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Visuomotor Impairments in Older Adults at Increased Alzheimer's Disease Risk

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Abstract.
Background and Objective: Recent evidence suggests that visuomotor behaviors may be disrupted in the very early stages of Alzheimer's disease (AD). Here we propose that using kinematic measures under conditions that place demands on visual-spatial and cognitive-motor processing may provide an effective behavioral means to detect subtle changes associated with AD risk.
Methods: To this end, we have tested 22 young adults (mean age = 26.4 ± 4.1) and 22 older adults (mean age = 64.3 ± 10.1) at low AD, and 22 older adults (mean age = 67.7 ± 11.3) at high AD risk (i.e., strong family history or diagnosis of mild cognitive impairment). Kinematic measures were acquired on four visuomotor transformation tasks (standard, feedback reversal, plane dissociated, and plane dissociated + feedback reversal) using a dual-touchscreen tablet.
Results: Comparing participants at increased AD risk with both young and old healthy control groups revealed significant performance disruptions in at-risk individuals as task demands increased. Furthermore, we were able to discriminate between individuals at high and low AD risk with a classification accuracy of 86.4% (sensitivity: 81.8%, specificity: 90.9%).
Conclusion: We suggest that the impairments observed in individuals at increased AD risk may reflect inherent brain alteration and/or early neuropathology disrupting the reciprocal communication between hippocampal, parietal, and frontal brain regions required to successfully prepare and update complex reaching movements. Such impairment has the potential to affect activities of daily living, and may serve as a sensitive measure of functional ability in at-risk adults.

Keywords: Aging, Alzheimer's disease, geriatric assessment, motor skills, movement, neurodegenerative disorder

INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia, affecting approximately 13% of individuals aged 65 years and older, and 40–50% of individuals aged 80 years and older [1]. Typically, the initial clinical manifestation of AD involves short-term memory deficits, which eventually progress and are accompanied by more global and pronounced cognitive impairments. By the time this behaviorally noticeable manifestation of the disease occurs, significant damage to the brain is already present and may be irreversible [2]. Thus, in order to develop effective treatments that may terminate or slow the neurodegenerative process, recent reports have emphasized the importance of developing better tools for the assessment of impairments in the early stages of AD before substantial neurodegeneration has occurred [3].

While AD is typically associated with hippocampal atrophy and memory deficits, research has also demonstrated that functional and structural alterations involving posterior parietal association areas are present in the very early stages of the disease [4, 5]. Posterior parietal cortex plays an important role in transforming visual-spatial information into goal-directed actions [6]. In particular, reciprocal parietal-frontal networks involving interconnected neuronal populations are required to transform

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extrinsic spatial representations into intrinsic joint and muscle representations necessary for the generation of an accurate motor output [6–10]. Disruption to these parietal-frontal networks in the early stages of AD may result in impaired visuomotor control.

In a typical or "standard" reach, the eyes are directed toward an object of interest then the hand moves to that same location in space. Many of the movements that we learn to perform however, require more complex sensorimotor transformations in which the motor system must integrate some form of cognitive information (e.g., visual-spatial, memorized, rule-based, semantic) into the motor program. In these learned "non-standard" sensorimotor transformations the end effector must move to a spatial location that is not directly aligned with the location of the visual target. These indirect visuomotor behaviors rely on the brain's ability to either recalibrate the sensory-motor relationship or use a cognitive strategy to realign the required limb movement relative to the spatial location of the target [11]. For example, guiding a computer mouse relies on the ability to incorporate visual and proprioceptive signals into the remapping of the visual location of the target and representation of the hand (i.e., cursor) in one plane, onto the true location of the target and hand in the other plane [12]. Furthermore, in order to sustain the motor plan throughout the course of the movement, the current position of the actual hand relative to the actual reach target (both of which the eyes are not looking at) must be continuously updated. On the other hand, when asked to integrate a specific rule into a movement, such as moving in the opposite direction of a visual target, the brain develops a cognitive strategy to generate the desired motor output [13].

While the neurological computations underlying the integration of cognition into action remain to be fully elucidated, it is likely that this behavior relies on the recruitment of additional neural networks [14], which may be more vulnerable to AD pathology than the primary sensorimotor networks known to be preserved until the later stages of the disease [15]. Stereotyped motor actions, such as interacting directly with an object, do not appear to be impaired in early AD relative to healthy aging however performance decrements have been observed under conditions in which direct visual feedback is not provided [16–22]. Similar impairments under indirect visuomotor conditions have also been observed in premanifest Huntington's disease [12]. These visuomotor deficits may reflect posterior parietal damage and/or white matter compromise in parietal-frontal networks.

Traditionally, motor control deficits (e.g., apraxia) have mainly been identified later on in the course of AD [23]. However, recent observations of visuomotor deficits under cognitively demanding task conditions in early AD suggest that deterioration of the neural networks involved in praxic function may occur early in the disease process, and could serve as an early identifying feature of the disease [19, 22, 24–30]. Thus, we hypothesized that using kinematic measures to quantify visuomotor performance under cognitively demanding conditions may successfully identify individuals at increased AD risk due to family history or a diagnosis of mild cognitive impairment (MCI). Both MCI and AD family history are known risk factors for the development of AD [1, 31–35]. Diagnosis of MCI typically includes the presence of memory complaints corroborated by a family member when possible, performance of at least 1.5 standard deviations below the normal age-standardized mean on standardized memory tests such as the Montreal Cognitive Assessment (MoCA), absence of dementia based on clinical evaluation, and absence of significant impairment in functional independence based on clinical judgment [31]. Increased risk due to family history includes the rare familial form of the disease resulting in early-onset AD [1], as well as late-onset AD in immediate family members [32–34], especially if multiple family members are affected [35]. Our specific predictions, based on pilot data, were that movement accuracy and precision would be disproportionately compromised as task demands increased in participants at high AD risk. Furthermore, we predicted that psychomotor slowing would be observed with normal aging, but would be exacerbated by AD risk. We also predicted that increasing the cognitive load by combining visual-spatial recalibration and strategic control demands would provide a more sensitive measure for separation between groups.

