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Cognitive-Motor Integration Performance Is Affected by Sex, *APOE* Status, and Family History of Dementia

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Abstract.
Background: Cognitive-motor integration (CMI) involves concurrent thought and action which requires the interaction of large brain networks. Given that early-stage dementia involves neural network dysfunction, deficits in CMI may prove useful for early dementia detection.
Objective: Our research objective was to investigate sex-related differences in the ability to integrate rules into action.
Methods: Based on family medical history, we recruited male and female participants both with and without dementia risk factors. Participants did not demonstrate cognitive impairment at the time of testing. Participants were tested on four increasingly dissociated visuomotor tasks (eye and hand movements were made in different spatial planes and/or visual feedback was reversed)
Results: We observed significantly greater hand movement endpoint error scores and corrective path lengths in at-risk females compared to at-risk males in the most complex CMI condition (plane-change + feedback reversal). Multiple regression analyses revealed both sex and family history as significant predictors of worse performance in a CMI condition requiring visual feedback reversal. Further, the regression analyses provided preliminary evidence that having an *APOE* ε4 allele was a significant predictor of poorer CMI performance in the two plane-change CMI conditions.
Conclusion: These data suggest that underlying brain networks controlling simultaneous thought and action may differ between the sexes in ways that may be clinically relevant in dementia progression. Preliminary data also suggest an important connection between *APOE* variant and CMI performance in individuals at risk of developing dementia.

Keywords: Aging, alzheimer's disease, apolipoprotein E4, dementia risk, geriatric assessment, motor skills, movement, visuomotor integration

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INTRODUCTION

Dementia is a syndrome characterized by 1) cognitive impairments in a variety of domains such as memory declines and language problems, and 2) disruption of activities of daily living [1]. Typically, these clinical symptoms appear only after there has already been significant damage to the brain [2, 3]. Converging evidence further suggests that the pathophysiological process of Alzheimer's disease (AD), the most common cause of dementia [4], precedes the diagnosis of clinical dementia by years, if not decades [5]. This means that early detection is not only essential, but it is also possible. Although there have been advances in the early detection of AD, these usually include neuroimaging or invasive procedures (taking blood or cerebrospinal fluid (CSF) samples), which are both costly and not easily accessible to the public. As an alternative, measuring the dysfunction of brain

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networks underlying visuomotor transformations in early-stage AD provides a novel behavioral target for its detection.

In everyday life we perform daily activities that require interaction with objects in our environment. The current study is guided by the theory that different types of visuomotor transformations are processed in separate, but overlapping, large-scale neural networks. Further, the frontal, parietal, and sub-cortical regions which comprise these skilled movement control networks are differentially affected by healthy aging versus neuropathology. Most reaching movements made in daily life are "standard" visuomotor transformations. These actions involve the spatially congruent guidance of the eyes, limbs, and body directly toward a visual target of a reach [6]. In other words, the gaze and limbs are directed toward the same spatial location. This process is automatic once learned early in life because the brain's default visuomotor mapping is thought to spatially couple gaze and hand position [7, 8]. However, with the advent of tool-use and technology, many learned movements have an element of dissociation between the targets of gaze, attention, and reaching, and are referred to as "nonstandard" visually-guided movements [6]. Such movements require the integration of cognitive information ("cognitive-motor integration", CMI) into the visuomotor transformation and the inhibition of the default coupling of gaze and reach. Nonstandard mapping can take a number of different forms [6, 9, 10]. Some are more implicit and require constant feedback monitoring, such as sliding a computer mouse forward to move a cursor upward on a monitor [11–13], while others are more explicit and require the application of express rules such as pushing a boat rudder to the right in order to steer the boat to the left. In general, movement performance always worsens in measures of timing and trajectory formation (e.g., precision and accuracy) when going from standard to nonstandard mapping, or in any situation requiring the integration of thinking and movement control [14].

Neurophysiological studies done in rhesus macaque monkeys showed differences between brain areas involved in standard versus nonstandard visuomotor transformation tasks. Specifically, differences in neuronal activity were found in the parietal and premotor areas [15–18]. Standard reaches showed enhanced activity within superior parietal lobule (SPL) regions surrounding the medial intraparietal sulcus (MIP), and the caudal dorsal premotor area (PMd). In contrast, caudal SPL and rostral PMd showed enhanced activity during nonstandard reaches where there was a decoupling of the eyes and hand. These results demonstrate a separation by region in the SPL and PMd during standard versus nonstandard visuomotor tasks. Furthermore, a functional MRI study in humans characterized the brain areas required for standard versus nonstandard mapping [19]. Common for all tasks, there was activity in the contralateral primary, premotor, and medial motor regions, as well as the postcentral gyrus. As tasks required motor outputs that were increasingly dissociated from the visual input, there were regions in addition to the basic pattern of activity that were required for visuomotor transformations. These regions included increased activity in the left precuneus, the right superior frontal and middle temporal gyri, and bilaterally in the angular gyri and inferior parietal lobule (IPL). IPL activity has been associated with tool-use in humans, which requires increasingly dissociated sensorimotor transformations [20]. There are further differences between cortical networks used for nonstandard tasks requiring implicit rules versus explicit rules. Specifically, patterns of activity in the cuneus, medial premotor cortex, IPL, and cerebellum differed during a nonstandard condition requiring an explicit rule (i.e., a 180° feedback reversal) compared to a standard mapping task [21]. While in an implicit nonstandard task (i.e., involving a plane change), patterns of activity differed in the anterior prefrontal cortex, large regions of the occipital lobe, and precuneus compared to a standard task [22].

Effects of Alzheimer's disease on visuomotor integration

Patients in the early stages of AD may not yet exhibit significant memory deficits typically associated with the disease. However, there are structural changes that occur in the brain. Brain autopsies of demented patients showed widespread amyloid-β (Aβ) deposits and characteristic distribution patterns of neurofibrillary tangles in parietal and frontal lobes [23]. Further, behavioral studies looking at AD patients found performance declines in eye-hand coordination tasks requiring nonstandard mapping [24, 25]. Early-stage AD patients with mild cognitive deficits show difficulties in movements requiring the integration of cognitive information (CMI tasks) [26–29]. Notably, these clinical populations performed no differently than healthy age-matched controls on a standard mapping

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task, but had significantly more difficulty once an element of decoupling was introduced between gaze and movement, thus requiring CMI. Further, when compared to healthy age-matched controls, women at an increased risk for AD but without any detectable cognitive decline demonstrated significant performance disruptions in CMI tasks [30]. Furthermore, these behavioral deficits in this dementia-risk group were associated with declines in white matter integrity and lower resting-state functional connectivity within the default mode network in the brain [31, 32].

