding task and the TMT-A) are affected in these individuals.

The smaller differences in motor behavior between aMCI and HC subjects compared to AD suggest that these aMCI subjects may be at an earlier stage along the AD spectrum (e.g., single domain amnestic MCI) where motor deficits may be less noticeable. Future work could focus on motor functioning along the MCI continuum [87]. One study has shown that late MCI subjects perform slower on the TMT-A than early MCI subjects, suggesting that motor dysfunction may increase with disease progression [88]. This hypothesis is corroborated by imaging studies that show differences between early and late MCI in (among other regions) structural connectivity with the thalamus [89], a neural relay station that processes inputs from multiple motor brain regions [90].

Associations between Manual Motor Performance and AD Biomarkers

We tested the association between manual motor performance and three AD biomarkers (i.e., amyloid β deposition, hippocampal volume, and APOE ε4 allele status). TMT-A and dominant hand grip force predicted amyloid β deposition. These associations were in the expected directions such that more amyloid deposition correlated with slower performance on the TMT-A and weaker grip strength. Previous studies observed a similar relationship between slower TMT-A performance and amyloid positivity in cognitively intact individuals [91], and a lack of a relationship between TMT-A performance and APOE ε4 alleles [92]. Slower TMT-A performance also predicted smaller hippocampi in the sample. This observation too, is in line with a previous report linking hippocampal atrophy to slower TMT-A performance in a

mixed sample of cognitively intact individuals and those with MCI [93].

In the current sample, TMT-A performance was more strongly affected in AD than in amnestic MCI, and grip strength was only affected in AD but not in amnestic MCI. Previous work linked grip force strength to volume of the cerebellum and of the primary motor cortex [94, 95], while other studies have shown with functional MRI that executing the Trail Making Test activates several motor areas including the primary motor cortex and the cerebellum [96], which are key regions for motor execution [97] and motor coordination, respectively [98]. The fact that these motor measures were most affected in AD and less in amnestic MCI supports the notion that amyloid β deposition is involved in the pathway of manual motor deficits in AD because the regional distribution of amyloid β deposition only later on in the disease process affects the primary motor cortex and the cerebellum [99].

Besides the TMT-A and dominant hand grip strength, no other motor measures predicted amyloid β deposition or hippocampal volume, and no motor measures were associated with APOE ε4 allele status. The observed association between amyloid β deposition and dominant hand grip strength corroborates results from the Framingham Heart Study showing negative associations between hand grip strength and plasma Aβ40 [100]. However, others have also reported a significant relationship between grip strength and hippocampal volume in cognitively intact individuals [101] and non-dominant hand grip strength and hippocampal volume in subjects with AD [102]. Considering that the hippocampus is not a primary motor area, it is possible that the observations in these studies reflect general brain atrophy including that of primary motor regions, or that frailty was correlated with AD pathology in these samples. This mechanism might also explain the observed association between TMT-A performance and hippocampal volume. Alternatively, this association could reflect reductions in spatial working memory that are required for completing TMT-A and which is mediated by the hippocampus [103].

The observed lack of an association between grip strength and APOE ε4 alleles has been reported previously in community dwelling older adults without dementia [104]. Stronger associations between poor motor function and higher levels of amyloid β deposition compared to associations between poor motor function and a larger number of APOE ε4 alleles is to be expected, given that amyloid β deposition reflects actual neuropathology, whereas an increased number of APOE ε4 alleles merely reflects an increased risk of developing AD due to less favorable neural lipid metabolism in carriers versus non-carriers [105].

Manual Motor Performance as a Classifier for MCI and AD

The SVC model had an overall accuracy of 58%. Although this model is 13% more accurate than a model that would simply assign the majority group label to each subject, this is a relatively small incremental yield when compared to other classification models. Our overall classification model performance was strongly influenced by its ability to accurately classify the individual groups. While the model could discriminate HC and AD subjects moderately well (AUC was 0.73 and 0.77, respectively), it's ability of discriminate MCI subjects (AUC = 0.51) was poor [78]. This highlights the fact that there is value in using manual motor measures for the classification of AD, but that they are less informative for discriminating individuals with MCI. Feature permutation analysis demonstrated that specifically Trail Making Test performance and simulated feeding task performance contributed most substantially to the classification model. Such information is of crucial importance when designing a sensorimotor test battery optimal for MCI and AD classification purposes.