MATERIALS AND METHODS

Participants

This study included 66 participants: 22 older adults at high AD risk, 22 older adults at low AD risk, and 22 young adults (see Table 1 for demographic statistics). Older adults were recruited in collaboration with the Canadian Association of Retired People (CARP), Southlake Regional Health Centre (SRHC) and Mackenzie Richmond Hill Hospital (MRHH). Individuals were classified as high AD risk based on AD family history ($n = 14$) or diagnosis of MCI ($n = 8$)

Table 1
Summary of participant information

	Young	Low AD Risk	High AD Risk
n	22	22	22
Age (SD)	26.4 (4.1)[a]	64.3 (10.1)[b]	67.7 (11.3)[b]
Range	21–34	54–84	54–91
High AD risk subgroups	–	–	FH+: 60.8 (5.4)[b] | MCI: 79.8 (8.2)[c]
Sex (% female)	50%	50%	77.3%*
High AD risk subgroups	–	–	FH+: 86%* | MCI: 62.5%
Handedness (% right)	90.9%	90.9%	90.9%
Years of education (SD)	NA	15.8 (3.5)[a]	14.6 (5.2)[a]
High AD risk subgroups	–	–	FH+: 17.4 (0.9)[a] | MCI: 9.8 (1.4)[b]
MoCA score (SD)	NA	27.6 (1.6)[a]	25.8 (4.3)[a]
Range	–	25–30	12–30
High AD risk subgroups	–	–	FH+: 27.3 (2.3)[a] | MCI: 22.9 (5.5)[b]
Computer experience (SD)	NA	2.3 (0.8)[a]	2.1 (1.2)[a]
High AD risk subgroups	–	–	FH+: 2.9 (0.1)[a] | MCI: 0.9 (0.4)[b]
Touchscreen experience (SD)	NA	1.0 (0.8)[a]	1.3 (1.2)[a]
High AD risk subgroups	–	–	FH+: 1.7 (0.3)[a] | MCI: 0.5 (0.4)[b]

NA, not applicable; AD, Alzheimer's disease; FH+, family history positive; MCI, mild cognitive impairment; SD, standard deviation. Superscripts denote significant differences between groups and asterisks denote a significantly greater proportion of female participants at $p < 0.05$.

using the Petersen criteria [31] at the MRHH geriatric outpatient clinic. Individuals classified as family history positive scored at or above age- and education-adjusted norms on the MoCA and reported either a maternal ($n = 6$), multiple ($n = 6$), or early-onset ($n = 2$) family history of AD. Paternal family history alone was not included in the high AD risk classification based on recent evidence that paternal history may not carry the same increased risk as maternal history [36–38]. Individuals classified as low AD risk reported no dementia of any type within their known family history, scored at or above age- and education-adjusted norms on the MoCA, and expressed no memory complaints beyond normal expectations for their age. Exclusion criteria included vision or upper-limb impairments, any medical condition that would hinder task performance (e.g., severe arthritis), any neurological or psychiatric illnesses (e.g., schizophrenia, depression, alcoholism, epilepsy, Parkinson's disease), and any history of stroke or severe head injury. For comparison between low and high AD risk older adults, cognitive (MoCA, version 7.1), computer experience, and touchscreen experience data are recorded in Table 1. Computer and touchscreen experience were assessed with a frequency of use rating scale (i.e., how frequently do you use a computer or touchscreen? 0 = never, 1 = rarely, 2 = occasionally, 3 = often). The study protocol was approved by the Human Participants Review Sub-Committee, York University's Ethics Review Board, and conforms to the standards of the Canadian Tri-Council Research Ethics guidelines.

Experimental task

All participants were tested on four visuomotor transformation tasks, similar to those used previously by Tippett et al. [16–18] and Salek et al. [27]. These tasks were presented on an Acer Iconia 6120 dual-touchcreen tablet: One standard (direct) task in which the spatial location of the viewed target and the required movement were the same, and three non-standard (indirect) tasks (feedback reversal, plane dissociated, and plane dissociated + feedback reversal) in which the location of the viewed target was dissociated from the required movement (Fig. 1A). Task conditions were presented in randomized blocks consisting of five pseudo-randomly presented trials to each of four peripheral targets (from a common central 'home' target), for a total of 20 trials per condition and 80 trials per participant. To ensure task comprehension each participant was given two practice trials per target prior to each condition. Throughout the experiment a webcam was used to monitor eye movements. If incorrect eye movements were made, participants were reminded to always look towards the target and not at their hand.

The peripheral targets were colored red and presented either directly to the left, right, above, or below the home target. Each peripheral target was centered on a point 75 mm from the middle of the home target (i.e., the center of the monitor). The size (20 mm diameter), position, and color of the targets were consistent across all conditions. In order to maintain a consistent visual border around the peripheral targets, the task was