Sex-differences in dementia and visuomotor research

There are known sex-related differences in dementia prevalence, progression, and genetic profiles [33, 34]. Approximately two-thirds of individuals diagnosed with AD in America are women [35]. While some areas of the world report higher incidence of AD in women [36, 37], others report no difference by sex or higher incidence in men [38, 39]. It is important to note that despite inconsistencies in the incidence of dementia, women appear to have a higher risk of progression from mild cognitive impairment (MCI) to AD [40]. Differences in brain changes are apparent in patients with probable AD, where the hippocampus has been shown to atrophy at a significantly faster rate in women compared to men [41]. Meanwhile, poorer global cognitive function and severe periventricular white matter hyperintensities were found to be significant risk factors for probable AD [42]. In terms of genetics, one of many genes that predisposes the carrier to AD is an isoform of the apolipoprotein E (*APOE*) gene, the *APOE* $\varepsilon4$ allele [43]. The risk of AD given a specific *APOE* genotype varies depending on sex, where *APOE* $\varepsilon4$ confers greater AD risk in women [44]. Just one copy of the *APOE* $\varepsilon4$ allele in women is equivalent to the increased AD risk associated with having two copies of the $\varepsilon4$ allele in men [33, 34].

Sex-related differences have also been reported on performance of eye-hand coordination tasks [45]. Typically, women excel in tasks requiring accuracy and bimanual coordination, while men outperform women in tasks requiring speed [46–49]. Not only has task performance differed between males and females, the underlying brain activity required for these tasks differs between the sexes, too. Functional neuroimaging studies in humans showed sex-related differences in normal motor control [50–54]. Furthermore, there are differences between men and women in how the brain controls movements and CMI, which could provide clinically relevant information. Our group previously used event-related BOLD fMRI in both sexes to study brain activity during tasks requiring movements that were increasingly dissociated from visual stimuli [55]. While there were no sex-related differences in behavioral performance of the tasks, there were differences in the underlying brain activity. In general, the right dorsal premotor cortex, right superior parietal lobule, and left sensorimotor cortex were more active in women compared to men in tasks with the hand movement dissociated from gaze. In contrast, the superior temporal gyri were bilaterally more active in men. There were also sex-related differences in the laterality of brain activity in the frontoparietal network during the preparation of movements for visually-guided reaching tasks. While both sexes showed activity in the PMd and SPL contralateral to arm movements, women also showed greater ipsilateral activity in these regions. This finding suggests a more bilateral pattern of activation in women during visually-guided reaching tasks. A related study used electroencephalography (EEG) to look at hemispheric laterality of event-related slow cortical potentials during visually-guided arm movement preparation [56]. Activity during the preparatory period for movement was mainly contralateral to reaching in men, and bilateral in women. Furthermore, ipsilateral PMd activity in females may provide a functional redundancy to potentially compensate for any decreased activity in the contralateral PMd [57]. Meanwhile, men may be more dependent on the contralateral PMd for movement planning.

It is important to expand on current combined-sex data, and look at data from males and females separately to better understand the aging brain. Preliminary research findings from a female population revealed deficits in performance of CMI tasks which were associated with alterations in structural and functional connectivity typically seen in individuals at risk for dementia [31, 32]. In the current study, we turn our attention to explicitly examining any sex-related differences that may exist in the performance of cognitive-motor integration. Our analyses are exploratory, with the aim of elucidating how CMI performance in males might be affected by dementia risk compared to females. Given the known sex-related differences in the underlying neural control of CMI, and the overlap in brain networks impacted by dementia and those important for CMI performance [23, 58–61], we expect dementia risk to affect CMI performance differently in men and women. Another

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Table 1
Summary of participant information

	FH- Male	FH+ Male	FH– Female	FH+ Female
n	12	13	12	12
Age years (SD)	59 (5.5)	58 (6.0)	58 (5.3)	59 (6.5)
Range	49–66	51–69	50–67	51–68
MoCA score (SD)	28.1 (1.56)	27.2 (1.36)	27.9 (1.62)	28.5 (1.45)
Range	26–30	26–30	26–30	26–30
Years of education (SD)	16.7 (3.31)	17.3 (3.77)	17.3 (2.87)	17.3 (3.39)
Range	12–22	11–22	12–24	12–23
Number with *APOE* ε4 allele (%)	3 (25)	2 (15.4)	2 (16.7)	9 (75)
Computer experience years (SD)	2.8 (0.45)	2.6 (0.51)	2.6 (0.67)	2.9 (0.29)
Touchscreen experience years (SD)	1.8 (0.75)	1.6 (0.87)	1.8 (0.71)	2.1 (0.93)

FH+, family history of dementia; FH-, no family history of dementia; SD, standard deviation; MoCA score, Montreal Cognitive Assessment score; *APOE*, apolipoprotein E.

exploratory component of this study is to assess the relationship between CMI performance and genetic markers.

MATERIALS AND METHODS

Participants

The present study collected data from the male population, and compared findings to the 20 previously collected right-handed female datasets which were reanalyzed for the current study: 10 females at high-dementia risk, and 10 females at low-dementia risk [30]. There were four additional female participants recruited for this study to increase the sample size in female groups. This study recruited 29 right-handed participants aged 49 to 69:13 males at high-dementia risk, 2 females at high-dementia risk, 12 males at low-dementia risk, and 2 females at low-dementia risk (see Table 1 for demographic information). Individuals were classified as high-dementia risk if they had a self-reported maternal or multiple immediate family history (parents, aunts, or uncles) of AD or probable AD (FH+), but no cognitive impairment. We excluded participants whose parents were deceased at a young age before dementia could be detected, or participants who were estranged from either of their biological parents and did not know their medical history. Cognitive function was measured with the Montreal Cognitive Assessment (MoCA), where no cognitive impairment is indicated by scoring at or above education-adjusted norms of 26 or higher. The choice of maternal history over paternal history is based on the higher risk for AD associated with a maternal history [62]. Low-dementia risk participants were age-balanced with high-dementia risk participants. Individuals were classified as low-dementia risk if they had no family history of AD or any other type of dementia (FH-), did not demonstrate memory impairments outside of their age range norm, and scored at or above age-average on the MoCA. Exclusion criteria included uncorrected visual impairments, upper-limb impairments, medical conditions that would hinder motor task performance (e.g., severe arthritis or dystonia), any neurological illnesses (e.g., Parkinson's disease, depression, schizophrenia, alcoholism, epilepsy), any history of head injury (e.g., mild, severe), stroke, and any medical diagnoses that might impact white matter integrity and brain connectivity (e.g., hypertension or diabetes). Signed informed consent was obtained from all participants prior to the start of the study. The study protocol was approved by the Human Participants Review Sub-Committee of York University's Ethics Review Board.

