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Delayed and More Variable Unimanual and Bimanual Finger Tapping in Alzheimer's Disease: Associations with Biomarkers and Applications for Classification

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Abstract.
Background: Despite reports of gross motor problems in mild cognitive impairment (MCI) and Alzheimer's disease (AD), fine motor function has been relatively understudied.
Objective: We examined if finger tapping is affected in AD, related to AD biomarkers, and able to classify MCI or AD.
Methods: Forty-seven cognitively normal, 27 amnestic MCI, and 26 AD subjects completed unimanual and bimanual computerized tapping tests. We tested 1) group differences in tapping with permutation models; 2) associations between tapping and biomarkers (PET amyloid-β, hippocampal volume, and *APOE* ε4 alleles) with linear regression; and 3) the predictive value of tapping for group classification using machine learning.
Results: AD subjects had slower reaction time and larger speed variability than controls during all tapping conditions, except for dual tapping. MCI subjects performed worse than controls on reaction time and speed variability for dual and non-dominant hand tapping. Tapping speed and variability were related to hippocampal volume, but not to amyloid-β deposition or *APOE* ε4 alleles. Random forest classification (overall accuracy = 70%) discriminated control and AD subjects, but poorly discriminated MCI from controls or AD.

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Conclusions: MCI and AD are linked to more variable finger tapping with slower reaction time. Associations between finger tapping and hippocampal volume, but not amyloidosis, suggest that tapping deficits are related to neuropathology that presents later during the disease. Considering that tapping performance is able to differentiate between control and AD subjects, it can offer a cost-efficient tool for augmenting existing AD biomarkers.

Keywords: Alzheimer's disease, biomarkers, finger tapping, manual dexterity, motor function

INTRODUCTION

In addition to well-defined cognitive problems, Alzheimer's disease (AD) and its precursor mild cognitive impairment (MCI) present with problems in a variety of motor domains. Some of the most prominent motor deficits that have been linked to an increased risk for AD include slower walking speed [1], poorer balance [2], larger cognitive-motor dual-tasking cost [3, 4], and weaker muscle strength [5, 6]. Gait dysfunction can already present during the preclinical phase of AD [7], even before the onset of cognitive deficits [8] and can predict incident dementia [9]. Relatively few studies have investigated manual performance in MCI and AD subjects [10], despite evidence that drawing [11] and dexterity as measured by pegboard tests [12–17] are slower, less accurate, and more variable in MCI and AD when compared to control subjects.

Finger tapping is also found to be affected in MCI and AD, with studies generally showing that compared to healthy controls these groups have longer response times (AD [18]), slower tapping speed [19–22] (although one study reported no significant differences in tapping speed between controls and AD subjects [23]), more variable tapping speed [20–22, 24, 25], longer tap intervals [18, 20, 21], longer tap duration [18, 21, 22], weaker tapping force [22], slower finger flexion [22], and less steady hands during tapping [19]. Although some of these results were less pronounced in MCI than in AD [18], index finger tapping speed was not different between individuals with MCI and unspecified dementia in another study [26], which could indicate that tapping is affected early in the disease process, but does not further deteriorate over later stages of AD. While most studies on finger tapping in AD focus on unimanual performance, there have been some reports that bimanual motor function may be more sensitive to the neurodegenerative processes of AD than unimanual function as it requires intact inter-hemispheric communication [15] and because of differences in brain activation underlying these conditions [27]. For instance, Suzumura and colleagues reported that bimanual tasks were more strongly impaired than unimanual tasks in MCI [21] and AD [28] and that contributions of the non-dominant hand more so than the dominant hand are affected during bimanual tasks [18]. Another study revealed that bimanual performance was more often affected than unimanual performance, especially when the bimanual test required the left and right fingers to operate alternating versus synchronous [15]. Changes in asymmetrical motor performance have been reported in MCI and AD before [17, 29–32] and may be related to lateralized differences in neural degeneration [33, 34]. Although there is some indication that deterioration of more complex motor function in AD is partly related to the cognitive dysfunction [35, 36], atrophy of motor brain regions such as the cerebellum suggests that primarily regression of core motor function underlies finger tapping degeneration [37–41]. Moreover, alterations of neurotransmitter systems may also be responsible for changes in tapping performance over the disease course, as AD is associated with a reduction in gamma-aminobutyric acid (GABA) [42], which is involved in motor inhibition [43]. Results from a study that measured primary motor cortex excitability with electromyography in AD during a finger tapping test showed that movement slowness correlated with reduced short-latency afferent inhibition, suggesting cholinergic system degeneration [24]. The cholinergic system is affected early on in MCI [44]. These studies indicate that finger performance, especially bimanual tapping, could be a potential early biomarker for AD. To the best of our knowledge, no studies have compared quantitative tapping measures to established AD biomarkers such as amyloid-β deposition, although one study reported that the $A\beta_{42}$ levels from cerebrospinal fluid were related to scores on part 3 of the Unified Parkinson Disease Rating Scale, which includes a finger-to-thumb tapping task [45]. Although hippocampal involvement in finger tapping has not been unequivocally determined [46], the limited number of investigations into this area warrant further study. Despite the reported tapping deficits in MCI and AD, only one study has evaluated tapping performance as a classification method [21]

and reported that tapping speed yields an area under the curve of 0.79 to distinguish MCI from controls.

In this study, we evaluated whether finger tapping, especially bimanual performance, could be a sensitive measure for the identification of MCI and AD. To this end, we 1) compared unimanual and bimanual motor performance between controls and amnestic MCI and AD subjects; 2) tested the association between finger tapping and well-validated and global biomarkers of AD; and 3) used machine learning to build and evaluate an optimized finger tapping classification model for MCI and AD by using information from multiple tapping measures. Achieving these aims could allow us to examine if finger tapping measures can serve as substitute markers or augment existing AD biomarkers to improve the diagnostic process and ultimately reduce clinical trial costs through enrichment [47]. Finger tapping tests are particularly well-suited to serve as biomarker considering that they are inexpensive, can be administered almost everywhere without the need for highly trained personnel, and have a short administration time. We hypothesized that both unimanual and bimanual performance would be better in controls than in participants with amnestic MCI or AD, and that across all individuals worse tapping performance would significantly correlate with a higher load of existing AD biomarkers. We further expected that by building a prediction model that combines multiple tapping measures, we would be able to accurately classify group membership.

MATERIALS AND METHODS

Participants

Participants were sampled from an ongoing study (R01AG055428; [48–50]) of brain imaging and neuropsychological testing across the dementia spectrum. Cognitively normal subjects were recruited from the community. The majority of amnestic MCI (single or multi-domain) and AD participants were recruited from the University of Utah cognitive disorders' clinic [51]. Their diagnosis was based on a neurological visit, neuropsychological evaluation, and brain imaging. A minority of amnestic MCI subjects ∼15% came from the community sample who met criteria for amnestic MCI after cognitive evaluation. Confirmation of group assignment was made with the Alzheimer's Disease Neuroimaging Initiative [52] classification battery, which comprises the Mini-Mental Status Examination [53], the Clinical Dementia Rating Scale [54], and the Wechsler Memory Scale-Revised [55] Logical Memory II Paragraph A. Forty-seven participants were classified as cognitively intact, twenty-seven as amnestic MCI (single or multi-domain), and twenty-six as 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. Control subjects and MCI subjects signed informed consent. Individuals with AD signed assent while a Legally Authorized Representative signed informed consent in their name.

