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Research Report

Visuomotor integration is impaired in early stage Alzheimer's disease

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ABSTRACT

When the sensory information guiding a reach movement is dissociated from the required motor output, humans must integrate rule-based information in order to reach accurately. Here, we examine the accuracy of movements requiring a visuomotor transformation in neurologically healthy elderly subjects and patients diagnosed with probable Alzheimer's disease. Participants made sliding finger movements over a clear touch-sensitive screen positioned in three spatial planes to displace a cursor from a central target to one of four peripheral targets viewed on a monitor. These spatial plane conditions were repeated under conditions where the direction of cursor motion was rotated 180° relative to the direction of hand motion. Significant main effects were observed between patient and control groups on reaction time and movement time measures. Also, significant increases in task completion errors were observed in the patient population. Further, performance was affected more by the visual feedback changes relative to the plane location changes. Notably, there were substantial performance deficits observed in the patient population, even those with minimal cognitive deficits. We suggest that the integration of eye and hand information may be impaired in these patients.

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1. Introduction

The majority of Alzheimer's disease (AD) research has focused on the memory-related deficits associated with this illness. Although memory deficits are the salient feature of AD, several other debilitating symptoms can affect the everyday functioning of individuals afflicted with AD before profound memory disturbances surface. One of these symptoms is an alteration in motor ability. Often motor deficits displayed by AD patients are dismissed as dysfunctions of advancing age (Morris et al., 1987) and are typically not the primary concern. However, visuomotor ability is crucial to everyday functioning and ranges from simpler skills, such as climbing stairs, to

more complex skills, such as operating a motor vehicle. Often, complex skills require more arbitrary associations, or “non-standard” mappings, where the goal of the movement is not in direct spatial alignment with the visual stimulus guiding it (Gorbet et al., 2004; Wise et al., 1996). In everyday life, we perform these types of movements (such as using a computer mouse) effortlessly. In these situations, the mapping between stimulus and response must be learned and calibrated. Such complex visuomotor tasks require the integration of cognitive information into a movement in the form of rules for guiding action.

An issue in visuomotor control is the integration of rule-based cognitive information into a movement plan. It is well

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known that cognitive functions are related to activity in the frontal areas (Mesulam, 1990; Moscovitch and Winocur, 1995; Petrides, 1995). In addition, dorsal premotor neurons have been shown to have both attentional, gaze-related activity and intentional, limb movement activity in response to targets that have both standard and nonstandard mappings (Boussaoud, 2001; Boussaoud and Wise, 1993; Jouffrais and Boussaoud, 1999; Wise et al., 1992; Wise et al., 1996). Importantly, the connectivity between frontal and parietal areas is crucial for the planning and execution of visually guided movement. Much recent work has gone into examining the role that parietofrontal networks play in eye–limb coordination in healthy adults, not only on a spatial scale (e.g., the contribution of specific cortical areas) but also on a temporal scale (e.g., the interaction between different areas over time) (Boussaoud et al., 1998; Caminiti et al., 1998; Caminiti et al., 1999; Classen et al., 1998; Johnson et al., 1996). One of the primary issues in visuomotor research is determining where the association between vision and movement converge. A recent fMRI study (Medendorp et al., 2003) found significant overlap of active regions in the posterior parietal cortex (PPC) (Andersen and Buneo, 2002) during eye and pointing movements. Together with numerous neurophysiological studies (Andersen et al., 1997; Duhamel et al., 1992; Kalaska, 1996; Snyder et al., 2000), these data suggest that information about eye and hand position can be pooled in the PPC. Researchers have also demonstrated that damage/disruptions to the human PPC results in deficits in programming eye and arm movements (Duhamel et al., 1992; Grea et al., 2002; Oyachi and Ohtsuka, 1995; Rossetti et al., 2005).

Previous studies have shown that AD patients have difficulty performing eye–hand coordination tasks under nonstandard mapping conditions. Discontinuous movement paths and prolonged movement times were observed in AD patients who were instructed to move a cursor to targets on a monitor without vision of their limb. Movement accuracy was affected both by the removal of continuous cursor position feedback and by the severity of the patients' disease and cognitive decline (Ghilardi et al., 1999; Ghilardi et al., 2000). These results suggest that the functionally salient motor deficit in AD may involve visuomotor integration for coordinated action. Other studies have shown that the slowing of reaction times are more pronounced in AD patients than in individuals with Parkinson's disease (Chong et al., 1999; Elble and Leffler, 2000). Experiments examining simple motor tasks involving the upper extremities in mild AD and PD individuals noted that AD individuals displayed greater motor deficits on a number of tasks compared to PD individuals (Elble and Leffler, 2000). Surprisingly, AD patients' skills were strongly compromised in relation to their mild diagnosis. Also interesting is that a patient population widely regarded as having only cognitive deficits performed worse on a motor task than a population regarded as having primarily motor deficits, which suggests that there are under-characterized motor deficits associated with AD.