Questionnaire

All subjects completed an entrance questionnaire to determine eligibility for the study. The questionnaire collected information about age, ethnicity, years of education, occupation, vision, computer and touchscreen experience, and video game use. Additionally, it covered health-related questions about any diagnosed neurological disorders, family history of dementia or other neurological disorders, type I or II diabetes, smoking history, acquired brain injury (such as stroke or traumatic brain injury), and any medications that the individual was prescribed. An analysis of several US clinical laboratories showed significant diversity in how race, ethnicity, and ancestry are determined [63]. Specifically, no two laboratories used the same descriptors to designate a group on their questionnaires. Due to concerns about how the imprecise use of ethnicity data in research may potentially miscommunicate the relationship

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between an individual's ancestry, socioeconomic status, and health, we did not report or analyze this data. Our sample sizes per self-reported ethnicity were not large enough to perform statistical analyses we could draw conclusions from.

Saliva samples

All participants were asked to provide a saliva sample to genotype for *APOE* $\varepsilon 4$, an allele of the *APOE* gene that is associated with an increased risk for AD [4]. A total of 2 mL of saliva were collected from each participant using microtubes from Diamed Lab Supplies Inc. in conjunction with collection aids from Cedarlane Labs. Samples were sent to DNA Genotek Inc. (Ottawa, ON, Canada) for DNA extraction and *APOE* genotyping. DNA was isolated from samples according to the manufacturer's protocols. Genotyping for *APOE* involved single tube SNP genotyping, and tested for SNPs rs429358 and rs7412. The proteins that are produced by the *APOE* gene are either $\varepsilon 2$, $\varepsilon 3$, or $\varepsilon 4$ combinations (for instance, $\varepsilon 2/\varepsilon 3$).

Behavioral data

All subjects completed four visuomotor transformation tasks, similar to those previously used by our laboratory [26–32]. This group of tasks has been found to discriminate between women at high- and low-AD risk with a classification accuracy of 86.4% (sensitivity: 81.8%, specificity: 90.9%) [30]. The tasks involved making simple sliding finger movements between targets displayed on an Acer Iconia 6120 dual-touchscreen tablet. These tasks included one standard mapping condition (gaze and hand movement were coupled) and three different nonstandard mapping conditions (gaze and hand movement were decoupled). In all four conditions, participants were instructed to slide the index finger of their right hand along the touch screen (either the vertical or horizontal screen depending on the condition) in order to displace the cursor from a central target to one of four peripheral targets (up, down, left, right) as quickly and as accurately as possible. In the standard mapping task (S), the location of the visual target and the required hand movement were spatially congruent. The nonstandard mapping tasks involved the finger movements being made either on a different plane than the visual target (plane-change, PC), in the opposite direction of the visual target (feedback reversal, FR), or both (PC+FR) (see Fig. 1 for depictions of all four visuomotor transformation task conditions). Eye movements were the same across all conditions (i.e., always to the guiding visual target on the vertical screen).

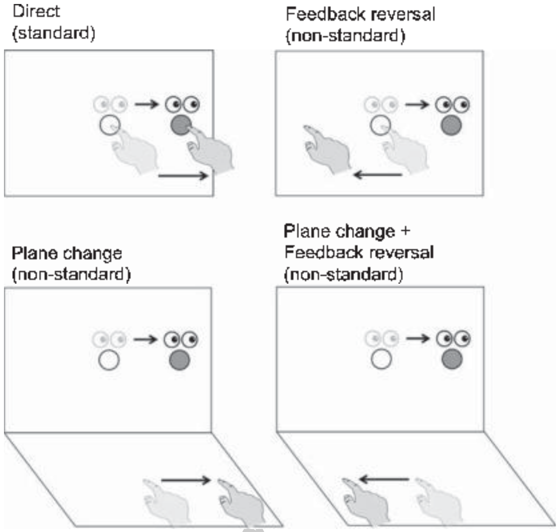

Fig. 1. Schematic drawing of the visuomotor transformation tasks. Lighter grey eye and hand symbols denote the starting position for each trial (central target). Darker grey eye and hand symbols denote the instructed eye and hand movements for each task. Grey-filled circles denote the peripheral (reach) target, presented randomly in one of four locations (left, up, right, or down relative to the central target). The direct interaction tasks require standard mapping, where participants slide their finger on a touch screen to move a cursor from a central target to one of four peripheral targets. The other three are nonstandard conditions that are cognitive-motor integration (CMI) tasks, where targets are either spatially dissociated from the plane of hand motion (plane-change), have a 180° feedback reversal (feedback reversal), or both (plane-change + feedback reversal).

The four conditions were presented in randomized blocks, each consisting of five pseudo-randomly presented trials to each of the four peripheral targets. Peripheral targets were located 75 mm from the central target, with target diameters set to 20 mm. The tasks were displayed on a 170 × 170 mm black square and a surrounding grey background. There was a total of 20 trials per condition, and thus each participant completed a total of 80 trials across the four conditions. To ensure task comprehension, each participant was given two practice trials per peripheral target prior to each of the four conditions. The sequence of events for each trial was as follows: 1) a yellow central (home) target was presented on the vertical tablet, 2) participants moved a white cursor to the central target, changing its color to green once they reached it, 3) after holding the central target for 4000 ms, one of four red peripheral targets appeared and the central target disappeared, serving as the 'Go' signal for

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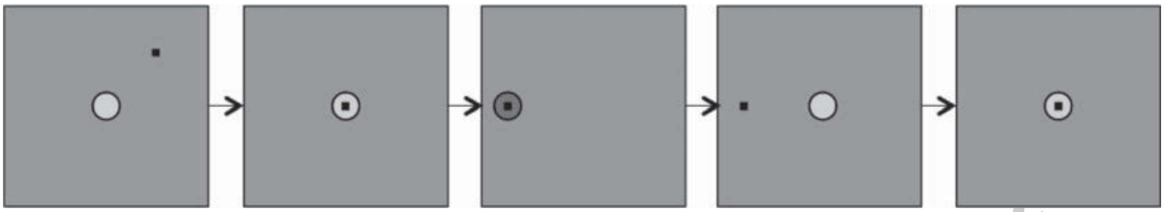

Fig. 2. Sequence of events during one trial of the visuomotor task. The central (home) target is where all trials begin. Once the participant moves the cursor (denoted by the black square) into the central target (denoted by the light grey circle), the target changes from yellow to green to signify a movement preparation period. After 4000 ms, a red peripheral target (denoted by the dark grey circle) appears in one of four directions (up, down, left, or right of the center) and serves as the ‘Go’ signal. Once the peripheral target is acquired and held for 500 ms it disappears, signaling the end of the trial. After an inter-trial interval of 2000 ms, the central yellow target reappears and the participant moves back to the central target to start the next trial.

initiation of a movement, 4) participants were told to look towards the visual target and slide their finger along the touchscreen to direct the cursor towards the target, 5) once the peripheral target was reached and the participant held it for 500 ms, it disappeared, signaling the end of the trial, 5) the next trial began with the presentation of the central target after an inter-trial interval of 2000 ms (see Fig. 2 for visual representations of a single trial completion).