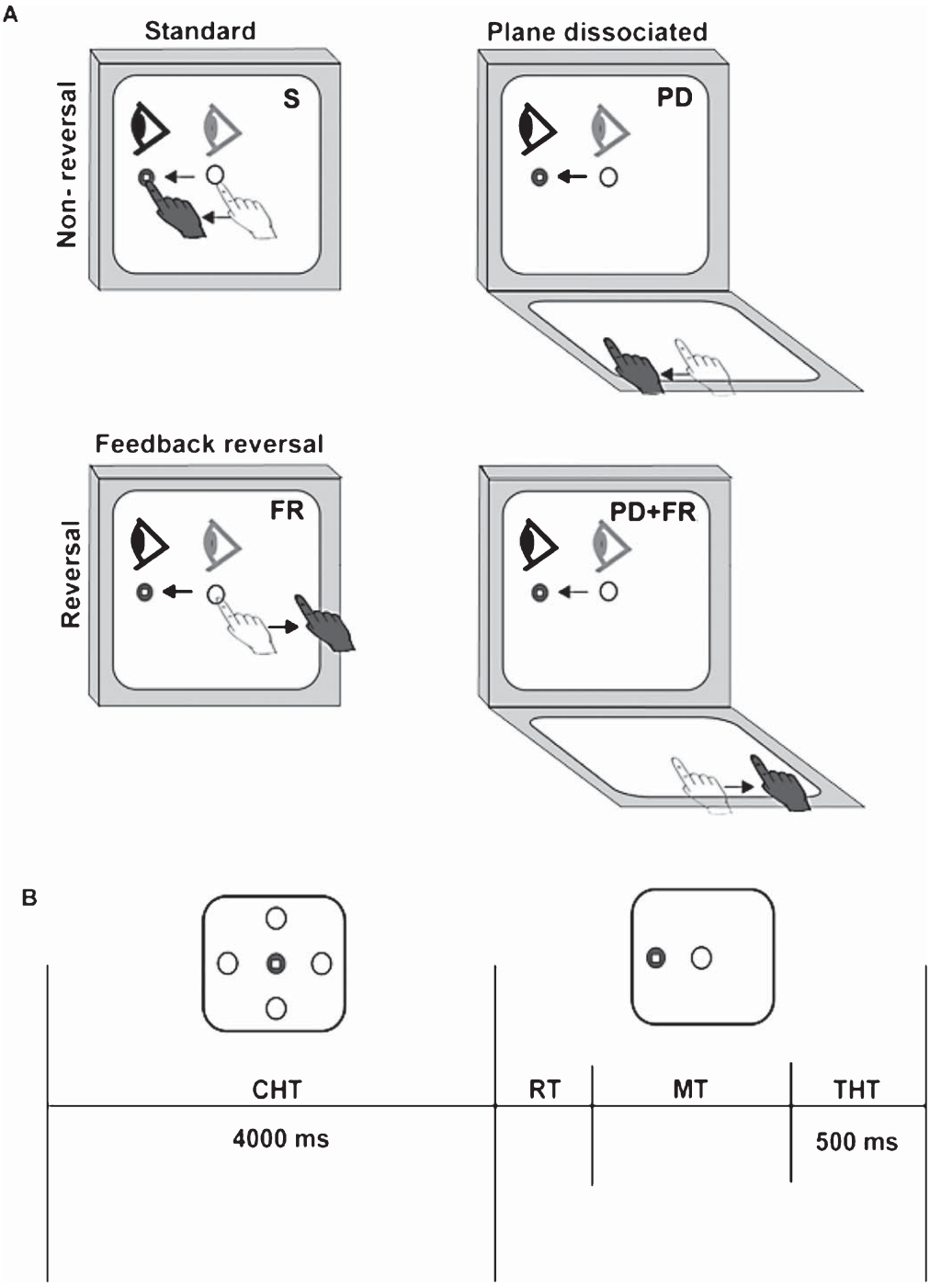

Fig. 1. A) Schematic drawing of the four experimental conditions. Light grey circle, eye, and hand symbols denote the starting position for each trial (i.e., the home target). Dark grey eye and hand symbols denote the instructed eye and hand movements for each task. Dark grey circle denotes the peripheral target, presented randomly in one of four locations. White square denotes the cursor feedback provided during each condition. B) Trial timing. Open circles denote non- illuminated target locations. Disappearance of the home target (which occurred at the same time as presentation of the peripheral target) served as the "go-signal" to initiate movement. CHT, center hold time, RT, reaction time, MT, movement time, THT, target hold time.

displayed on a 170 × 170 mm black square with the surrounding background colored grey. The trial timing and participant responses consisted of the following: 1) a green colored home target was presented on the vertical tablet, 2) participants touched the home target (either directly or with the cursor using the horizontal tablet depending on the condition), which changed its color to yellow indicating that they had acquired the home target, 3) after holding the home target for a center hold time (CHT) of 4000 ms a red peripheral target was presented and the home target disappeared, serving as a 'go-signal' for participants to look towards the visual target and slide their finger along the touchscreen in order to direct the cursor to the target, 4) once the peripheral target was acquired and held for a target hold time (THT) of 500 ms it disappeared and the trial ended, 5) the next trial began with the presentation of the home target after an inter trial interval of 2000 ms (Fig. 1B).

In all conditions, participants were instructed to move as quickly and accurately as possible. In the standard (S) condition, participants were asked to slide their finger directly to the targets on the vertical tablet (i.e., the cursor was under their finger). In the feedback reversal (FR) condition, the cursor moved in the opposite direction of the participant's finger movements, requiring them to slide their finger away from the visual target in order to direct the cursor towards it. In the plane dissociated (PD) condition, participants slid their finger along the horizontal tablet in order to direct the cursor towards visual targets in the vertical plane. And finally, when feedback reversal (PD+FR) was added, movements in the opposite direction of the visual targets, as well as in a different spatial plane, were required. In all conditions participants were instructed to look at the location of the presented target, regardless of whether their finger was sliding to that target or in a different direction/spatial plane. Thus, in all but the standard condition the final spatial locations of gaze and hand were decoupled.

Data processing

Timing, finger position (x, y coordinates; 60 Hz sampling rate), and error data were recorded for each trial and converted into MATLAB readable format using a custom written C++ application. Unsuccessful trials were coded by the software and resulted in trial termination if the finger left the home target too early (<4000 ms), reaction time was too short (<150 ms), reaction time was too long (>8000 ms), or movement time was too long (>10000 ms). Velocity profiles were computed for each successful trial and displayed alongside a Cartesian plot illustrating finger position data and target locations using a custom-written analysis program (MATLAB). Movement onsets and offsets for the first ballistic movement (i.e., the initial muscular impulse) were scored as 10% peak velocity then verified visually to ensure that computed offsets appropriately reflected the first point at which movements stopped or slowed significantly (i.e., the end of the first ballistic movement before any corrective movements). Total movement offsets were identified visually as the point at which velocity reached a final zero-crossing and position data plateaued (i.e., stopping the cursor inside the peripheral target). In the feedback reversal conditions, trials in which the first ballistic movement exited the boundaries of the home target in the wrong direction (i.e., moving the finger towards as oppose to away from the visual target) were coded as direction reversal errors and eliminated from further trajectory endpoint analyses. These processed data were then loaded into a custom written analysis program to compute accuracy, precision and timing outcome measures, as well as generate velocity and trajectory plots.

Dependent measures

The dependent measures of interest in this study were on- and off-axis constant errors, variable error, corrective path length, reaction time, total movement time, and direction reversal errors. Accuracy of the first ballistic movement was determined by computing the absolute on-axis (i.e., distance) and off-axis (i.e., direction) constant errors (CE) which reflect components of reaching accuracy that have been shown to be controlled independently by the motor system [39]. CEs were calculated as the average distance between the actual target position (defined as the coordinates at the center of the target) and the on- or off-axis ballistic movement offset for that target (t) [$\sum (x_i - t)/n$ or $\sum (y_i - t)/n$]. Absolute on- and off-axis CEs were then averaged across targets, resulting in single measures that reflected the magnitude of distance and direction errors for each condition. Precision was determined by computing the variable error (VE), which is the standard deviation (i.e., variation from the mean) of the ballistic movement offsets [$\sqrt{\Sigma}(x_i - \mu)^2/n$, $\sqrt{\Sigma}(y_i - \mu)^2/n$]. The Pythagorean resultant VE (i.e., $\sqrt{VEx^2 + VEy^2}$) was then averaged across targets to generate a single measure for each condition. Corrective movements were quantified by subtracting the ballistic path length from the total path length, resulting in a measure of corrective path length (CPL). Reaction

time (RT) was calculated as the time between disappearance of the home target (i.e., the 'go signal') and movement onset. Total movement time (TMT) was calculated as the time between movement onset and the total movement offset upon positioning the cursor inside the peripheral target. Direction reversals (DR) (only applicable in the feedback reversal conditions) were recorded as a percentage of completed trials.