Inclusion criteria were 1) age 65 years or older; and 2) availability of a knowledgeable collateral source to comment on their cognition and daily functioning. Exclusion criteria comprised 1) medical comorbidities likely to affect cognition (i.e., neurological conditions, current severe depression, substance abuse, and major psychiatric conditions); 2) inability to complete magnetic resonance imaging (MRI) or positron emission tomography (PET) imaging; 3) inability to complete cognitive assessments due to inadequate vision, hearing, or manual dexterity; 4) being enrolled in a clinical drug trial related to anti-amyloid agents; 5) elevated depression as indicated by a score of greater than 5 on the 15-item Geriatric Depression Scale; and 6) severe dementia as indicated by a Clinical Dementia Rating score of 2 or greater or a Mini-Mental Status Examination score of less than 20.

Complete finger tapping data was available for 100 subjects. Demographic and clinical information is presented in Table 1. The overall group mean age was 74.5 ± 5.9 years of age. Of the participants in our sample, 58.0% were female, and 98.0% were Caucasian or white. Mean premorbid intellectual functioning, as measured by the Reading subtest of the 4th edition of the Wide Range Achievement Test [56], was in the normal range for all three groups. Symptoms of depression, which were assessed using the Geriatric Depression Scale [57], were minimal and below the cut-off score for clinical depression.

Finger tapping

Collection of finger tapping data

Finger tapping performance was measured using a computerized test that we developed in-house using version 3 of the PsychoPy software suite [58–60]. The task can be downloaded from: https://github.com/vnckppl/FingerTappingTask [61]. We used the same 2017 13" MacBook Pro for task

Table 1
Demographics

Variable	Metric	Controls	MCI	*p*	AD	*p*	Total
Sample size	n	**47**	**27**		**26**		**100**
Age (y)	m (sd)	73.7 (5.5)	74.6 (6.3)	0.53	75.7 (6.1)	0.17	74.5 (5.9)
Sex (female)	n (%)	31 (66)	11 (40.7)	0.1	16 (61.5)	0.1	58 (58)
Right-handed	n (%)	44 (93.6)	26 (96.3)	0.84	25 (96.2)	0.84	95 (95)
Education	m (sd)	16.6 (2.3)	16 (2.7)	0.31	15.2 (2.3)	0.02	16.1 (2.5)
WRAT	m (sd)	112 (7.2)	108.7 (8.8)	0.1	108 (9.1)	0.049	110 (8.3)
GDS	m (sd)	1 (1.3)	1.6 (1.3)	0.09	1.5 (1.4)	0.16	1.3 (1.3)
MMSE	m (sd)	28.9 (1.2)	26.4 (1.9)	<0.001	22.8 (2.6)	<0.001	26.6 (3.1)
Caucasian	n (%)	47 (100)	26 (96.3)	0.4	25 (96.2)	0.4	98 (98)
AD Biomarkers							
SUVR	m (sd)	0.52 (0.11)	0.73 (0.15)	<0.001	0.77 (0.16)	<0.001	0.6 (0.2)
Hippocampal Volume	m (sd)	4.3 (0.48)	3.66 (0.82)	<0.001	3.19 (0.85)	<0.001	3.8 (0.8)
Number of *APOE* ε4 alleles				<0.001		<0.001	
0	n (%)	35 (76.1)	7 (28.0)		9 (34.6)		51 (52.6)
1	n (%)	10 (21.7)	12 (48.0)		11 (42.3)		33 (34.0)
2	n (%)	1 (2.2)	6 (24.0)		6 (23.1)		13 (13.4)

Linear regression analysis was used for continuous variables and Chi-square tests to compare proportions. m, mean; sd, standard deviation; n, number; p, *p*-value compared to the control group.; 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.

presentation and recording of all the participants' input. Throughout the data collection period, no software updates (of either the operating system, or the PsychoPy software) were performed. The task that was built to be run independently, without the need for interaction with a study coordinator, has four conditions (left index finger tapping, right index finger tapping, simultaneous index finger tapping, and alternate finger tapping). Each condition consists of three trials which last 10 s. Finger taps are registered by left and right finger presses on the corresponding shift keys on the keyboard. The test starts with on-screen written and video instructions on how to perform each of the four conditions. Next, participants are instructed to place their finger(s) on the correct key(s) and to start the trial by pressing a tapping key. Upon the key press, a 'Get Ready!' message appears on the screen for 3 s, immediately followed by 'Start Pressing!'. During the 10-s trial, a message is displayed on the screen to encourage the participant to press as fast as possible. For example: 'Press AS FAST AS POSSIBLE with your RIGHT INDEX FINGER'. After 10 s, the screen shows 'Done!' for 3 s, immediately followed by information for the next trial. After all conditions are completed once, they are being repeated two more times in the same order. For single finger tapping, participants are instructed to press as fast as possible. For dual finger tapping, participants are 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 are instructed to tap using one index finger after the other, as fast as possible. Subjects are allowed to start with either their left or right index finger.

Pre-processing and outcome measures of finger tapping data

Handedness was recorded with the Dutch Handedness Questionnaire [62]. These scores were binarized into left/right handedness and subsequently used to recode left and right hand tapping into dominant and non-dominant tapping scores.

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. An overview of continuous outcome measures is presented in Table 2. Supplementary Figure 1 provides a graphical overview of the outcome measures. Each outcome measure was collected three times. We selected the subject's median score for each of these outcome measures to yield scores robust against outliers at the subject level.

By selecting a broad variety of tapping outcome measures, while also statistically adjusting for multiple comparisons, we were able to evaluate the effects of AD pathology on multiple aspects of tapping performance, while also preventing Type I errors.

Table 2
Overview of Continuous Tapping Metrics. 'All Conditions' indicates that these measures are collected for unimanual dominant and non-dominant, and bimanual synchronous and alternate tapping. Supplementary Figure 1 provides a graphical overview of these outcome measures

Condition	Tapping Measure	Description
All Conditions	Initial Reaction Time	Time in seconds from the start of the test to the first key press
	Taps per Second	Rate of finger tapping speed expressed as taps per second
	Taps per Second Variance	Variance in rate of finger tapping speed expressed as taps per second
Dual Tapping	Unpaired Taps Rate	Total number of left or right taps that could not be paired with a right or left tap respectively, divided by the total number of taps
	Tap Pair Duration	Average time between the two taps that make up a pair
	Tap Pair Duration Variance	Variance in time between the two taps that make up a pair
	Number of Pairs	Total number of left and right tapping pairs
Alternating	Error Rate	The number of incorrect transitions (i.e., left-to-left tap, or right-to-right tap) divided by the total number of taps
	Alternating Transition Time	Average time between taps in seconds for correct transitions only (i.e., left-to-right tap and right-to-left tap transition)
	Alternating Transition Time Variance	Variance in average time between taps for correct transitions only (i.e., left-to-right tap and right-to-left tap transition)
	Alternating Transitions	Number of consecutive taps for correct transitions only (i.e., left-to-right tap and right-to-left tap transition)

Alzheimer's disease biomarkers

The well-established AD biomarkers [63] that we cross-correlate with tapping performance are 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 amyloid-β neuritic plaque density. The ligand was produced under PET cGMP standards and conducted under an approved FDA Investigational New Drug application (IND). 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 [64, 65]. Emission imaging took 20 min and was performed 90 min after the injection of approximately 185 mBq (5 mCi) of ^{18}F-Flutemetamol. We used a regional semi-quantitative technique described by [66] and refined by Thurfjell et al. [67] to analyze the ^{18}F-Flutemetamol binding. The CortexID Suite software (GE Healthcare) was used to automatically obtain a composite standardized uptake value ratio (SUVR) in the cerebral cortex which was normalized to the pons [68]. PET imaging was collected on average 27.7 ± 43.2 weeks prior to the motor behavioral assessments.