In comparison to our results, Yamada and colleagues reached an overall 93% classification accuracy of cognitively normal, MCI and AD subjects using a similar SVC model that used information from gait, speech, and drawing tests [28]. One caveat is that this rate was obtained using training and tests sets that were completely independent, as a single cross-validation step where all data were randomly assigned to a training set or a test set 10 times, after which the classification results of the 10 models were averaged was used. This 10-fold cross-validation was then run twenty times. Despite this rigorous approach, the lack of clean separation of training and test data could have resulted in an inflated accuracy statistic [106]. As such, the 93% observed accuracy is more compatible to the 70% accuracy of our training set. The study by Yamada and colleagues further showed that combining the gait, speech and drawing measures substantially increased the classification accuracy over classification models using only information of speech. This indicates that combining information from multiple motor measures indeed boosts predictive power, that combining manual motor measures alone is not sufficient. One reason for this may be that manual motor measures are correlated and therefore including other less correlated measures that bring unique

variance into the classification model will results in higher accuracy.

None of the spiral tracing outcome measures were selected for the classification model and none of the spiral measures were significantly different between HC and MCI or HC and AD. By contrast, in a recent study, a classification model built from digital spiral tracing data alone yielded 81.5% accuracy when labeling subjects as either HC ($n = 45$) or AD ($n = 30$) [107]. This elegant study used regional pen-pressure and regional pen-altitude angle information in addition to the velocity, x and y coordinates of the traced spiral trajectory. This information was color-coded into spiral images where colors indicated regionally on the spiral how much pressure was used while drawing. These images were then fed into a transfer learning algorithm that was trained for Parkinson's disease feature extraction using deep learning, to extract 4,096 features from the data. Finally, these features were entered in to a SVM classification model. The optimal accuracy of 81.5% (79.0% sensitivity and 84/0% specificity) was obtained by replacing the pressure coding with drawing velocity and pen-altitude, and running a majority vote on the three classification outcomes. Kachouri and colleagues thus show that using a large number of features derived from the raw data can yield a more accurate classification model than using pre-defined summary-statistical features (e.g., average speed, speed variability, spiral deviation) that were used here. In our study, no information was collected on pen-angle or pen-pressure, which could also have refined the model. However, similar to Yamada and colleagues, Kachouri and colleagues also only applied 10-fold cross-validation without true separation of training and test data, which has potentially resulted in inflated classification performance [106].

Strengths, Limitations, and Future Directions

This comprehensive study evaluated if manual motor performance can distinguish between HC, amnestic MCI and AD subjects. In total, information from five different manual motor tests was used for building a classification model. These tests capture the breadth of manual motor variance, including strength, dexterity, reaction time, precision, consistency, and speed. Linking these motor outcome measures to established neuroimaging and genetic AD biomarkers provided novel insight in the pathophysiology of manual motor dysfunction in AD.

A limitation of selecting only manual motor measures is that it does not allow building a classification model that incorporates the variance of different motor domains such as gait, balance, motor learning, and others. Previous studies have already shown that combining motor measures more strongly predicts adverse health outcomes over single measures [27]. However, selecting which motor measures to include in a motor battery for classification performance is an ongoing area of investigation. The current study contributes to that by identifying that Trail Making Test A and the simulated feeding task are measures that are most sensitive to MCI and AD pathology.

The population under study was homogeneous in terms of race and ethnicity, with 97.4% of the sample being Caucasian white. This is problematic because there are ethnic and racial differences in physical performance [108], morphology of motor brain regions such as the primary motor cortex [109], incidence of dementia [110], and amyloid positivity in individuals with dementia based on PET scans [111]. It is therefore possible that the associations between manual motor function and MCI or AD, and their observed relationship with amyloid β deposition, are different for non-Caucasian whites. To evaluate generalizability of the observed results, future studies should include more ethnic and racially diverse samples.