Statistical analysis

Partial correlations were used to examine the relationship between our task outcome measures and MoCA scores, while controlling for age, in the older adult groups. To test for significant differences in demographic variables between groups, one-way ANOVAs were used to compare means (i.e., age, years of education, MoCA scores, computer experience, touchscreen experience) and Chi-squared tests were used to compare proportions (i.e., sex; Table 1). While most of the potentially confounding demographic characteristics were not significantly different between the young, low AD risk and high AD risk groups, a significantly larger proportion of the high AD risk group was female, thus sex was included as a covariate in the mixed-design analysis of covariance (ANCOVA) tests that were used to compare our dependent measures across the four task conditions (repeated), and between the three experimental groups (young, low AD risk and high AD risk). Percent DRs in the FR and PD+FR conditions were compared between groups using a one-way ANOVA. To overcome violations of the sphericity assumption, Greenhouse-Geisser correction was applied, altering the degrees of freedom and producing an F-ratio where the Type I error rate was reduced. When there were significant main or interaction effects, *post hoc* analyses were adjusted for multiple comparisons using Bonferroni correction. Dependent measures from the most cognitively demanding task, which demonstrated the strongest predictive potential based on the ANOVA results, were entered as predictor variables in a stepwise discriminant analysis comparing low and high AD risk groups. MoCA scores were also included as a potential predictor in this stepwise discriminant analysis in order to compare discriminability between high and low AD risk groups based on visuomotor versus cognitive measures. Applying this discriminant analysis to our data allowed us to identify the weighted linear combination of task outcome variables that contributed maximally to the separation between low and high AD risk groups, and provided estimates of sensitivity, specificity, and overall classification accuracy. In order to demonstrate that this separation between low and high AD risk participants based on cognitive-motor performance exists for both family history positive (FH+) and MCI subgroups, we also conducted separate stepwise discriminant analyses comparing the low AD risk group to each subgroup. Statistical significance levels were set to 0.05. All statistical analyses were carried out using SPSS statistical software.

RESULTS

Significant negative correlations between MoCA scores and visuomotor performance in older adults were mainly found in the plane dissociated condition (Table 2). These correlations indicate that older adult participants with lower cognitive scores (i.e., those diagnosed with MCI) exhibit greater impairments in visuomotor control under spatially dissociated conditions. The lack of significant correlations between MoCA scores and all but one performance measure in the most cognitively-demanding condition, suggests that the performance decrements observed on this task in the high AD risk group may be independent of more global impairments in cognition detected by standardized cognitive tests.

As predicted, a marked deterioration in movement control was observed in high AD risk participants as the cognitive demands of the task increased. The mean ballistic trajectories plotted in Fig. 2 illustrate a pronounced disruption in the performance (i.e., larger variability and endpoint errors) of high AD risk participants, including both FH+ and MCI subgroups, during the most cognitively demanding PD+FR condition. Example full trajectories from the PD+FR condition are also displayed in Fig. 2 in order to demonstrate the typical trajectory deviations observed in the high AD risk group. Figure 3 illustrates mean velocity profiles across task conditions for young, low AD risk, FH+ and MCI participants. Again,

Table 2
Significant correlations between MoCA scores and kinematic measures

Kinematic measures	r	r^2	p-value
On-axis constant error (PD condition)	−0.399	0.159	0.008
On-axis constant error (PD+FR condition)	−0.345	0.119	0.024
Variable error (PD condition)	−0.336	0.113	0.028
Corrective path length (PD condition)	−0.379	0.144	0.012
Reaction time (PD condition)	−0.429	0.184	0.004
Total movement time (PD condition)	−0.393	0.154	0.009

PD, plane dissociated; PD+FR, plane dissociated + feedback reversal.