Hippocampal volume

MRI images were acquired on a 3.0 Tesla Siemens Prisma scanner with a 64-channel head coil. T1-weighted data were acquired using a sagittal MP2RAGE sequence (TR = 5000 ms, TE = 2.93 ms, flip angles = 4° and 5° respectively, acquisition matrix = 256x256, field of view = 256x256 mm, slice thickness 1 mm, resolution = 1x1x1 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 (https://surfer.nmr.mgh.harvard.edu/) to estimate total intracranial and hippocampal volumes. Technical details have been described previously [69–71]. Hippocampal volumes were expressed as proportion of the estimated total intracranial volume to account for differences in head size [72]. MRI scans were collected on average 32.3 ± 39.9 weeks prior to the motor behavioral assessments.

APOE genotyping

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

Statistical analysis

Except for classification modeling, all statistical analyses were conducted in R version 4.2.1. The alpha level was set at 0.05 and false discovery rate

(FDR) correction was applied to adjust for multiple comparisons.

Demographical information

Group differences in continuous potentially confounding variables were compared using linear regression models. Group differences in categorical potentially confounding variables were compared using χ^2 tests using the MASS package (7.3-58).

Group comparisons of motor performance

Logistic regression analysis was used to compare control subjects to the amnestic MCI and AD groups on presence or absence of tapping gaps, defined as periods of 1 s or longer during the 10-s tapping trial where no key was tapped.

Non-parametric tests in the framework of the linear model were conducted using the lmPerm package (2.1.0) to evaluate measures of initial reaction time, tapping rate, tapping variance, and specific measures for alternate and dual tapping (see Table 3). We selected permutation tests in favor of their parametric equivalents for robustness against non-normality of residuals. Permutation tests were set to complete 100,000,000 random permutations. Because we were interested in how (pre)clinical AD differed from cognitively intact individuals with respect to motor function, we tested differences between 1) control subjects and amnestic MCI subjects; and 2) control subjects and AD subjects. 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. All models were adjusted for age and sex.

Multiple comparison correction was applied by running FDR correction on the total, single array of *p*-values resulting from both the logistic regression analyses and non-parametric linear models for both the comparisons of controls versus amnestic MCI subjects and controls versus AD subjects.

Associations between motor performance and AD biomarkers

We assessed the association between finger tapping performance and our continuous biomarkers (hippocampal volume and amyloid-β) using linear regression models adjusted for age and sex. We report partial correlations (adjusted for age and sex) as a measure of effect size. Variables with a skewness ≥ 1 (i.e., Initial Reaction Time and Taps per Second Variance for all tapping conditions, Tap Pair Duration Variance for dual tapping, and Error Rate, Alternating Transition Time, and Alternating Transition Time Variance for alternating finger tapping) were transformed to ensure assumptions for linear associations were met. This transformation process was a two-step approach: First outliers, defined as values that were outside the range of the mean $\pm$ 2.5 standard deviations, were set to the mean $\pm$ 2.5 standard deviation. Note that applying or not applying this step did not result in significantly different outcomes. Second, a log transformation was applied to the variable. Associations between tapping performance and our categorical biomarker measure (*APOE* ε4 alleles) were tested using Poisson regression models, adjusted for age and sex, with Incidence Rate Ratios as a measure of effect size.

Classification modeling

We used Balanced Random Forest Classification from the Imbalanced Learn (0.9.1) package, implemented in Python 3.8.10 for classification. Variables considered in the model included 1) the set of 20 continuous tapping performance measures reported in Table 4; 2) a count variable that lists the number of trials with either an onset delay of more than 1 s, a gap of more than 1 s or both; and 3) age and sex. Age and sex were considered to account for any imbalances in these metrics between groups. To reduce the number of variables in the model, we only selected variables that correlated (Spearman) for less than 90% with other variables in the dataset. This resulted in the exclusion of the variable 'Number of Pairs' for dual tapping and three alternating tapping variables: 1) 'Alternating Transition Time'; 2) 'Alternating Transition Time Variance'; and 3) 'Alternating Transitions'.

Balanced random forest classification was selected to account for differences in the sample sizes per group, which could otherwise lead to a classification model that has a higher likelihood to predict the largest class [73]. GridSearchCV from the Scikit Learn (1.1.2) package was used to detect the optimal set of hyper parameters with the maximum tree depth ranging from 1-10, 5 levels of number of trees in the forest (5, 10, 25, 50, 100), and either 'gini' or 'entropy' as the information gain criteria. The data were divided into a training set (70% of the data) and a test set (30% of the data) using the train_test_split algorithm. GridSearchCV was then run on the training set using five-fold cross-validation to obtain a model robust against overfitting. Results indicated that a model with a maximum tree depth of 5, 50 trees in the forest, and 'gini' as information gain criteria were optimal given our training data. We finally

trained our random forest classification model using these parameters on our training data and applied it to our hold-out testing set.

To investigate the contribution of individual variables to the classification model, we conducted permutation feature importance analysis. This tool, which is part of Scikit learn, recalculates the model accuracy after randomly permuting one individual feature at a time. More specifically, all values of the feature in question are randomly shuffled after which the entire random forest model is being recalculated but now with the reshuffled variable instead of the original data. Changes in the overall model accuracy with the reshuffled values compared to the original data provide an indication how much the particular variable contributes to the overall accuracy of the model. By shuffling the values of the feature multiple times and calculating the new model accuracy each time, a distribution of the feature contribution to the model can be obtained. This process is being repeated for each feature in the model, and each feature was set to be permuted 200 times.

Exploratory analysis of the association between motor brain volume and finger tapping

Frontal regions such as the primary motor cortex (M1) [74–76] and the inferior frontal gyrus (IFG) [77] are involved in rhythm production and perception. Furthermore, degeneration of these areas in MCI and AD has been related to motor dysfunction [10]. Another brain region that regulates finger tapping rhythm [78] and which is affected in AD is the cerebellum [37–39].

In an exploratory analysis, group differences in bilateral volume of the IFG, M1, and the cerebellum were tested. Bilateral motor volumes were obtained in the same FreeSurfer process used to obtain hippocampal volumes and were expressed as percentage of the total intracranial volume to adjust for premorbid brain volume. Group differences were tested using the same linear models as described for testing hippocampal volume. Additionally, motor brain volumes were tested for associations with all tapping outcome measures as described in Table 2, using the same linear regression models as those used to test hippocampal volume and tapping outcome measure associations.

RESULTS

No group differences were observed in mean age or average amount of depressive symptoms as measured with the Geriatric Depression Scale, or the distribution of sex or race. Control subjects had on average completed 1.5 years more education than AD subjects and scored higher on the MMSE than both amnestic MCI and AD subjects. AD subjects had a slightly lower premorbid verbal intelligence as measured with the WRAT.

Group comparisons of motor performance

Binary tapping measures

Logistic regression analysis showed that, compared to control subjects, both amnestic MCI and AD subjects had higher odds of having gaps of 1 second or more during dual tapping, but not for the other tapping conditions (see Table 2). This was potentially related to the rareness of this outcome; for both dominant and alternate tapping none of the control subjects had any gaps.