The types of deficits early stage AD patients experience initially are likely related to those brain structures affected first by the disease. In the early stages of AD, the accumulation of amyloid deposits are normally restricted to the pyramidal layers of the subiculum and CA1, with minor or no accumula-

tions observed in the hippocampal formation (Braak and Braak, 1991). Behaviorally, many individuals at this point may not experience any significant memory-related difficulties. However, a number of other brain regions can undergo larger amounts of Alzheimer's-related anatomical changes (Price et al., 1998), including large portions of the parietal and frontal lobes (Braak and Braak, 1991). Given the early structural degradation in the parietal area, it is reasonable to posit that PPC function may be compromised in these patients, even at an early stage. Knowing the central role of these networks in visuomotor skill, one might expect that AD patients whose memory-based ratings indicate only a mild cognitive impairment would nonetheless demonstrate compromised abilities for movements that require integrating cognitive information, such as complex eye–hand coordination tasks.

In the current study, we characterize the performance of AD patients assessed as being at different stages of impairment (using a memory-based rating) on an increasingly complex eye–hand coordination task. Our task requires participants to integrate progressively greater amounts of cognitive information (i.e., arbitrary "nonstandard" visuomotor mapping rules) into the motor plan. We hypothesize that even minimally impaired patients will show deficits relative to age-matched controls. Further, patients within a given range of cognitive impairment should show a progressive decline in performance as the visuomotor task becomes increasingly complex. The characterization of performance in a fairly simple, easily administered visuomotor task can enhance the current repertoire of functional outcome measures for neurological patient populations, and could provide a useful parameter for studying disease progression and the success of discrete pharmacological treatments (Ott et al., 1995).

2. Results

2.1. General observations

With the introduction of nonstandard mapping conditions (i.e., either an altered spatial plane of limb motion relative to the plane of the viewing monitor, a visual feedback rotation or both), there was a systematic decline in movement performance in both groups. Further, substantial declines in performance were noted within the patient group but also within our control group. These performance deficits took the form of reduced rates of task completion (i.e., failed individuals trials; see Experimental procedures) and increases in both reaction time (RT) and movement time (MT). Some individuals showed greater performance declines than others, particularly when the task became increasingly nonstandard. These individual variations in performance were evident not only between our control and patient groups, but also within our patient group.

2.2. Performance timing

A univariate analysis between participant groups was performed based on all trials, for both reaction time and movement time. Results yielded a significant main effect of group on RT (Group: $F_{1, 144} = 62.41, P < 0.01$). We also observed

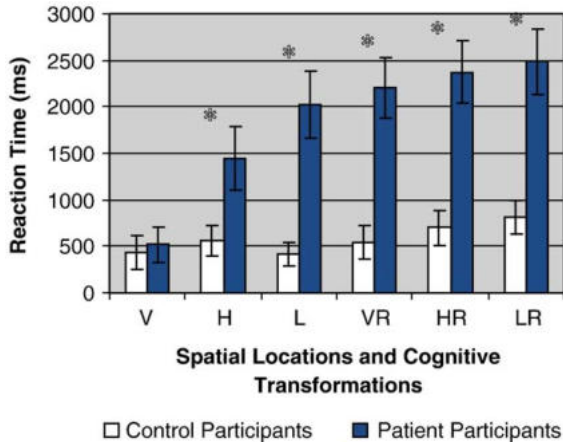


Fig. 1 – Reaction time (RT) for all six conditions (three spatial locations and two visual feedback conditions). R = cursor rotated 180° from hand movements and vertical (V), horizontal (H) and lateral (L) represent spatial locations. Error bars represent standard error of the mean, asterisks represent statistically significant differences.

a main effect of condition on RT (SP: $F_{5, 144} = 4.74, P < 0.01$). Fig. 1 presents the mean RT data across all trials for each group. Note that across conditions the RT for the patient group was at times triple that of the control group. Post hoc analysis revealed a significant difference between groups ($P < 0.05$) for all experimental conditions (see Fig. 1), except for the vertical condition where the touch screen was placed directly over the computer monitor displaying the visual targets (“V”, standard mapping; see Experimental procedures). Thus, when a change in either spatial plane or in visual feedback (nonstandard mapping procedures) was introduced, the patients’ ability to move the cursor to the target location was compromised.

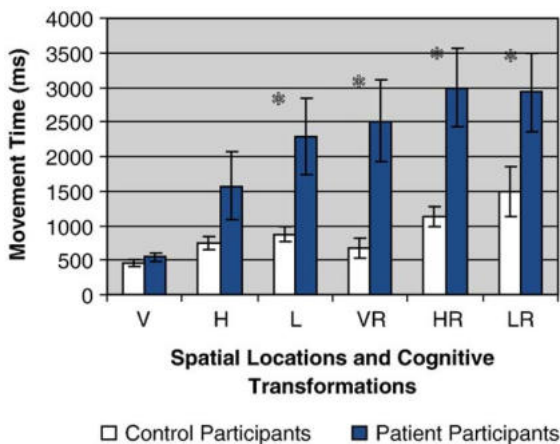


Fig. 2 – Movement time (MT) for all six conditions (three spatial locations and two visual feedback conditions). Labels are as described for Fig. 1. Error bars represent standard error of the mean, asterisks represent statistically significant differences.