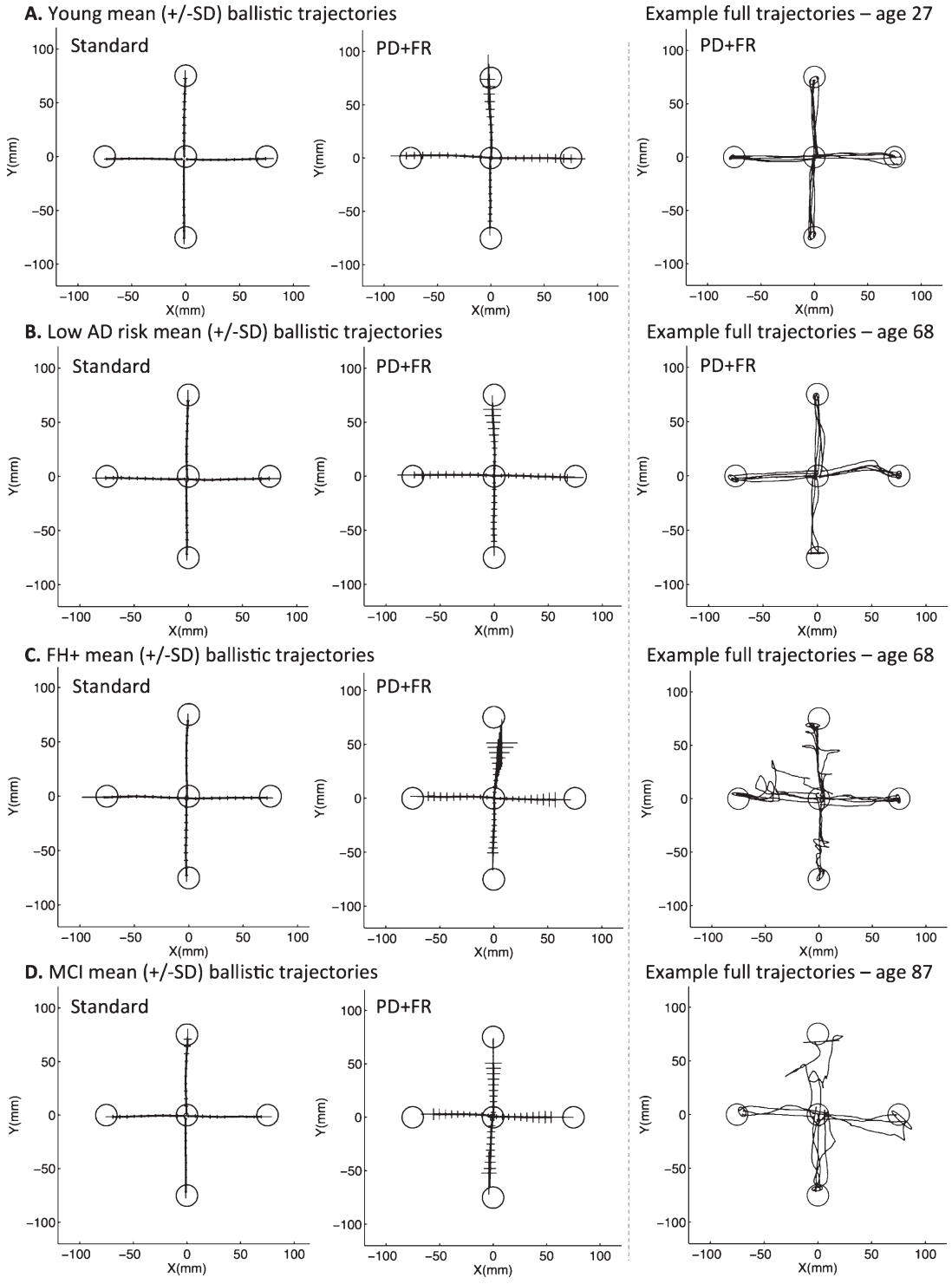

Fig. 2. Left panel: mean ballistic trajectories (±SD) in the standard and plane dissociated + feedback reversal (PD+FR) conditions across groups: A) Young, B) Low Alzheimer's disease (AD) risk, C) Family history positive (FH+), and D) Mild cognitive impairment (MCI). Crosshairs reflect variability in reach performance, calculated as the standard deviation (SD) at ten equal points along the reach trajectory. Right panel: examples of the typical full reach trajectories observed during the plane dissociated + feedback reversal (PD+FR) condition in each group (note the pronounce trajectory deviations in the high AD risk participants).

performance disruptions in high AD risk participants, including both FH+ and MCI subgroups, were most pronounced in the PD+FR condition. Figure 3 also demonstrates that the performance of MCI patients was affected at lower levels of cognitive demand (i.e., in the FR and PD conditions) than FH+ participants. Our ANOVA tests resulted in significant condition by group interactions for all dependent measures (on-axis CE: $F_{(3.9,122)} = 14.78$, $p < 0.001$, $\eta_p{}^2 = 0.323$; off-axis CE: $F_{(4.5,141)} = 10.06$, $p < 0.001$, $\eta_p{}^2 = 0.245$; VE: $F_{(3.8,116)} = 8.02$, $p < 0.001$, $\eta_p{}^2 = 0.206$; CPL: $F_{(2.8,85.6)} = 24.79$, $p < 0.001$, $\eta_p{}^2 = 0.444$; RT: $F_{(3.5,110)} = 8.59$, $p < 0.001$, $\eta_p{}^2 = 0.217$; TMT: $F_{(2.9,91)} = 11.61$, $p < 0.001$, $\eta_p{}^2 = 0.272$), indicating impairments in performance with increasing task difficulty that were influenced primarily by the high AD risk group. Figure 4 illustrates these interaction effects with the high AD risk group subdivided into FH+ and MCI subgroups. Displaying these subgroups separately demonstrates that the impairment in performance observed in the conditions with only one level of dissociation (i.e., FR and PD) were mainly influenced by MCI participants, while the pronounced performance disruptions observed when combining spatial dissociation and feedback reversal (i.e., in the PD+FR condition) were influenced by both FH+ and MCI participants within the high AD risk group.

Group means in each condition for all dependent variables and effect sizes reflecting the effect of group within each condition are listed in Table 3. *Post-hoc* analyses revealed significantly larger on-axis constant errors in the high AD risk group relative to both the young and low AD risk groups during the PD and PD+FR conditions. On-axis constant errors were also significantly larger in both older adult groups relative to the young group in the standard condition (Fig. 4A). Significantly larger off-axis constant errors were observed in the high AD risk group relative to both the young and low AD risk groups in the PD+FR condition, and relative to the young group only in the PD condition (Fig. 4B). Performance variability (i.e., variable error) and corrective path length were significantly increased in the high AD risk group relative to the low AD risk group for the FR condition and relative to both the young and low AD risk groups for the PD and PD+FR conditions (Fig. 4C-D). Post-hoc analyses of the timing outcome variables also revealed effects of AD risk, however effects of normal aging were also clearly present. Reaction time was significantly longer in high AD risk participants relative to young participants in all task conditions. However, reaction time was also significantly longer in low AD risk participants relative to young participants in the FR and PD+FR conditions. Reaction time was only significantly different between high and low AD risk groups in the FR condition (Fig. 4E). Lastly, movement time was significantly longer in high AD risk relative to young participants in all task conditions, as well as in low AD risk relative to young participants in the non-standard conditions. Movement time was only significantly different between high and low AD risk groups in the PD+FR condition (Fig. 4F).

The one-way ANOVA tests for differences in the percentage of direction reversals between groups for the FR and PD+FR conditions were not significant. Notably, however, we did observe that within the high AD risk group, individuals diagnosed with MCI tended to commit more direction reversal errors. In order to test this observation, we separated the high AD risk group into FH+ and MCI subgroups and compared percent DR between MCI, FH+, low AD risk, and young groups in the FR and PD+FR conditions using non-parametric Kruskal-Wallis tests. The omnibus Kruskal-Wallis test revealed no significant differences in DR errors between groups in the FR condition (young: $M = 1.39 \pm 0.6$; low AD risk: $M = 2.73 \pm 0.91$; FH+: $M = 1.79 \pm 1$; MCI: $M = 11.25 \pm 9.29$), however in the PD+FR condition, percent DR was significantly different between groups ($p = 0.042$). Specifically, *post-hoc* analyses revealed that in the PD+FR condition, percent DR was significantly higher in the MCI group relative to the young group ($p = .006$), as well as relative to the low AD risk group with marginal significance ($p = .056$; young: 3.91 ± 1.86; low AD risk: $M = 6.31 \pm 2.28$; FH+: $M = 7.62 \pm 2.45$; MCI: $M = 19.04 \pm 7.35$).