In the standard condition (S), participants were asked to slide their finger directly to the target on the vertical screen (the cursor was directly under their finger). In the PC condition (nonstandard), participants moved their finger on the horizontal screen while looking at the vertical screen in order to direct the cursor toward the visual target displayed on the vertical screen. In the FR condition (nonstandard), the cursor moved in the opposite direction of the participant’s finger movements, requiring them to slide their finger on the vertical screen away from the visual target in order to move the cursor toward it. Finally, in the PC+FR condition (nonstandard), participants moved their finger on a different plane from the visual target (i.e., on the horizontal screen) and in the opposite direction of the visual target in order to direct the cursor toward the visual target.

Data processing

Kinematic measures, including timing, finger position (x, y coordinates; 50 Hz sampling rate), and error data were recorded for each trial and converted into a MATLAB readable format using a custom written (C++) application. Custom analysis software (Matlab, Mathworks Inc.) was used to process finger trajectories with a fourth-order (dual pass) low-pass Butterworth filter at 10 Hz. Finger trajectories were generated from these filtered paths for each successful trial, and were displayed on a Cartesian plot illustrating finger location data superimposed on central and peripheral target locations. Movement onsets and ballistic movement offsets (the initial movement prior to any corrective movements) were automatically scored by the software at 10% peak velocity. Total movement offsets were scored as the final 10% peak velocity point once the finger position was within the correct peripheral target. If the initial movement successfully resulted in the finger reaching the peripheral target, then ballistic and total movement offsets were the same. These profiles were then verified by visual inspection, and manually corrected when necessary.

Unsuccessful trials (error data) were detected by the data collection software by meeting the following criteria: finger left the home target too early (<4000 ms), reaction time (RT) was <150 ms or >8000 ms, or total movement time was >10 000 ms. Trials in which the first ballistic movement exited the boundaries of the central target in the wrong direction (>90° in either direction from a straight line to the target) were coded as direction reversals (DR), and were not included in metrics from correct trials but were analyzed as a separate variable. All scored data were then processed to compute 11 different timing, accuracy, and precision measures described below. Any trials exceeding 2 standard deviations from the participant’s mean for any of the outcome measures were eliminated as outliers from final outcome calculations.

Dependent measures

The kinematic measures of interest in this study were reaction time (RT), full movement time full (MTf), peak velocity (PV), full path length (PLf), ballistic path length (PLb), absolute error (AE), variable error (VE), and percentage of direction reversal

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errors (DR). RT (ms) was the time interval between the central target disappearance and movement onset. MTf (ms) was the time between movement onset and offset. AE (mm) was a measure of end-point accuracy, and is the average distance from the individual ballistic movement endpoints $(\Sigma\ x/n, \Sigma\ y/n)$ to the actual target location. VE (mm) was a measure of end-point precision, and is the distance between the individual ballistic movement endpoints $(\sigma 2)$ from their mean movement. PL (mm) was the total distance (calculated from the x and y trajectories) travelled between movement onset and offset. It was calculated as both PLf (full movement offset) as well as PLb (initial movement offset). Corrective path length (CPL) represents corrective movements, and was quantified by subtracting the PLb from the PLf. PV was the maximum velocity obtained during the ballistic movement, and was used to calculate the 10% threshold for determining movement onsets and offsets. Direction reversal errors were recorded as a percentage of total completed trials. All kinematic measures were averaged across the four peripheral targets for each condition.

Composite scores

With the large number of outcome metrics derived from data scoring, measures were combined into composite scores to decrease the number of comparisons in the data analysis. Kinematic measures to be combined into composite scores were standardized using z-scores. Z-scores were used to assess how the at-risk individuals compared to all of the healthy controls. For this analysis, we combined male and female control groups' means and SD (which were not statistically different, see Results section) in order to form the z-scores for comparison to the at-risk participants. The means and standard deviations of RT, MTf, PV, AE, VE, and PLf were first calculated for all control participants. A positive value indicates the score was above the control mean, a negative value indicates the score was below the control mean, and a value of 0 indicates the score is identical to the control mean. The z-score for PV was multiplied by –1 to match the other two timing measures RT and MT (where a lower value indicates better performance). Composite scores were created using simple averaging, which is the most commonly used approach when original variables are continuous [64]. The timing score $(\alpha = 0.879)$ is a composite score of RT, MTf, and PV. The endpoint error score $(\alpha = 0.772)$ is a composite score of absolute error and variable error.

Statistical analysis

All statistical analyses were carried out using SPSS statistical software (SPSS 24, IBM). A Shapiro-Wilk test was used to test for normality of each kinematic measure for both the male and female groups across the four conditions. All statistical testing was carried out using nonparametric analysis techniques as not all dependent measures were normally distributed. A Kruskal-Wallis test was used to test for differences between several independent groups. The groups analyzed for differences were the at-risk (FH+) males, control (FH–) males, at-risk (FH+) females, and control (FH-) females on timing scores, endpoint error scores, corrective path lengths, and percentage of direction reversals. Mann-Whitney tests were used for *post hoc* analysis to follow up on statistically significant findings, with comparison between 1) FH+ and FH– males, 2) FH+ and FH– females, 3) FH+ females and FH+ males, and 4) FH- females and FH- males. A Bonferroni correction was applied so all effects are reported at a 0.0125 level of significance. Effect sizes were calculated for *post hocs*. Note that non-parametric tests do not allow the use of covariates. As an exploratory component to this study, we performed multiple linear regression analyses to account to examine the effect of *APOE* status on performance.

All groups were age-balanced, with no statistically significant differences in age observed between the four experimental groups $(H = 0.408, p = 0.939)$. There were also no statistically significant differences observed between groups on MoCA scores $(H = 4.622, p = 0.202)$, years of education $(H = 0.350, p = 0.950)$, computer experience $(H = 3.268, p = 0.352)$, and touchscreen experience $(H = 1.995, p = 0.573)$.