Continuous tapping measures

Results from our permutation-based linear models to assess group differences in tapping performance are displayed in Table 4. AD subjects performed worse on all single finger tapping measures than control subjects, except for dominant hand Taps per Second (see Fig. 1). Dominant hand tapping was not different between amnestic MCI and control subjects. For the non-dominant finger, however, those with

Table 3
Group differences in presence of tapping gaps

	aMCI versus Controls			AD versus Controls		
Condition	OR	SE	*p*	OR	SE	*p*
Dominant	Inf	Inf	NA	Inf	Inf	NA
Non-Dominant	2.76	2.06	0.159	1.69	2.16	0.495
Dual Tapping	20.26	3.16	**0.009**	25.99	3.06	**0.004**
Alternating	Inf	Inf	NA	Inf	Inf	NA

All metrics are calculated from the maximum values over the subjects' completed trials; aMCI, amnestic mild cognitive impairment; OR, odds ratio; SE, standard error; Inf, approaches infinity because for these conditions, there were no control subjects with tapping gaps; NA, unable to estimate *p*-value; **bold** indicate tests that retain significance after FDR correction.

Table 4
Group differences in continuous tapping metrics

		MCI versus Controls			AD versus Controls		
Condition	Tapping Measure	beta	p	η^2	beta	p	η^2
Dominant	Initial Reaction Time (s)	0.16	0.093	0.03	0.24	**0.011**	0.06
	Taps per Second	–0.01	0.974	0.00	–0.30	0.108	0.03
	Taps per Second Variance	0.00	1.00	0.02	0.01	**0.003**	0.08
Non-Dominant	Initial Reaction Time (s)	0.46	**0.006**	0.07	0.57	**0.001**	0.11
	Taps per Second	–0.14	0.523	0.00	–0.42	0.047	0.04
	Taps per Second Variance	0.01	0.019	0.05	0.01	**0.009**	0.06
Dual Tapping	Initial Reaction Time (s)	0.49	**<0.001**	0.12	0.19	0.152	0.02
	Unpaired Taps Rate[a]	0.00	1.00	0.00	0.00	0.758	0.00
	Taps per Second	–0.30	0.425	0.01	–0.79	0.039	0.04
	Taps per Second Variance	0.01	**0.002**	0.09	0.01	0.014	0.05
	Tap Pair Duration (s)	0.00	0.129	0.02	0.00	0.228	0.01
	Tap Pair Duration Variance (s)	0.00	0.385	0.01	0.00	0.548	0.00
	Number of Pairs	–1.68	0.402	0.01	–4.28	0.035	0.04
Alternating	Initial Reaction Time (s)	0.17	0.097	0.01	0.40	**<0.001**	0.14
	Error Rate[b]	0.00	0.548	0.00	0.00	1.00	0.00
	Taps per Second	0.31	0.414	0.01	–0.83	0.033	0.04
	Taps per Second Variance	0.00	0.14	0.02	0.01	**<0.001**	0.15
	Alternating Transition Time (s)[c]	–0.01	0.619	0.00	0.02	0.077	0.03
	Alternating Transition Time Variance (s)[c]	0.00	0.782	0.00	0.01	0.058	0.03
	Alternating Transitions[c]	3.61	0.35	0.01	–8.31	0.033	0.04

All metrics are calculated from the median values over the subjects' completed trials; [a]number of unpaired taps divided by total number of taps; [b]number of incorrect transitions (i.e., left-to-left tap, or right-to-right tap) divided by the number of taps; [c]Applies to correct transitions only (i.e., left-to-right tap and right-to-left tap transitions). Values printed in **bold** indicate tests that retain significance after FDR correction.

amnestic MCI had a longer Initial Reaction Time and larger Taps per Second Variance when compared to control subjects.

Amnestic MCI subjects had a longer Initial Reaction Time and larger Taps per Second Variance in the dual tapping condition (see Fig. 2) than control subjects. AD subjects also had larger Taps per Second Variance than controls, but also fewer Taps per Second during dual tapping. They also had fewer Number of Pairs than control subjects.

AD subjects performed worse than control subjects (see Fig. 3) on the alternate tapping condition. Specifically, they showed a longer Initial Reaction Time, fewer Taps per Second, larger Taps per Second Variance, and completed fewer Alternating Transitions. Alternating tapping performance was not statistically different between control and amnestic MCI subjects.

Associations between motor performance and AD biomarkers

For the entire sample, hippocampal volume was positively related to 1) Taps per Second (Cohen's $d = 0.53$, $p = 0.014$) and Taps per Second Variance (Cohen's $d = 0.60$, $p = 0.005$) for dominant finger tapping; 2) Taps per Second (Cohen's $d = 0.58$, $p = 0.007$), Taps per Second Variance (Cohen's $d = 0.50$, $p = 0.019$), and Number of Pairs (Cohen's $d = 0.57$, $p = 0.008$) for synchronous dual finger tapping; and 3) Taps per Second Variance (Cohen's $d = 0.58$, $p = 0.007$), Alternating Transition Time (Cohen's $d = 0.44$, $p = 0.038$), and Alternating Transition Time Variance (Cohen's $d = 0.44$, $p = 0.037$) for alternate finger tapping. The four significant associations with a Cohen's $d \geq 0.57$, i.e., medium to large effect size [79], survived FDR correction for multiple comparisons. Correlation plots of these outcomes are displayed in Fig. 4. Only one association between finger tapping performance and *APOE* ε4 allele status was observed (non-dominant hand Initial Reaction Time, Incidence Rate Ratio = 1.35, $p = 0.033$) and one association between finger tapping performance and amyloid-β was observed (dual synchronous finger tapping Initial Reaction Time, Cohen's $d = 0.54$, $p = 0.010$). These two observations did not survive FDR correction.

Tapping performance as classifier of group

The overall classification accuracy of the training data was 56%, while the overall classification accuracy of the test data was 70%. This indicates that 70% of the subjects of an independent data set were accurately labeled by our classification model. This is a 22% increase over a null model that would simply predict the most frequent class for all observations