In order to determine the predictive potential of kinematic measures from a cognitively demanding visuomotor task in discriminating between high and low AD risk participants, the dependent measures from the PD+FR condition, along with MoCA scores, were entered into a stepwise discriminant analysis. The minimum partial F for entrance into the discriminant analysis was 3.84 and the maximum partial F for removal was 2.71. The most correlated, and thus first predictor variable entered into the analysis by the stepwise program, was corrective path length, next was variable error, and the last variable adding significant predictive power to the canonical R squared was off-axis constant error. In a fourth and final step, corrective path length was removed from the analysis with an F to remove value of 2.51. The resulting discriminant function was significant (Wilks' Lambda = 0.468, $p < 0.001$), with a canonical correlation of 0.73. The

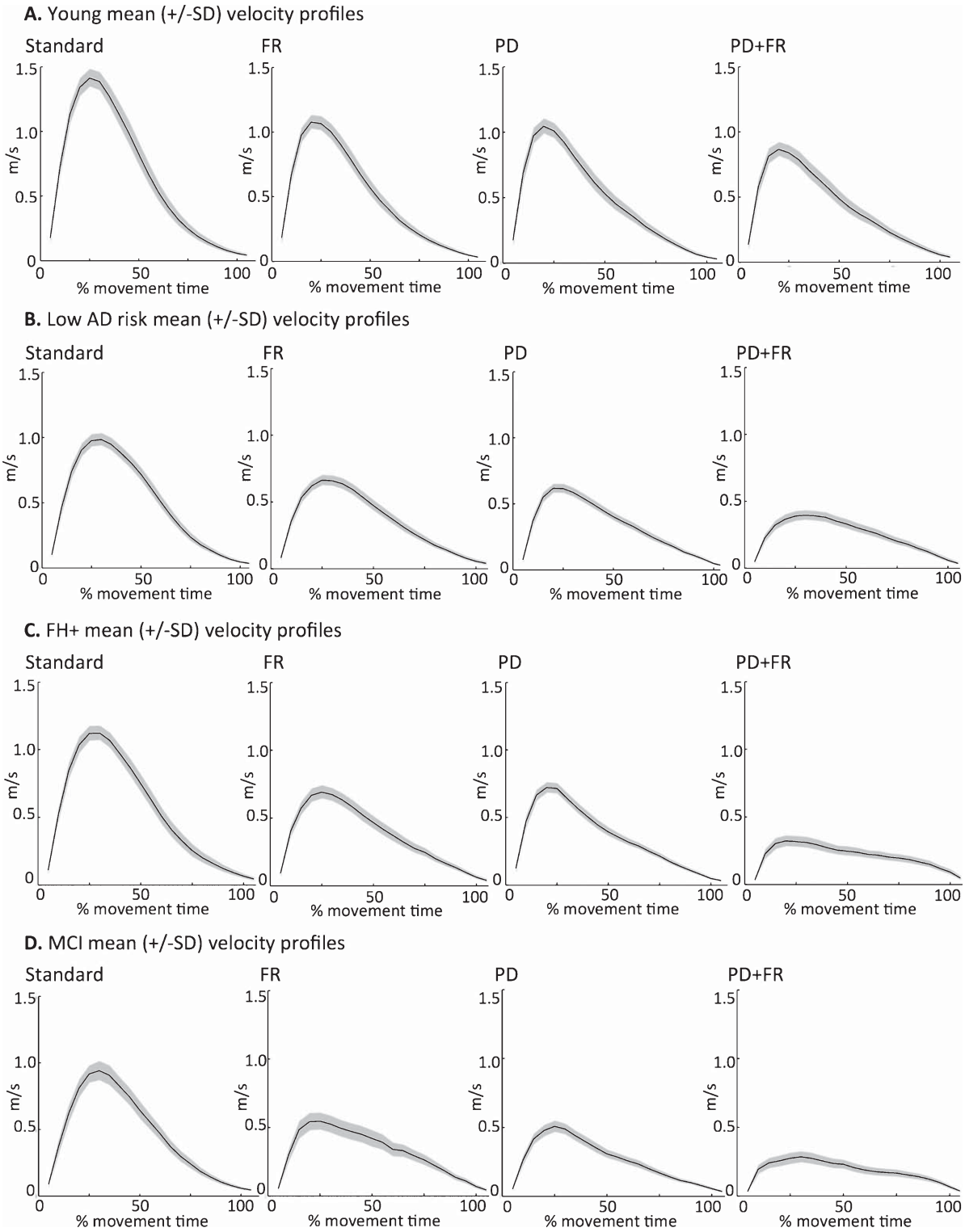

Fig. 3. Mean velocity profiles (filtered using a 10 Hz low pass Butterworth filter) across task conditions for each group: A) Young, B) Low Alzheimer's disease (AD) risk, C) Family history positive (FH+), and D) Mild cognitive impairment (MCI). Shading represents standard deviation. FR: feedback reversal, PD: plane dissociated, PD+FR: plane dissociated + feedback reversal, m/s: meters per second.