RESULTS

Cognitive Motor Integration behavior: General findings

Based on the non-parametric and multiple linear regression analyses described below, we observed that FH+ participants demonstrated a deterioration in movement control as cognitive demands of the task increased compared to age-matched controls (FH-). The full movement trajectories plotted in Fig. 3 show a disruption in performance of hand movements, evident as increased deviations from a straight trajectory between the central target to the four

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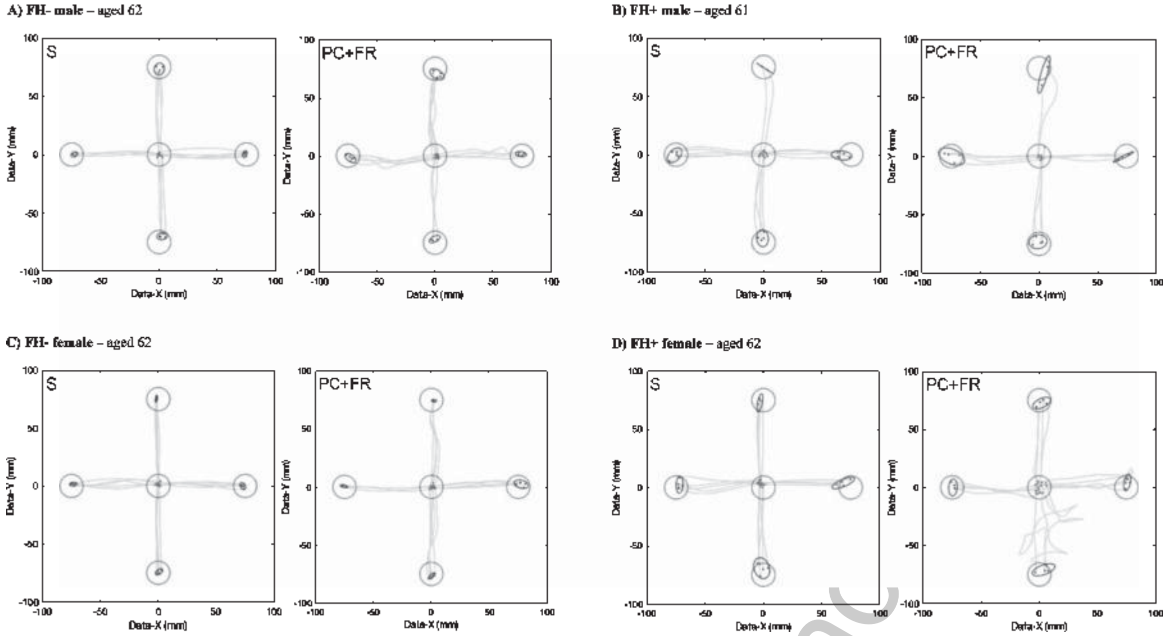

Fig. 3. Examples of typical full hand movement trajectories in the standard (S) and plane-change feedback reversal (PC+FR) conditions for a: A) FH- (no family history of dementia) male, B) FH+ (family history of dementia) male, C) FH- (no family history of dementia) female, and D) FH+ (family history of dementia) female. Hand trajectories begin at the central target and move toward one of four peripheral targets, where each light grey line represents a single movement trajectory. Ellipses at peripheral targets denote the 95% C.I. for the final end point of the finger movements. Only correct trials are shown. Any peripheral target with less than 5 trajectories indicates error trials, which are not shown.

Table 2
Descriptive statistics of participant groups

	FH- Male	FH+ Male	FH- Female	FH+ Female
Kinematic measure	*Mean (SEM)*	*Mean (SEM)*	*Mean (SEM)*	*Mean (SEM)*
Timing score				
S	0.446 (0.7402)	–0.093 (0.7477)	–0.446 (0.8385)	–2.359 (0.8411)
FR	–1.097 (0.5935)	0.967 (1.4111)	1.006 (0.7234)	–0.680 (0.7976)
PC	–0.369 (0.8505)	0.787 (0.9492)	0.338 (0.7124)	–1.522 (1.1091)
PC+FR	–0.999 (0.6597)	–0.619 (0.6467)	0.999 (0.6321)	2.089 (1.6806)
Endpoint error score				
S	0.091 (0.5314)	0.337 (0.6289)	–0.091 (0.4193)	0.874 (0.5759)
FR	0.787 (0.6069)	2.812 (1.1043)	–0.722 (0.3699)	1.431 (0.5977)
PC	0.467 (0.6304)	–0.031 (0.6628)	–0.429 (0.4558)	2.921 (0.9664)
PC+FR	0.423 (0.5085)	–0.016 (0.7263)	–0.423 (0.5513)	3.870 (1.2484)
Corrective path length				
S	0.041 (0.0298)	0.053 (0.0286)	0.000 (0.0000)	0.306 (0.3057)
FR	0.691 (0.1886)	1.980 (0.6852)	0.382 (0.2126)	0.865 (0.3441)
PC	0.755 (0.4381)	0.667 (0.4512)	0.448 (0.2203)	1.584 (0.6429)
PC+FR	4.310 (1.2667)	3.591 (1.6316)	2.317 (0.9085)	13.450 (3.2946)
% Direction reversals				
S	0.490 (0.4902)	0.481 (0.4808)	0.463 (0.4630)	0.000 (0.0000)
FR	3.624 (1.7891)	7.163 (3.2811)	1.046 (0.7067)	3.288 (1.6321)
PC	0.000 (0.0000)	0.000 (0.0000)	0.000 (0.0000)	0.439 (0.4386)
PC+FR	8.119 (3.5078)	7.392 (2.2257)	7.298 (3.4000)	7.498 (2.4127)

FH+, family history of dementia; FH-, no family history of dementia; S, standard; FR, feedback reversal; PC, plane-change; PC+FR, plane-change feedback reversal; SEM, standard error of the mean.

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peripheral targets in the most cognitively demanding CMI condition (PC+FR). For comparison, the standard condition illustrates minimal deviations from a straight trajectory across all four participant groups.

Descriptive statistics of participant groups are summarized in Table 2. Mean and SEM values of the kinematic measures of timing, endpoint error, corrective path length, and direction reversals are

Table 3
Statistical outcomes of the Kruskal-Wallis H and Mann-Whitney U tests

Kinematic measure	KW test		Mann-Whitney *post-hoc*		
	H-statistic (*p*)	FH+ versus FH– females (*p*)	FH+ versus FH– males (*p*)	FH+ females versus FH+ males (*p*)	FH– females versus FH– males (*p*)
Endpoint error score					
S	1.116 (0.773)	–	–	–	–
FR	10.330* (0.016)	27.000** (0.008)	34.000 (0.152)	47.000 (0.418)	34.000 (0.051)
PC	9.526* (0.023)	27.000** (0.008)	46.000 (0.557)	26.000 (0.025)	51.000 (0.379)
PC+FR	11.357** (0.010)	22.000** (0.003)	56.000 (0.247)	31.000** (0.005)	50.000 (0.219)
Corrective path length					
S	3.180 (0.365)	–	–	–	–
FR	6.669 (0.083)	–	–	–	–
PC	3.200 (0.362)	–	–	–	–
PC+FR	11.895** (0.008)	21.000** (0.002)	64.000 (0.468)	26.000** (0.004)	54.000 (0.316)

Significant values are: $^{*}p < 0.05$ for Kruskal-Wallis test; $^{**}p <$ Bonferroni criterion = 0.0125 for Mann-Whitney *post-hoc* FH+, family history of dementia; FH–, no family history of dementia; S, standard; FR, feedback reversal; PC, plane-change; PC+FR, plane-change feedback reversal; NS, no significance; KW test, Kruskal-Wallis test.

provided for the four participant groups based on sex and family history. These values were used for non-parametric and multiple regression analyses described below.