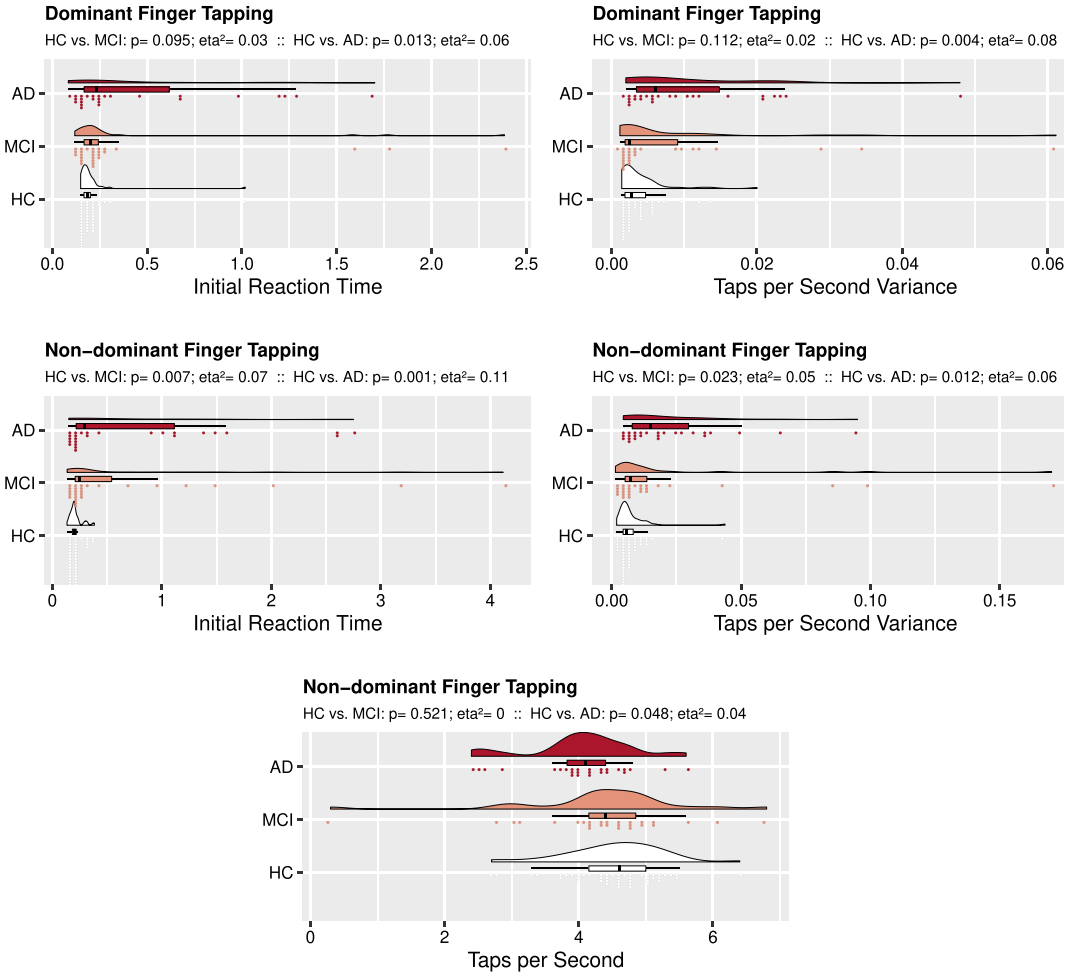


Fig. 1. Unimanual Finger Tapping: Group Comparisons. Rain cloud plots with density curves, boxplots, and individual subject scores divided over 75 bins. The top cloud (red) presents data from the AD subject group, the middle cloud (salmon colored) presents data from the amnestic MCI subject group, the bottom cloud (white) presents data from the control group. Above each figure, *p*-values and eta^2 as measure 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 dominant finger tapping AD performed worse than controls on Initial Reaction Time and Taps per Second Variance. For the non-dominant finger tapping, both AD and amnestic MCI performed worse on these measures, while AD also had fewer Taps per Second than controls.

(i.e., 47 controls would be accurately predicted out of 98 participants).

The group-specific precision, defined as the proportion of a group that was classified correctly (i.e., 'true positives') was 76% for controls, 100% for amnestic MCI, and 45% for AD. The *confusion matrix* (see Fig. 5a) shows in each cell the proportion of the class in the row that is predicted as the class in the column. The diagonal represents the group-wise 'recall' of the classification model. It shows that 76% of the healthy controls among all control subjects and 86% of AD subjects among all AD subjects were accurately classified, while 33% 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 [80], which is defined as:

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

F1 is less biased against disproportional sample size of classes and ranges from 0-1 with higher scores indicating more specific and sensitive models. F1 scores for control, amnestic MCI, and AD subjects were 0.76, 0.50, and 0.67 respectively. The overall multi-class area under the curve (AUC) score

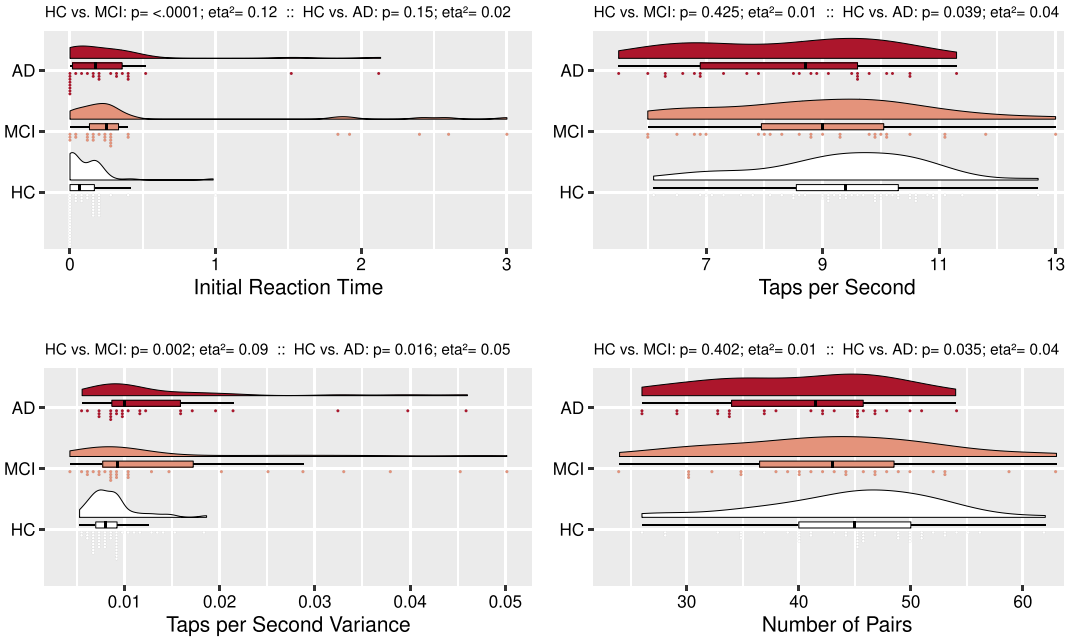


Fig. 2. Synchronous Dual Finger Tapping: Group Comparisons. Rain cloud plots with density curves, boxplots, and individual subject scores divided over 75 bins. Compared to controls, amnestic MCI subjects had a longer Initial Reaction Time and larger Taps per Second Variance. Compared to controls, AD subjects had fewer Taps per Second, larger Taps per Second Variance, and fewer Number of Pairs.

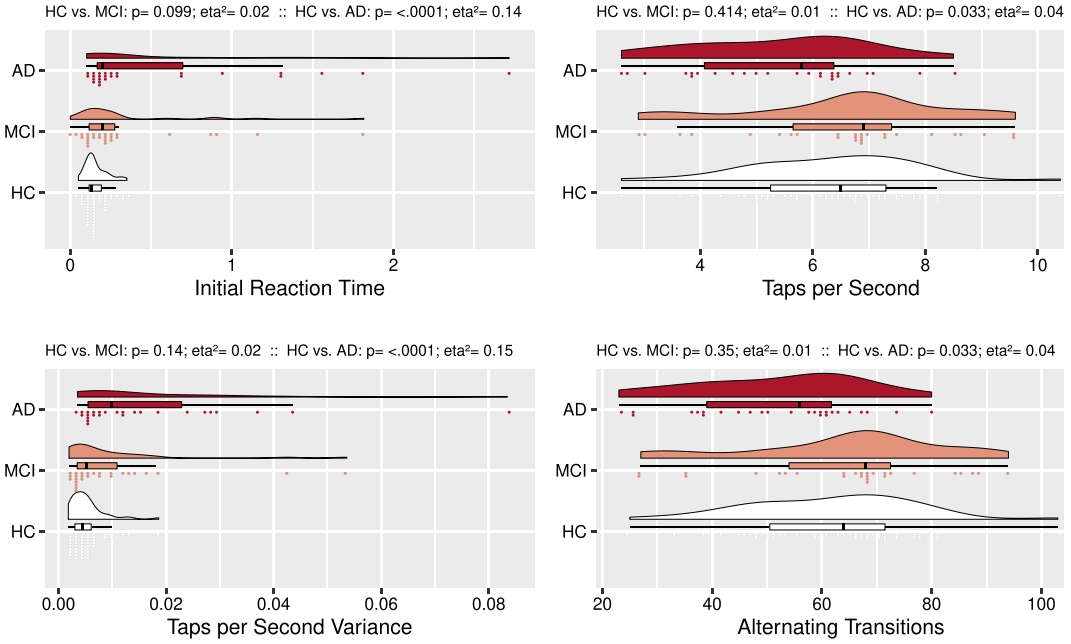


Fig. 3. Alternate Finger Tapping: Group Comparisons. Rain cloud plots with density curves, boxplots, and individual subject scores divided over 75 bins. Compared to controls, AD subjects had a longer Initial Reaction Time, fewer Taps per Second, larger Taps per Second Variance, and fewer Consecutive Taps.