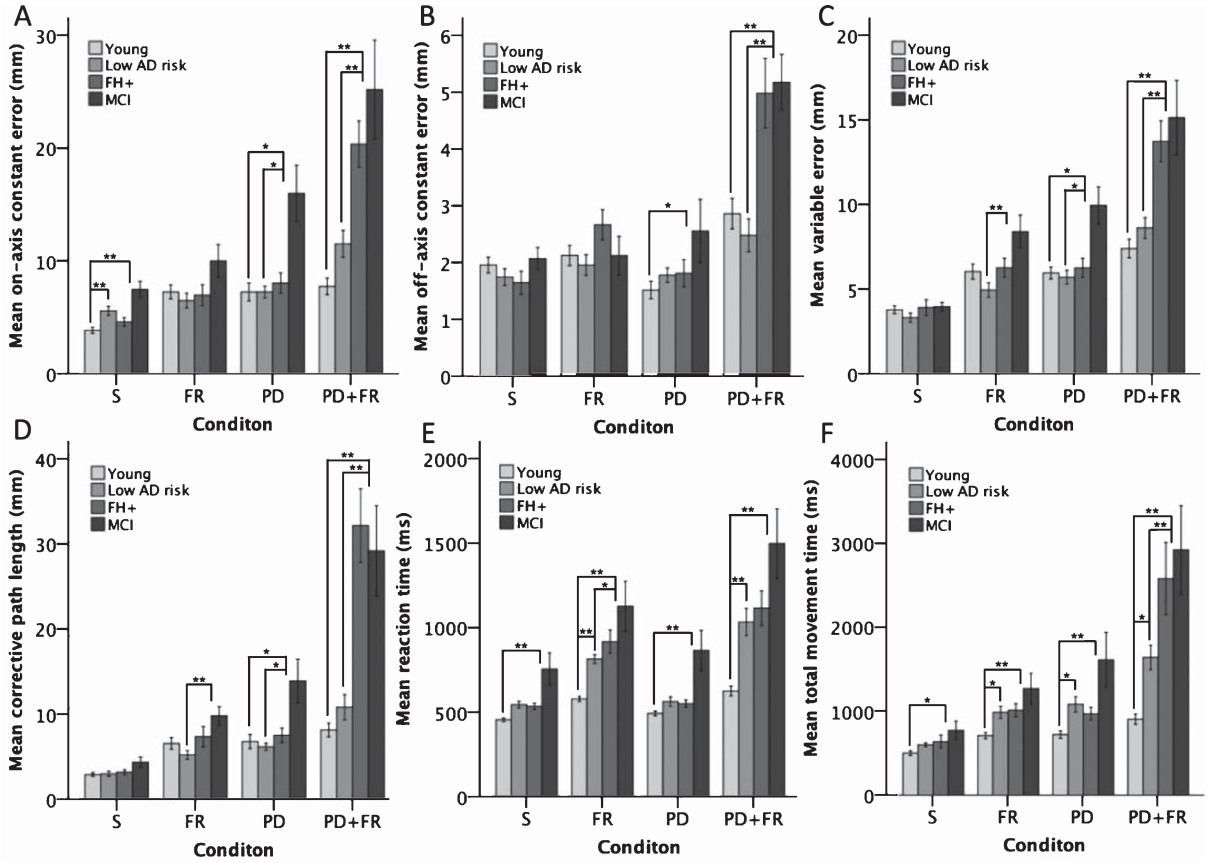

Fig. 4. A–F) Results of group (young: light grey bars, low AD risk: medium grey bars, FH+: dark grey bars, MCI: black bars) by condition (S, standard, FR, feedback reversal, PD, plane dissociated, PD+FR, plane dissociated + feedback reversal) mixed ANOVAs on task dependent measures. Means ± 1 standard error of the mean, $*p \leq 0.05$, $**p \leq 0.001$. AD, Alzheimer's disease; FH+, family history positive; MCI, mild cognitive impairment.

structure matrix indicated that off-axis constant error was the strongest predictor ($r = 0.73$), next was variable error ($r = 0.64$), followed by corrective path length ($r = 0.53$) and on-axis constant error ($r = 0.34$). The correlation between MoCA scores and the standardized canonical discriminant function ($r = 0.06$) indicated that cognitive scores were not useful in predicting group membership. The resulting canonical discriminant function was: D = (0.453 × off-axis constant error) + (0.168 × variable error) −3.614. The grouping of cases resulted in an overall classification accuracy of 86.4%, with a sensitivity of 81.8% and specificity of 90.9%.

The discriminant analyses conducted separately on the high AD risk subgroups also demonstrated good separation from the low AD risk group (FH+: Wilks' Lambda = 0.474, $p < 0.001$, canonical correlation = 0.73; MCI: Wilks' Lambda = 0.344, $p < 0.001$, canonical correlation = 0.81). The predictors included in the discriminant function classifying FH+ versus low AD risk participants were corrective path length ($r = 0.89$) and variable error ($r = 0.68$) [D = (0.131 × variable error) + (0.067 × corrective path length) – 2.67]. Again, MoCA scores were not useful in predicting group membership in this analysis ($r = 0.16$). However, in the discriminant function classifying MCI versus low AD risk participants, MoCA scores did add significant predictive power, as would be expected since impaired MoCA performance was one of the diagnostic criteria for MCI classification. Importantly, several kinematic measures were also significant predictors and were better or as good as MoCA scores at predicting group membership, including off-axis constant error ($r = 0.65$), corrective path length ($r = 0.62$), on-axis constant error ($r = 0.57$), and variable error ($r = 0.51$). MoCA scores were negatively correlated with the discriminant function ($r = -0.52$), reflecting lower scores in the MCI group. The predictors included

Table 3
Group means and effect sizes for all kinematic measures in each task condition

Kinematic Measures	Condition	Young	Group Means (SE)		η_p^2
			Low AD Risk	High AD Risk	
On-axis constant error	Standard	3.85 (0.39)[a]	5.57 (0.39)[b]	5.66 (0.40)[b]	0.176
	FR	7.13 (0.69)	6.36 (0.69)	8.33 (0.71)	0.059
	PD	7.19 (0.96)[a]	7.18 (0.96)[a]	11.06 (0.98)[b]	0.142
	PD+FR	7.69 (1.46)[a]	11.45 (1.46)[a]	22.23 (1.49)[b]	0.450
Off-axis constant error	Standard	1.97 (0.15)	1.76 (0.15)	1.77 (0.15)	0.021
	FR	2.15 (0.19)	1.99 (0.19)	2.41 (0.19)	0.038
	PD	1.48 (0.19)[a]	1.74 (0.19)	2.15 (0.19)[b]	0.090
	PD+FR	2.81 (0.33)[a]	2.43 (0.33)[a]	5.16 (0.34)[b]	0.376
Variable error	Standard	3.73 (0.27)	3.26 (0.27)	4.03 (0.28)	0.060
	FR	6.01 (0.47)	4.92 (0.47)[a]	7.09 (0.48)[b]	0.141
	PD	5.92 (0.50)[a]	5.66 (0.50)[a]	7.69 (0.50)[b]	0.131
	PD+FR	7.41 (0.79)[a]	8.63 (0.79)[a]	14.02 (0.81)[b]	0.376
Corrective path length	Standard	2.92 (0.29)	2.99 (0.29)	3.67 (0.29)	0.059
	FR	6.49 (0.70)	5.14 (0.70)[a]	8.46 (0.72)[b]	0.148
	PD	6.72 (0.90)[a]	6.10 (0.90)[a]	10.03 (0.92)[b]	0.143
	PD+FR	7.97 (2.16)[a]	10.65 (2.16)[a]	31.49 (2.20)[b]	0.519
Reaction time	Standard	460 (28)[a]	549 (28)	613 (28)[b]	0.191
	FR	587 (42)[a]	823 (42)[b]	982 (43)[c]	0.411
	PD	493 (37)[a]	563 (37)	670 (38)[b]	0.152
	PD+FR	636 (79)[a]	1044 (79)[b]	1239 (80)[b]	0.325
Total movement time	Standard	509 (43)[a]	609 (43)	676 (43)[b]	0.109
	FR	718 (65)[a]	996 (65)[b]	1093 (67)[b]	0.218
	PD	728 (102)[a]	1089 (102)[b]	1196 (104)[b]	0.154
	PD+FR	929 (212)[a]	1666 (212)[b]	2665 (216)[c]	0.342

Superscripts denote significant differences between group means. Partial eta-squared (η_p^2) effect sizes reflect the effect of group within each condition and are based on the linearly independent pairwise comparisons among the estimated marginal means. AD, Alzheimer's disease; SE, standard error; FR, feedback reversal; PD, plane dissociated.

Table 4
Classification results of stepwise discriminant analyses.