Family history and sex-related differences in motor behavior performance

Statistical outcomes of the non-parametric Kruskal-Wallis and *post hoc* tests by group are summarized in Table 3. There were no significant differences in timing scores between groups on any of the conditions ($H < 5.3$, $p > 0.05$ for all conditions) (Fig. 4a, Table 3). We did observe that endpoint error scores were significantly affected by group for all three nonstandard conditions. *Post hoc* analysis for endpoint error scores revealed that performance by FH+ males did not differ from FH- males, and FH- females did not differ from FH- males, on any of the conditions (Fig. 4b, Table 3). Notably however, FH+ females had greater endpoint errors (lower accuracy and precision) compared to FH- females on all three nonstandard conditions ($U_{FR} = 27.00$, $r_{FR} = –0.53$; $U_{PC} = 27.00$, $r_{PC} = –0.53$; $U_{PCFR} = 22.00$, $r_{PCFR} = –0.59$). FH+ females also had significantly worse accuracy and precision scores compared to FH+ males on the most demanding PCFR condition ($U_{PCFR} = 31.00$, $r_{PCFR} = –0.51$).

In addition, in terms of movement performance, corrective path lengths were also significantly affected by group in the PCFR condition. *Post hoc* analysis revealed that performance by FH+ males did not differ from FH- males, and FH- females did not differ from FH- males, on any of the conditions. However, as seen with the movement endpoint performance, FH+ females had greater corrective path lengths (greater hand path deviations from start to end targets) compared to FH- females on the PCFR condition ($U_{PCFR} = 21.00$, $r_{PCFR} = –0.60$) as well as compared to FH+ males on the PCFR condition ($U_{PCFR} = 26.00$, $r_{PCFR} = –0.57$ (Fig. 4c, Table 3). Males tended to have more direction reversals than females, and FH+ participants tended to have more direction reversals compared to FH- participants, but there were no statistically significant differences in this metric ($H < 2.8$, $p > 0.05$ for all conditions) (Fig. 4d, Table 3).

Comparing APOE status, family history, and sex as predictors of skilled performance impairment

Genetic testing revealed that a greater proportion of FH+ females had the *APOE* ε4 allele compared to FH+ males (see Table 1). Specifically, the breakdown of the *APOE* allele genotype results were: ε2 allele (2 FH+ males) and ε4 allele (2 FH+ males, 3 FH- males, 9 FH+ females, 1 FH- female). The rest of the par-

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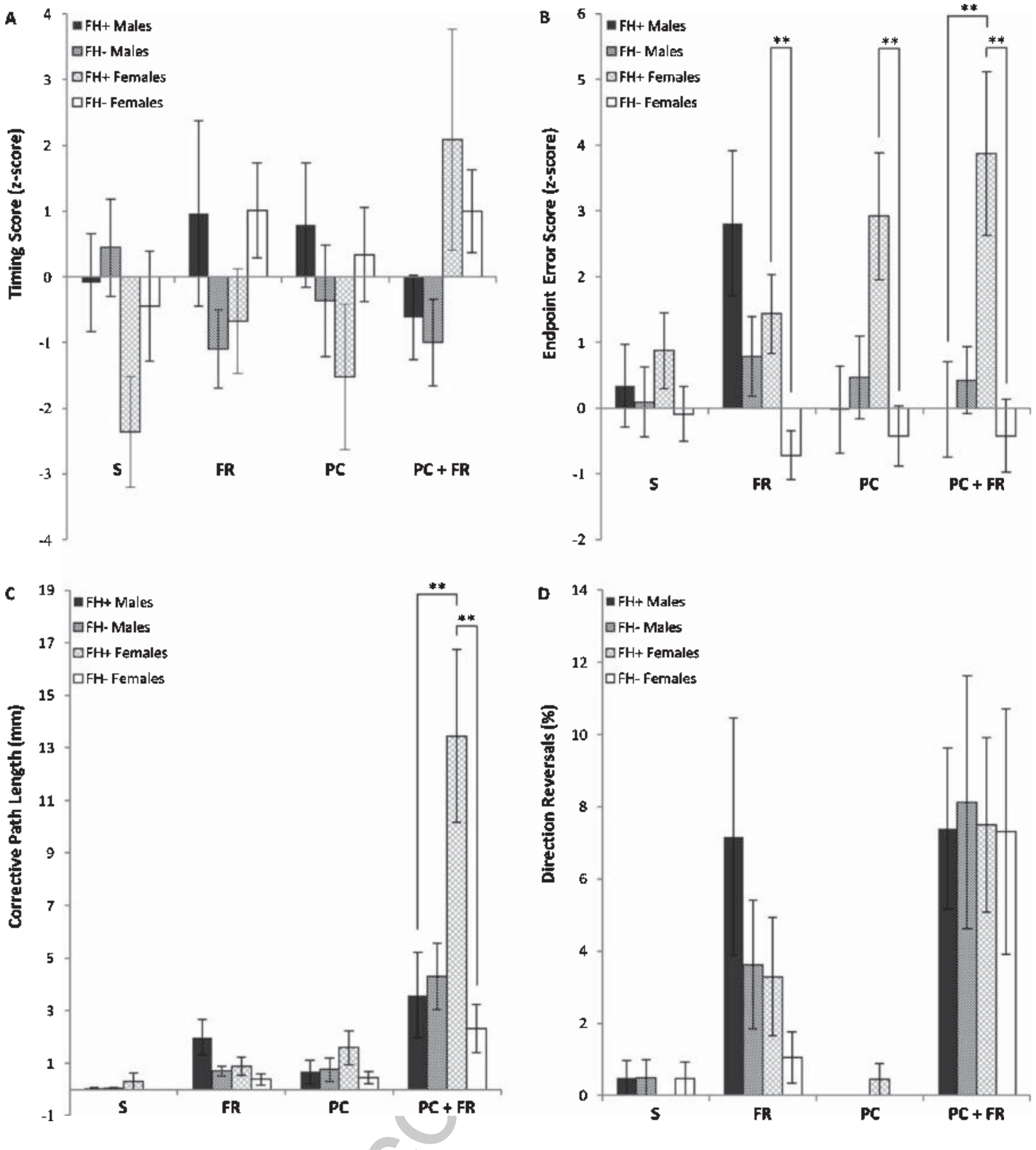

Fig. 4. (A–D) Results by group (FH+ males: black bars, FH- males: dark grey bars, FH+ females: medium grey bars, FH- females: light grey bars) across all four conditions (S: standard, FR: feedback reversal, PC: plane-change, PC+FR: plane-change + feedback reversal) of Kruskal-Wallis tests on task-dependent measures. Means ± SEM, $^{*}p < 0.05$, $^{**}p <$ Bonferroni criterion = 0.0125. FH+, family history of dementia; FH-, no family history of dementia.

ticipants had an ε3/ε3 genotype. Multiple regression analysis was used to test whether *APOE* ε4 status, family history, or sex significantly predicted participants' behavioral performance in the three conditions requiring cognitive-motor integration. Our regressor model included all three predictors (i.e., family history, sex, and *APOE* status) across our four dependent measures (timing score, endpoint error score, corrective path length, and direction reversals) and for all three conditions requiring CMI (see Table 4). The results reported for each predictor are the values after having controlled for the other two predictors. Family history, sex, and *APOE* status were not significant predictors of timing scores or direction reversals.