for the classification model was 0.76. Figure 5c shows receiver-operator curves 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 0.75, 0.60, and 0.78 respectively. While the AUC for the con-

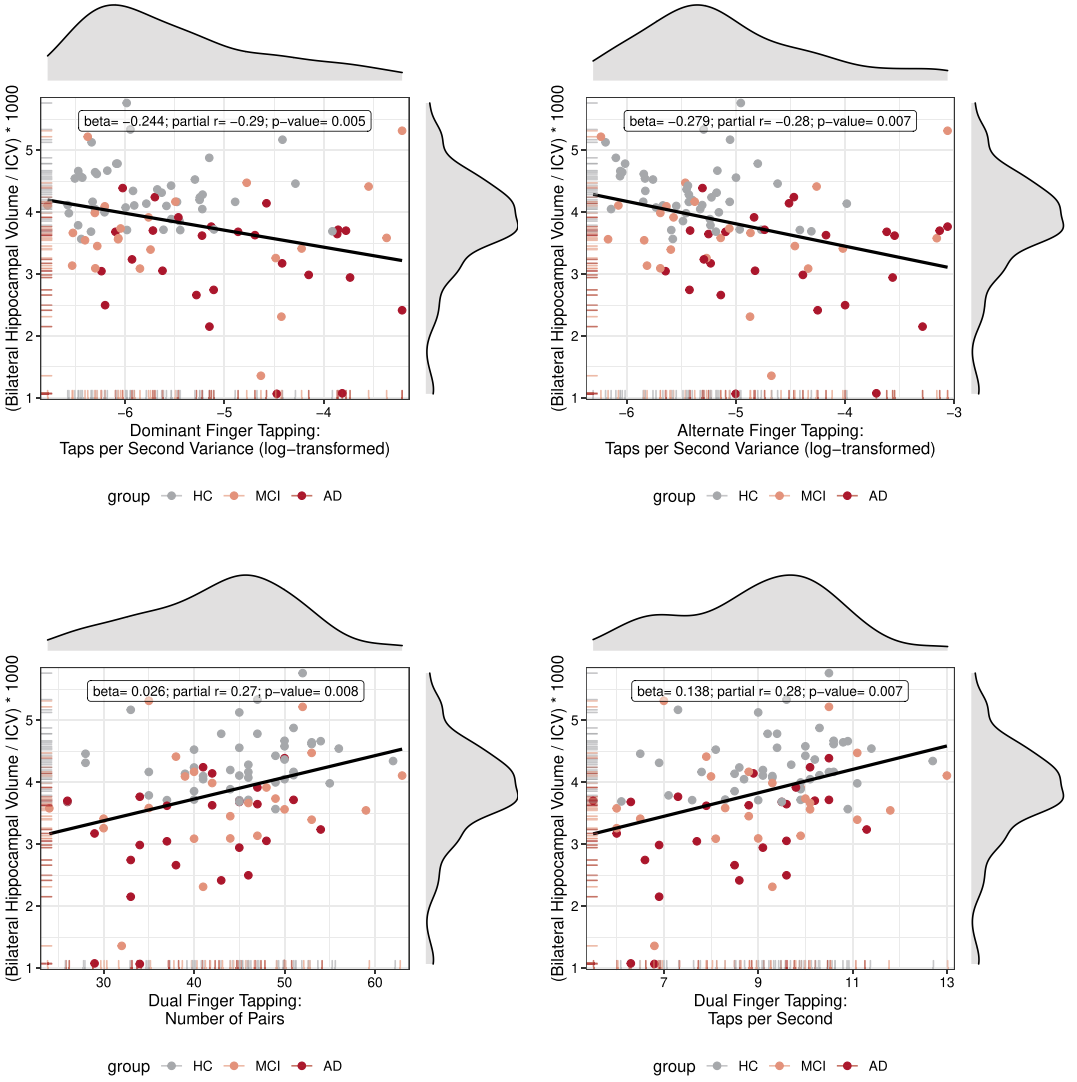


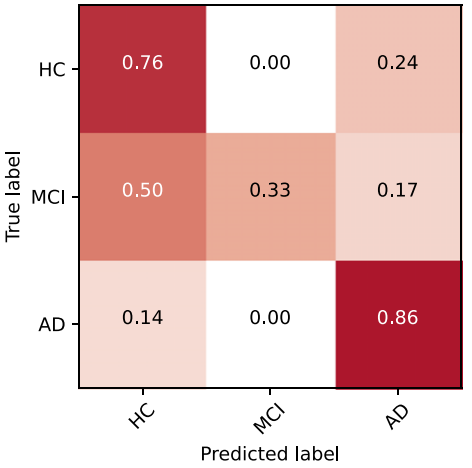
Fig. 4. Correlations between Hippocampal Volume and Tapping Performance. Scatter plots with density curves (on top and on the right side of each graph) and carpet plots (on the left and bottom side of axis) for both variables. Each graph shows the individual observations color coded for group, and a regression line. Inside the graph is a text box with summary statistics of the partial correlation (adjusted for age and sex) and regression, as well as the *p*-value for the analysis. Note that, even though individual values are color coded for group, the statistics were calculated for the entire collapsed sample.

trol and AD groups indicates acceptable, bordering excellent, discrimination, the AUC for the amnestic MCI group equals poor discrimination [81].

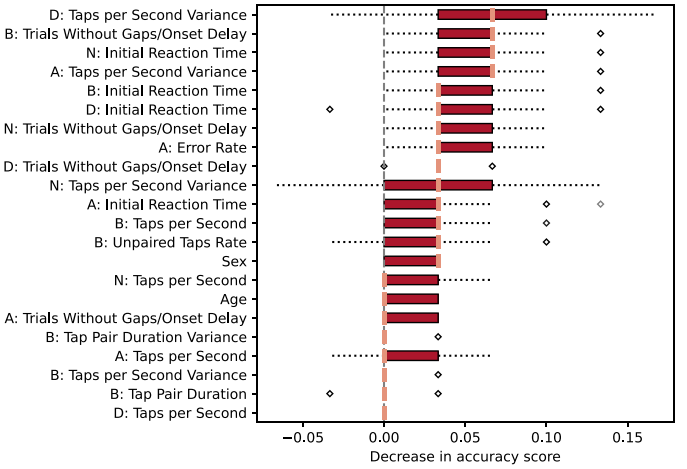
An overview of the permutation feature importance is displayed in Fig. 5b. Values indicate the decrease in model accuracy after random permutation of its values. The five most important features that were used for classification of the test hold-out data were 1) variance in tapping speed during dominant hand finger tapping; 2) the number of dual tapping trials without gaps or onset delays; 3) initial reaction time for non-dominant hand finger tapping; 4) variance in tapping speed during alternate finger tapping; and 5) initial reaction time during dual finger tapping.