		Group	Predicted group membership		Total
			Low AD Risk	High AD Risk	
Classification[a]	Count	Low AD Risk	20	2	22
		High AD Risk	4	18	22
	%	Low AD Risk	90.9	9.1	100.0
		High AD Risk	18.2	81.8	100.0
			Low AD Risk	FH+	Total
Classification[b]	Count	Low AD Risk	20	2	22
		FH+	3	11	14
	%	Low AD Risk	90.9	9.1	100.0
		FH+	21.4	78.6	100.0
			Low AD Risk	MCI	Total
Classification[c]	Count	Low AD Risk	21	1	22
		MCI	2	6	8
	%	Low AD Risk	95.5	4.5	100.0
		MCI	25	75	100.0

Each case in the analysis is classified by the functions derived from all cases other than that case. *a*, 86.4% of cases correctly classified; *b*, 86.1% of cases correctly classified; *c*, 90% of cases correctly classified. AD, Alzheimer's disease; FH+, family history positive; MCI, mild cognitive impairment.

in the discriminant function were off-axis constant error, variable error, and MoCA score [D = (0.534 × off-axis constant error) + (0.145 × variable error) – (0.149 × MoCA score) −0.745]. These discriminant analysis classification results are summarized in Table 4.

DISCUSSION

The results of the present study demonstrate a striking impairment of visuomotor integration under cognitively demanding task conditions in high AD risk older adults relative to both low AD risk and young par-

ticipants. Specifically, we found that when performing the plane dissociated + feedback reversal task, participants at increased AD risk, due to both family history and MCI, demonstrated significant impairments on measures of accuracy, consistency and timing. Furthermore, we demonstrated that these kinematic measures are useful in discriminating between older adults who are and are not at increased AD risk.

Visuomotor impairment in MCI and AD populations has received little study to date, thus the present state of knowledge in this area is low. Most research involving the assessment of AD in its early stages is cognitive based, and only recently has it been recognized that complex movements may also be affected [19, 24, 25, 27]. The results of the current study indicate that measurable impairments in visuomotor control are already present in individuals at increased risk of developing AD. We suggest that these impairments may reflect inherent brain alterations and/or early neuropathology disrupting the connectivity between hippocampal, parietal, and frontal brain regions required to successfully control complex reaching behaviors. In support of this prediction, recent diffusion tensor imaging (DTI) studies in MCI and early AD have revealed disruption to the integrity of prominent association fiber tracts, including parietal-frontal connections [40, 41] and projections from the hippocampus to inferior parietal regions [42]. Furthermore, DTI studies in cognitively normal participants at increased AD risk due to family history and carrying one or more apolipoprotein $\varepsilon 4$ allele have shown decreased microstructural integrity in WM tracts with direct and secondary connections to the medial temporal lobes, years before the expected onset of cognitive symptoms [43, 44].

Taken together the above findings indicate that disconnection between the medial temporal lobes and neocortex, as well as between parietal and frontal cortex, may occur very early in the course of AD. In order to investigate whether or not these brain alterations are responsible for the visuomotor impairments observed in this study, our lab is currently using MRI techniques to correlate anatomical and functional connectivity with visuomotor performance in individuals at increased AD risk.

Interpretation of visuomotor deficits associated with AD risk

Our results suggest that visuomotor networks involved in both visual-spatial recalibration and strategic control may be compromised in individuals at increased AD risk. Specifically, we found that the performance of MCI patients was impacted at lower levels of cognitive demand when either strategic control (FR condition) or visual-spatial recalibration (PD condition) were required, whereas performance impairments in FH+ participants only became apparent at higher levels of cognitive demand when both strategic control and visual-spatial recalibration were required at the same time (i.e., PD+FR condition). Furthermore, MCI patients showed direction reversal errors in the feedback reversal conditions reflecting impaired inhibition of prepotent responses, as well as overall slowing in reaction and movement times across task conditions that were not present in FH+ participants. These findings suggest that visuomotor tasks with increasing levels of cognitive demand may be useful not only in detecting AD risk before cognitive declines on standardized tests are present, but also in monitoring disease progression from preclinical to MCI stages.

We propose three putative mechanisms (which are not mutually exclusive) to account for the visuomotor deficits observed in high AD risk participants in the current study. First, increased ballistic endpoint errors may reflect disruption to motor programming, and thus more reliance on online sensory feedback. In turn, these corrective mechanisms may also be disrupted or delayed, resulting in trajectory deviations and extended corrective path lengths. In other words, the internal feedback loop required to update the current location of the hand relative to the position of the target, which relies on intact parietal-frontal connections [45], may be disrupted. Studies examining the control of arm movements in older adults have demonstrated that increased reliance on visual feedback is present in normal healthy aging, which is often interpreted as compensation for deficiencies in central motor planning [46–49]. Furthermore, online corrective mechanisms have been shown to be less efficient in older individuals [50, 51]. Our results suggest that these changes associated with normal aging may be exacerbated in individuals at increased AD risk.

Second, disruption to attentional control networks [52, 53] may also play a role in the errors and slowed performance observed under indirect task conditions. Such disruption would impair the ability to inhibit stereotyped eye-hand coupling and divide attention (i.e., neural resources) between incongruent eye and hand movements. Baddeley and colleagues [52] have demonstrated that individuals in the early stages of AD exhibit substantial impairment in the ability to combine performance on two simultaneous tasks, indicating that an attentional processing deficit exists in early AD.

Lastly, poorer accuracy and precision under conditions of spatial dissociation may also be explained by disruption to hippocampal-parietal processing, which is required for the integration of visual-spatial information into a motor program [54].

Study limitations

Considering the relatively small sample size used in the present study, future research is required in order to determine the generalizability of our results and to apply appropriate cross-validation to the discriminant analyses. Furthermore, longitudinal studies are required in order to fully elucidate the predictive potential of kinematic measures in identifying individuals who will later go on to develop AD. Lastly, while there were similarities between the FH+ and MCI participants combined to form the high AD risk group in the present study, there were also important differences that could not be fully examined statistically due to the small number of MCI participants included. These MCI patients were also older, less educated, and had less computer/touchscreen experience than the other study participants, adding potential confounds that may have exacerbated their impaired performance. Again, future studies with larger sample sizes and better separation between different levels of risk would clarify this issue.

Conclusions and clinical implications

Based on the findings of the current and previous research from our lab, clinical assessment tools incorporating cognition and action together would be useful not only in providing information about the functional abilities of a patient, but also in alerting clinicians to increased dementia risk before cognitive symptoms are consistently present. Furthermore, we speculate that the early detection of visuomotor deficits may serve to identify individuals at increased risk for subsequent clinical decline in areas such as balance and gait [53, 55], driving, and activities of daily living. Several studies have demonstrated an association between motor symptoms and adverse health effects in old age [22], thus assessments that employ motor measures may provide more accurate identification of individuals at increased disease risk. Importantly, our results provide strong evidence that the integration of cognition and movement control can provide valuable, clinically-relevant information that may be more useful than measuring performance in either of these domains in isolation.

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