Table 4
Multiple linear regression analysis examining associations of family history (reference = no family history of dementia), sex (reference = females), and *APOE* status (reference = no *APOE* ε4 allele) on timing score, endpoint error score, corrective path length, and percentage of direction reversals

Kinematic	Predictor	Estimate (Unstandardized β)	*p*	SE	R^2 (*p*)
Timing score					
S	Family history	–0.516	0.503	0.76	**0.261****
	Sex	1.207	0.127	0.78	**(0.004)**
	APOE status	**–2.271****	**0.010**	**0.84**	
FR	Family history	0.001	0.999	1.03	0.001
	Sex	–0.098	0.924	1.02	(0.999)
	APOE status	–0.155	0.892	1.13	
PC	Family history	0.133	0.889	0.95	0.339
	Sex	0.889	0.352	0.94	(0.339)
	APOE status	–1.274	0.230	1.04	
PC+FR	Family history	0.237	0.822	1.05	(0.115)
	Sex	–1.969	0.071	1.06	0.127
	APOE status	1.164	0.318	1.15	
Endpoint error score					
S	Family history	0.441	0.427	0.55	0.140
	Sex	0.073	0.897	0.56	(0.088)
	APOE status	1.329	0.033	0.60	
FR	**Family history**	**1.752***	**0.023**	**0.74**	**0.281****
	Sex	**1.770***	**0.021**	**0.73**	**(0.005)**
	APOE status	1.183	0.153	0.81	
PC	Family history	0.674	0.371	0.74	0.321**
	Sex	–0.440	0.555	0.74	(0.002)
	APOE status	2.706**	0.002	0.82	
PC+FR	Family history	1.131	0.176	0.82	0.349***
	Sex	–0.887	0.294	0.83	(<0.001)
	APOE status	**3.251*****	**<0.001**	**0.90**	
Corrective path length					
S	Family history	0.115	0.482	0.16	0.053
	Sex	–0.065	0.695	0.16	(0.499)
	APOE status	0.176	0.330	0.18	
FR	Family history	0.534	0.193	0.40	0.265
	Sex	1.023*	0.015	0.40	(0.07)
	APOE status	1.037*	0.024	0.44	
PC	Family history	0.047	0.921	0.47	**0.223***
	Sex	0.109	0.818	0.47	**(0.019)**
	APOE status	**1.585****	**0.004**	**0.52**	
PC+FR	Family history	3.272	0.116	2.04	**0.359*****
	Sex	–2.225	0.288	2.07	(**<0.001**)
	APOE status	**8.018*****	**<0.001**	**2.24**	
% Direction reversals					
S	Family history	–0.168	0.707	0.44	0.04
	Sex	0.135	0.767	0.45	(0.622)
	APOE status	–0.490	0.322	0.49	
FR	Family history	1.920	0.354	2.05	0.169
	Sex	3.922	0.060	2.03	(0.063)
	APOE status	4.030	0.080	2.24	
PC	Family history	0.360	0.169	0.26	0.093
	Sex	–0.336	0.194	0.25	(0.280)
	APOE status	–0.413	0.150	0.28	
PC+FR	Family history	–0.634	0.839	3.09	0.008
	Sex	–0.064	0.984	3.14	(0.954)
	APOE status	–1.558	0.649	3.40	

$^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$. Statistically significant predictors are presented in bold.
FH+, family history of dementia; FH-, no family history of dementia; S, standard; FR, feedback reversal; PC, plane-change; PC+FR, plane-change feedback reversal; SE, standard error.

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APOE status was a significant predictor of corrective path length (CPL). Specifically, after controlling for sex and family history, having the ε4 allele was associated with a mean increase of 1.6 mm ($p = 0.004$) in the PC condition and 8.0 mm ($p < 0.001$) in the PCFR condition. We observed a similar effect for endpoint error scores, whereby having the ε4 allele was associated with an increase of 2.7 SD ($p = 0.002$) in the PC condition and 3.3 SD ($p < 0.001$) in the PCFR condition after controlling for sex and family history. For CPL, the regression models accounted for 22.3% ($p = 0.019$) and 35.9% ($p < 0.001$) of the overall variance in CPL for the PC and PCFR conditions, respectively. For endpoint error scores, the regression models explained 32.1% ($p = 0.002$) and 34.9% ($p < 0.001$) of the overall variance in the PC and PCFR conditions, respectively.

Sex and family history were significant predictors of endpoint error scores in the FR condition. Being a male increased the endpoint error score by 1.8 SD ($p = 0.021$) after controlling for family history and *APOE* status, and having a family history increased the endpoint error score by 1.8 SD ($p = 0.023$) after controlling for sex and *APOE* status. These two factors together accounted for 28.1% ($p = 0.005$) of the overall variance in endpoint error scores.

DISCUSSION

The aims of this study were to characterize any sex-related differences in performance on cognitive-motor integration tasks in individuals with and without a family history of dementia. As predicted, performance during standard visuomotor mapping (i.e., gaze and hand movements made to spatially congruent locations) showed no significant differences between any of the groups for any of the kinematic measures. The standard condition reflects the ability to interact directly with objects (or, standard mapping), which is not typically impaired in early AD relative to healthy aging [27]. This result supports previous findings from our laboratory, where behavioral performance did not differ between the sexes of cognitively healthy young adults on CMI tasks [65]. We did, however, observe measurable impairments in visuomotor control in the more cognitively-demanding nonstandard conditions that require large-scale CMI brain networks involving frontal, parietal, and subcortical areas. Analyses of the female groups supported previous findings, where FH+ females had less accurate movements compared to FH- females in the three nonstandard conditions [30]. Notably these observed impairments in FH+ females occur in the absence of any cognitive deficits. Notably, and in contrast to our findings with female participants, we found no CMI impairments for increasingly dissociated visually-guided reaching tasks in FH+ males when compared to FH- males. Further, we found that when performing the most challenging plane dissociated + feedback reversal task, FH+ females showed significant impairments in endpoint error scores and corrective path lengths compared to FH+ males.