Exploratory analysis of the association between motor brain volume and finger tapping

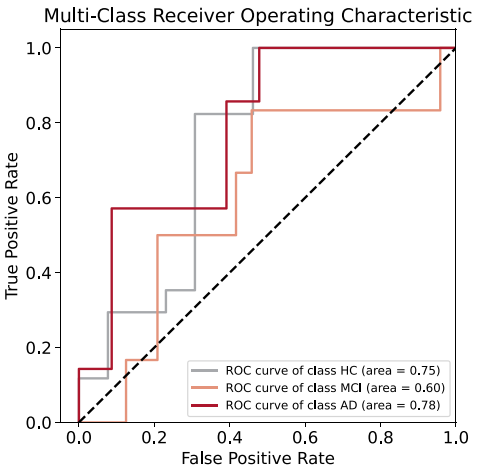
No significant between-group differences in the volume of the bilateral IFG, M1, and the cerebellum were observed between controls and aMCI subjects (all $p > 0.26$), or controls and AD subjects (all $p > 0.82$). Dominant hand Taps per Second was significantly associated with volume of the bilateral inferior



(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; D= Dominant; N= Non-Dominant B= Both (dual tapping); A= Alternate



(c) Multiclass ROC curves: each class is compared to the two other classes

Fig. 5. Random forest classification metrics for the classification of group.

frontal gyri (beta=-0.05, $p = 0.005$, Cohen's $d = 0.61$), but none of the brain-behavioral associations survived FDR correction for multiple comparisons.

DISCUSSION

Finger tapping performance in AD

We studied the association between different stages of AD and uni/bimanual finger tapping performance, as significant associations could point towards this motor task as a quick and affordable screening measure for AD. Our results show that both amnestic MCI and AD are associated with slower initial reaction time, regardless of tapping condition or hand side. Relative to control subjects, amnestic MCI subjects performed worse on 4/20 tapping outcome measures, while AD subjects performed worse on 12/20 outcome measures. Finger tapping variability of the non-dominant hand and during dual tapping were affected in both amnestic MCI and AD. The AD group additionally showed more variability in dominant and alternate finger tapping, slower non-dominant, dual, and alternate finger tapping, as well

as fewer dual tapping pair construction, and alternate tapping correct consecutive taps.

While AD subjects performed worse on both the dominant and the non-dominant hand tapping tests, amnestic MCI subjects only performed worse than controls when using their non-dominant hand. This gradual loss of asymmetry has been observed in MCI and AD previously and is independent of aging in general [29–31]. For example, compared to control subjects, MCI participants displayed more symmetric grasping and inserting movements on the Purdue Pegboard test [17], and AD subjects exhibited more similar finger tapping pace for both hands [32]. Considering handedness-related cortical morphological asymmetry (e.g., deeper central sulcal depth of the hemisphere controlling the dominant hand [33]), our observed pattern could potentially be explained by accelerated asymmetric cortical thinning that has been observed in AD [34]. Alternatively, between-group differences in cognitive function required for learning a novel motor task [82] could explain why AD subjects performed worse than amnestic MCI subjects [83]. Yet another potential explanation is that non-dominant hand performance is more susceptible to pathological changes related to AD, because the non-dominant hand is less trained than the dominant hand. As such, there is less motor reserve [84] of non-dominant hand performance, and deterioration of non-dominant performance will therefore show up earlier in the course of the disease than dominant-hand performance. Our results show that in comparison with controls, alternate tapping was worse in AD subjects but not in amnestic MCI subjects. Gamma-aminobutyric acid (GABA) is an amino acid that is involved in cerebral inhibition of motor function required for alternating bilateral movements [43]. Reductions of GABA levels that have been observed in AD, but not in MCI, could explain the discrepancy in alternate tapping performance of these two groups [42]. Changes in the cholinergic system may also be underlying the performance deficits in AD, as previous research has shown that tapping slowness in AD correlated with reduced short-latency afferent inhibition measured with transcranial magnetic stimulation that could be explained by reduced cholinergic interneuron excitability [24].

Of all measures affected in amnestic MCI and AD participants, Initial Reaction Time and Taps per Second Variance had the largest effect sizes for all tapping conditions that survived multiple comparisons correction. Taps per Second was significant for all but the dominant hand condition, but these outcomes did not survive multiple comparison correction. A meta-analysis on simple reaction time in MCI corroborates our findings and suggests that slower response time in this population is related to attention as well as motor processes at the neural level [35]. Previous research has shown that tapping variability, but not tapping speed in older adults is affected when adding a secondary task [36], thus suggesting a cognitive component to performance. Variability in tapping speed [40] as well as bimanual coordination [41] have been linked to cerebellar functioning, a region that until recently was thought to be relatively unaffected by AD because it exhibits much less amyloid deposition than supratentorial regions [85]. Current research, however, has indicated that the cerebellum is in fact affected by AD pathology and could therefore be a region of interest when studying motor dysfunction in AD [37–39].

It should be noted that while our tapping speed and pair-forming outcome measures did not exhibit significant deviations from normality, the distributions of the initial reaction time and variance measures were highly skewed. The long tail of the skewed distributions suggests that only a small subset of individuals with amnestic MCI and AD performed extremely poorly, while the majority performs more similar to control subjects. Potentially, tapping performance deficits and motor problems in general define a subgroup of AD patients [86]. Alternatively, subjects with substantially poorer motor performance may have other neurological comorbidities that commonly present with AD, that we were unable to detect during subject screening such as cerebrovascular disease including atherosclerosis, white matter pathology, and infarctions, but also Lewy bodies [87, 88]. Lewy body disease in particular is known to be associated with motor dysfunction, including slower tapping speed [89]. Ideally, future studies would evaluate such comorbidities to statistically control for them.

Associations between motor performance and AD biomarkers

Hippocampal volume was related to finger tapping speed and variability under both unimanual and bimanual conditions. These observations remained significant after multiple comparisons correction. Although we found some indications that finger tapping performance was related to global amyloid-β deposition and the number of *APOE* ε4 alleles, these results did not survive multiple comparison correc-

tion. The pattern of associations of finger tapping with individual AD biomarkers indicates that tapping performance is more affected by structural brain changes that generally occur later in the disease process [90], and less by amyloidosis which starts earlier in the disease process [91, 92]. Surprisingly, volume of brain regions that had previously been implicated in finger tapping performance such as the cerebellum, primary motor cortex, and IFG were not associated with tapping performance in our sample. Potentially, functional compensation through increased brain activation may have attenuated the volumetric associations [93]. A previous study reported a positive association in AD patients between $A\beta_{42}$ levels from cerebrospinal fluid and scores on part 3 of the Unified Parkinson Disease Rating Scale, which measures various motoric functions including gait, balance, finger-to-thumb tapping, tremor, and speech [45]. Potentially, the gait and balance measures may have been driving this association, explaining the discrepancy between these results and those reported here. The lack of a statistically significant association between finger tapping performance and well-validated, global amyloid-β depositions resembles reports that show amyloid-β deposits in cognitively normal individuals [94], underlining that not all brain pathology directly affects behavior, potentially due to motor reserve [95]. Alternatively, despite our observation that a global amyloid-β measure may be relatively insensitive to motor function, regional measures of amyloid-β could be predictive, the same way different cognitive functions display region-specific associations with amyloid-β deposition [96]. Future studies should estimate regional depositions of amyloid-β, for example of the primary motor cortex, to assess if they are predictive of finger tapping performance.

Although there is limited evidence that the hippocampus plays a role in simple finger tapping [46], we did observe an association between several tapping measures and hippocampal volume. It is possible that, in this case, hippocampal volume reflects general brain atrophy or even that of motor brain regions, which has resulted in the observed brain-behavioral association. To the best of our knowledge, few studies have explicitly looked at the neural underpinnings of finger tapping performance in AD [10]. A recent study however has revealed that reduced short-latency afferent inhibition partially explains slow movement in AD [24]. To better understand if motor dysfunction in AD is related to general neurodegeneration, or linked to specific brain regions, whole-brain functional and structural imaging mechanistic studies are warranted. More specifically, morphological and brain activation studies of the primary motor cortex could explain variation in our observed tapping deficits in aMCI and AD, as previous work indicates that tapping performance largely depends on primary motor cortex activation [97], bradykinesia in AD is related to motor cortex dysfunction [24, 45], and primary motor cortex plasticity and excitability are affected already in MCI [25, 98, 99].