The sample size of the current study was insufficient to run deep learning models that could leverage additional hidden information from the spiral images. Collecting a much larger sample of spiral images from individuals across the AD spectrum would be a viable option, considering that administration of this test takes less than a minute and requires only a laptop and a pen tablet. This makes the spiral test also ideal to be implemented in a clinical setting.

It is estimated that the majority of individuals with dementia have mixed-brain pathology [112] that can include for example amyloid deposition, vascular damage, and Lewy bodies. In a post-mortem study, 52% of individuals with pathologically-confirmed AD had a mixed-pathology, with ~15% of this group presenting with neocortical Lewy body disease [113]. It is therefore likely that a subset of subjects may have had concomitant Lewy body disease. Because this neurodegenerative disorder is characterized by motor problems [114] that in some cases are similar to those observed in AD (e.g., dominant hand 9-hole pegboard performance deficits [115]), it is possible that the observed results do not exclusively apply to- or reflect AD pathology. Future studies should investigate the specificity of the breadth of manual motor performance for AD by including individuals with Lewy body dementia and Parkinson's disease.

The motor deficits in aMCI and AD subjects described here are unlikely to be specific to AD dementia. Given that motor problems have been identified in multiple types of dementia, including dementia with Lewy bodies, vascular dementia, and AD [116, 117], future studies should focus on the specificity of motor deficits by

including multiple types of dementia and examining classification models to evaluate if differential patterns and levels of motor measures can help distinguish between subtypes of dementia.

Conclusions

Dominant hand grip strength and psychomotor speed are affected in AD, while psychomotor speed is also affected in MCI. Speed, accuracy, and consistency of tracing an Archimedes spiral seems to be relatively preserved in both MCI and AD. Amyloid β deposition correlated with psychomotor speed and dominant hand grip strength and hippocampal volume negatively correlated with psychomotor speed, suggesting that build-up of amyloid and atrophy could be responsible for manual motor deficits in AD. The association between hippocampal volume and psychomotor speed could reflect both cognitive dysfunction (e.g., attention, visual scanning, psychomotor speed), as well as general brain atrophy including that of motor brain regions. The classification model used here combined information from five manual motor tasks and yielded acceptable discrimination of HC and AD subjects, but was sub-optimal for the classification of MCI subjects. Adding additional motor measures and combining motor information with sensory and cognitive measures is a logical next step for improving behavioral prediction models for MCI and AD. Overall, this work further adds to the literature of motor deficits in amnestic MCI and AD and their relevance for building classification models that could refine the diagnostic process.

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Statement of Ethics

This study protocol was reviewed and approved by the University of Utah Institutional Review Board, Approval No. IRB_00106377. Control subjects and MCI subjects provided written informed consent. Individuals with AD provided assent while a legally authorized representative provided consent on their behalf.

Conflict of Interest Statement

Sydney Schaefer is co-founder and managing member of Neurosessments LLC; Kevin Duff is a member of Neurosessments LLC. The remaining authors have no conflict of interest to report.

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Author Contributions

K.D.: conceptualization, funding acquisition, methodology, resources, and writing – review and editing; J.M.H.: conceptualization, funding acquisition, and writing – review and editing; J.M.J., J.B.K., and B.P.S.: data curation and writing – review and editing; V.K.: conceptualization, data curation, formal analysis, funding acquisition, methodology, software, visualization, and writing – original draft; A.F.M. and T.T.: formal analysis and writing – review and editing; M.F.L.R.: conceptualization and writing – review and editing; S.Y.S.: writing – review and editing; and J.G.: software and writing – review and editing.

Data Availability Statement

The data that support the findings of this study are not publicly available due to information that could compromise the privacy of research participants but are available from the corresponding author (V.K.) upon reasonable request.

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