The primary purpose of this study was to test for potential sex-related differences in CMI performance in individuals with a family history of dementia. However, access to saliva samples from participants allowed us to also perform *APOE* genotyping. Genetic analyses revealed that more FH+ females had the *APOE* ε4 allele than FH+ males in our sample. Multiple linear regression analyses were used to account for this difference. Results from the regression demonstrated that in the FR condition, both being male and having a dementia family history were significant predictors of worse performance. However, *APOE* status was a significant predictor of endpoint error scores and CPLs in the two plane change conditions after adjusting for sex and family history. Therefore, some of the sex-related differences seen in task performance at the behavioral level may be driven by having the *APOE* ε4 genotype.

Potential mechanisms underlying family history and sex-related differences in the feedback reversal condition

The feedback reversal task involves strategic control, where there is integration of sensory information with explicit, cognitively-related information in order to guide the hand movement [14]. Strategic control networks appear to involve prefrontal communication with the IPL and inferotemporal cortex [66]. When performing a nonstandard task, there needs to be inhibition of the brain's natural tendency to spatially couple the gaze and hand position [19]. Inhibition is a component of executive function, and is also associated with activation of widespread areas of the prefrontal cortex [67, 68]. Deficits in feedback reversal task performance may therefore reflect executive dysfunction.

Our laboratory has previously shown that the brain regions used by males and females for tasks requiring

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CMI are different even when behavioral task performance is equivalent between groups [55]. Among these difference, greater amounts of bilateral STG activity were observed in male subjects in rotated conditions in which the directions of eye and arm movements were made in opposite directions, a task that was equivalent to the FR condition in the current study. Although many brain regions are affected throughout AD progression, numerous studies have worked at identifying specific brain regions that are particularly vulnerable to the effects of AD. An extensive study of changes in gene expression associated with AD was conducted across 15 brain regions, and the authors found that the STG presented significant gene abnormalities [69]. Therefore, the fact that males have a greater reliance on the STG than females do in visual feedback reversal tasks may provide an explanation for our observation that FH+ males were affected to a greater extent than FH+ females in the FR condition.

Potential mechanisms underlying APOE status differences in the plane change conditions

Normal aging appears to show a frontal dominance in its effects in a number of ways. These include a reduction in overall grey matter volume and cortical grey matter thickness in frontal regions, a loss of white matter tracts in the frontal lobe (but a preservation in the posterior regions), and decreases in glucose metabolism in the frontal lobe [70–75]. Conversely, AD pathology appears to be concentrated in posterior cortical regions. The brains of AD patients have shown maximal cortical degeneration spanning the posterior temporal areas, as well as the parietal and occipital lobes [76]. Both the superior and inferior regions of the posterior parietal cortex (PPC) have also shown hypoperfusion in patients with AD [77]. The PPC is an area hypothesized to be critical for updating hand trajectory during reaching movements [78–80]. Further, advances in brain imaging have allowed for a better understanding of AD pathophysiology. Specifically, imaging studies have demonstrated reductions in brain glucose uptake, changes in brain lipid metabolism, loss of blood-brain barrier integrity, and decreased cerebral blood flow [81–83]. Many similar alterations have been found in individuals with the *APOE* $\varepsilon4$ allele, in some cases early in life and in the absence of cognitive impairment [81, 84]. These findings demonstrate a potential inability of individuals with the $\varepsilon4$ allele to efficiently regulate cerebral metabolism. Furthermore, it is not known exactly where in the brain abnormal Aβ accumulation begins in individuals with AD. In a recent imaging study investigating non-demented individuals, researchers used PET scans to measure fibrillar Aβ pathology, and CSF samples to measure the levels of $A\beta_{42}$, total tau, and phosphorylated tau [85]. Using these approaches, they were able to identify the earliest preclinical AD stage in participants, and showed that Aβ accumulation preferentially began in the precuneus, posterior cingulate cortex, and medial orbitofrontal cortex. This early Aβ accumulation predominantly overlapped with the default mode network, as well as with the frontoparietal network (i.e., regions known to be involved in CMI task performance). While a correlation between decreased functional connectivity in these networks and Aβ pathology has been shown previously, this was the first study to demonstrate such a relationship in the earliest stages of AD for individuals who are still cognitively healthy [86, 87].

The potential Aβ accumulation in regions of the frontoparietal network crucial for skilled movement control could explain why performance deficits in CMI tasks that required a plane change were observed between participants genetically at risk for dementia versus those that do not have the $\varepsilon4$ allele. Many of the regions showing atrophy and early Aβ accumulation in AD patients also overlap with regions of the brain found to be involved specifically in performing a plane change task. Patterns of activity in the anterior prefrontal cortex, precuneus, and large regions of the occipital lobe differed during plane change tasks relative to standard mapping tasks [22]. Based on these findings and in conjunction with the current study's results, we propose that the PPC and occipital lobe (both involved in plane change tasks) may be impaired to a greater degree in individuals at increased dementia risk due to having the $\varepsilon4$ allele. Endpoint error scores and CPLs both reflect the ability to successfully perform online corrective movements. A previous study investigated patients with probable AD compared to healthy controls on a plane-change movement task with little to no feedback of their limb [24]. They found that without visual feedback, the AD patients had more inaccurate movements compared to controls; because the initial directions of the movements were more accurate than the endpoint locations, the authors suggested that patients could successfully plan but not maintain an accurate motor plan in the early stages of the disease. The cerebellum, in addition to the PPC, has

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been shown to be important in the visual guidance of movement, as well as for feedback loops and online control of movement [88–90]. Perhaps having the *APOE* ε4 allele affects brain regions responsible for online correction of rule-based movements early on in the disease; specifically, the PPC, cerebellum, and occipital lobe.

Study limitations

This study was cross-sectional in nature. Thus, while we observed that specific factors were predictive of impaired skilled performance in this cross-sectional group, we were unable to test if poor performance was predictive of future conversion from dementia risk to dementia. Future work will follow participants longitudinally in order to study the predictive utility of this integrated cognitive-motor approach. Further, our preliminary findings on the relationship between having the ε4 allele and deficits in CMI performance indicate that it will be important for future research to increase the sample size of both males and females with and without the *APOE* ε4 allele so that this relationship can be better understood.

Conclusions and clinical implications

While research in the last decade has led to developments in the early detection of dementia risk, these techniques involve invasive and costly procedures such as PET scans and blood tests. The findings presented here suggest that measurements of CMI performance, taken together with other forms of assessment, could provide a non-invasive and cost-effective alternate method of detecting the early stages of decline in brain regions known to be affected by dementia. In addition, our data suggest that there are potentially clinically relevant sex-related differences in the underlying brain networks that control thinking and moving at the same time. Therefore, the sex of an individual should be considered when measuring potential CMI deficits associated with dementia risk. Preliminary evidence presented here also suggests that the CMI tasks used are sensitive to performance decrements in asymptomatic individuals who are genetically at-risk for AD, irrespective of their family history. Thus, further examination of the relationships between sex, genetic variant, and CMI performance are called for.

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