The range of Cohen's d coefficients for the four observed significant associations between hippocampal volume and finger tapping performance that survived multiple comparisons correction was 0.57-0.60. This equates to medium-to-large effect sizes [79]. Taps per Second Variance for alternating tapping was the measure that most strongly differed between controls and AD subjects ($\eta^2 = 0.15$) and also significantly correlated with hippocampal volume, while surviving multiple comparisons correction for both analyses. All finger tapping outcome measures that significantly related to hippocampal volume also showed significant differences between controls and either amnestic MCI or AD subjects. Based on these results, finger tapping speed may substitute hippocampal volume as AD biomarker but is not suited to substitute amyloid-β or *APOE* ε4 allele status. It may also provide non-redundant information, considering that even these existing biomarkers are limited in predicting AD development [100]. Tapping measures could also be a cost-efficient tool for augmenting existing biomarkers [47] or they can form part of a set of motor measures that together make up a sensitive biomarker for AD [101, 102].

Tapping performance as classifier of group

Our random forest classifier that used finger tapping performance measures to predict group membership had an overall accuracy of 70%, outperforming the null model. Permutation feature analysis revealed that dominant hand Taps per Second Variance contributed most strongly to the classification model. This is in line with the results of our regression models that show that dominant hand Taps per Second Variance is moderately to strongly affected in AD, but not significantly in amnestic MCI.

Inspection of individual classes indicates that prediction model accuracy is driven by the classification of control and AD subjects. Our model predicted control subjects with both good precision (i.e., 'most

subjects classified as controls were truly controls in the sample') and recall (i.e., 'most true control subjects in the sample were classified as controls'). For AD subjects, precision was lower (i.e., not everybody who was classified as AD was actually an AD subject, sometimes they were control subjects), but recall was even higher. For amnestic MCI subjects, however, the model precision was high (i.e., if a subject was classified as amnestic MCI they were always truly amnestic MCI), but the recall was at chance level: amnestic MCI subjects had an equal chance to be classified as controls, amnestic MCI and AD. The AUC metrics further demonstrate the discrepancy in the predictive ability of our model for controls and AD versus amnestic MCI. The overall AUC value of 0.76 and those for the control and AD groups are comparable to a classification study that used random forest classification on speech and eye-tracking data to distinguish control subjects from a mixed sample of subjects with MCI, subjective memory complaints, and AD [103]. A meta-analysis on machine learning methods employing neuropsychological tests to discriminate controls from MCI and AD participants showed that cognitive measures had similar sensitivity to distinguish controls from AD as we report here, but that cognitive measures are better at telling apart controls from MCI [104] than our tapping measures. Although our outcomes thus suggest that finger tapping performance may not be suited as an early detection tool, it is a simple, inexpensive, 10-min test that requires little training and for which the scoring is fully automated that is able to accurately distinguish individuals with and without AD, at 86% accuracy. As such, it could be used in conjunction with other measures and biomarkers as combined outcome measure for clinical trials aiming to prevent development of MCI or AD. Decreases in tapping performance could contribute to this joint outcome measure, as an indicator of disease progression.

Strengths and limitations

This is one of few studies applying an elaborate assessment of unimanual and bimanual finger tapping function in a well-defined sample along the AD continuum. Our study is unique in that it directly relates motor performance measures to three established AD biomarkers: hippocampal volume, brain amyloid-β deposition, and *APOE* ε4 allele status. By combining frequentist statistical methods and machine learning modeling we were able to yield an understanding of how AD pathology affects motor function and how it can be used as a disease classifier. Although we collect a variety of validated, global biomarkers, we did not collect tau, which plays a major role in AD neuropathology [105]. Because tau deposits present later in the AD trajectory than amyloid-β, but before hippocampal atrophy [90], finger tapping may be more sensitive to this biomarker.

Our sample included almost exclusively white, Caucasian subjects. Although, to the best of our knowledge, there are no studies showing racial differences in finger tapping performance, we cannot rule out that they exist. It is thus not possible to extrapolate our results to other populations, and we should therefore aim to include diverse populations in studies on tapping performance and dementia.

AD has been investigated thoroughly from a neural and cognitive perspective and large datasets with such features are readily available in the public domain. Motor measures have been studied much less in AD, and large datasets of motor behavior in MCI and AD are not available. Though our moderate sample size allowed us to gauge tapping performance in AD, it was less optimal for classification model construction. Combining datasets or adding motor measures to ongoing large studies will help identifying if motor measures could be viable predictors for preclinical AD.

Our finger tapping test is light-weight and can be freely installed on any operating system. It also does not require special hardware to run. However, this test has not been validated, although it has been modeled after existing tapping tests in terms of the information that is recorded. Additionally, because it only uses a keyboard as input device, it is not able to collect certain information, such as pressure of the key press, that may be informative. To collect such information, additional hardware and alterations of the software are required.

Although we excluded individuals with neurological disorders and those who were using antipsychotic or anticonvulsant medications that could affect the motor system, we did not exclude individuals taking medications that might have adversely affected motor function. Future studies should record medications affecting the motor system to allow adjustment or stratification to explore such potential effects.

The time difference between collection of our MRI and PET imaging biomarkers and our tapping data was approximately 30 weeks on average. Although this amount of time is relatively short for considerable neurodegeneration to accumulate [106], we acknowledge that not collecting the behavioral and

biomarker data at the exact same time may have led to weaker correlations. Future studies should aim to collect motor and AD imaging biomarkers closer in time to reduce the chance of Type II errors.

Conclusions and future directions

This study indicates that unimanual and bimanual finger tapping performance are affected in amnestic MCI and more so in AD. Especially initial reaction time and tapping speed variability are affected, though it seems that these differences are driven by a select group of amnestic MCI and AD participants that perform particularly poor, even compared to other amnestic MCI and AD subjects. In AD subjects, both dominant and non-dominant unimanual finger tapping and alternate and simultaneous tapping were significantly affected, while in amnestic MCI subjects only unimanual non-dominant hand and synchronous bimanual tapping were affected. Finger tapping speed and variance in speed were predictive of hippocampal volume, but tapping measures were not significantly related to other conventional AD biomarkers such as amyloid-β deposition and *APOE* ε4 allele status. The link between tapping performance and hippocampal volume could reflect general neurodegeneration rather than hippocampal atrophy in particular. A machine learning classification model was well able to discriminate control subjects from AD subjects but did poorly when trying to distinguish MCI from the other two groups. Our findings indicate that AD is linked to poorer finger tapping, but that this may not be used to identify patients early in the AD disease process but may be better suited for later in the course of the disease. In their current form, finger tapping tests could be a cost-efficient tool for augmenting existing AD biomarkers.

Future research should focus on the specificity of unimanual and bimanual finger tapping dysfunction for amnestic MCI and AD. Comparing finger tapping performance between individuals with amnestic MCI, AD, dementia with Lewy bodies [89] and Parkinson's disease [20] can help identify if there are differences in patterns of tapping performance that are unique to these groups. This in turn could facilitate the development of prediction and classification models. Combining motor measures with assessments of activities of daily living (see for example [107]) in individuals with amnestic MCI and AD can provide information on the clinical relevance of motor measures assessed in a lab environment.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available on request from the corresponding author.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-221297.

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