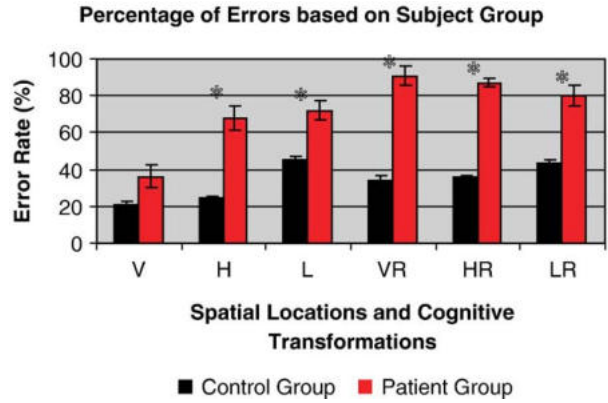


Fig. 3 – Percentage of errors for all six task conditions (three spatial locations and two visual feedback conditions). Labels are as described for Fig. 1. Error bars represent standard error of the mean, asterisks represent statistically significant differences.

We also observed significant main effects of group on movement time ($F_{1, 144} = 27.61, P < 0.01$). A significant main effect was also observed for condition on MT ($F_{5, 144} = 4.61, P < 0.01$; Fig. 2). Post hoc results for MT displayed significant differences between groups ($P < 0.05$) for the lateral (“L”, touch screen horizontal and laterally displaced relative to the midline), lateral rotated (“LR”, lateral screen placement plus visual feedback rotated), vertical rotated (“VR”, screen over monitor plus feedback rotated) and horizontal rotated (“HR”, screen placed horizontally at midline plus visual feedback rotated) conditions. Thus, patients had great difficulty completing movements to target locations, especially when there was a manipulation in visual feedback. Figs. 1 and 2 show a similar relationship, demonstrating the patients’ inability to handle changes in either the visual feedback or spatial plane transformations. Note that for both RT and MT,

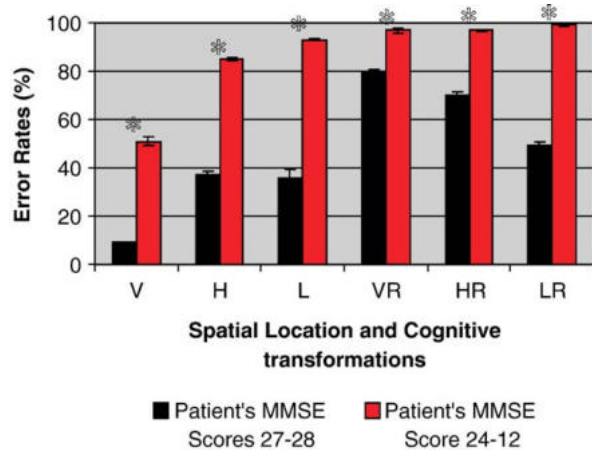


Fig. 4 – Percentage of errors for all six task conditions (three spatial locations and two visual feedback conditions). Labels are as described for Fig. 1. Error bars represent standard error of the mean, asterisks represent statistically significant differences.

Table 1 – Error difference results

Participants	Error range, highest to lowest		Average error totals
Control (12 subjects), no impairment	64	10	44
Patients (MMSE 27/28), questionable impairment (5 subjects)	75	35	56.20
Patients (MMSE 21–24), mild impairment (4 subjects)	106	96	99.20
Patients (MMSE 12–20), moderate impairment (5 subjects)	118	103	109.40

as task complexity increased the disparity between groups also increased.

In addition to the overall group analysis, we also examined a subset of subjects in each group that were similar in age, in an effort to demonstrate that AD was the main factor effecting motor performance results rather than age. Six control subjects (mean age 74 ± 8) were compared to five patients (mean age 75 ± 4) on both MT and RT measures. A main effect of group was observed for both RT ($F_{1, 58} = 50.72, P < 0.01$) and MT ($F_{1, 58} = 32.41, P < 0.01$). In addition, post hoc analysis for RT displayed significant differences ($P \leq 0.01$) between groups for all experimental conditions, with the exception of the vertical condition. Post hoc analysis for MT displayed significant difference between groups ($P \leq 0.05$) for conditions H, L, LR, VR and HR. Thus, with the exception of a movement time result in the horizontal condition (observed in the full group only), all other results for this subsample (subjects in their seventies) mirror that of the overall group results.

2.3. Task completion errors

A substantial increase in the number of errors can be observed within the patient population when completing tasks that require a transformation of either spatial plane or visual feedback. In fact, tasks that include both nonstandard components present great difficulty for these individuals, to the extent where on many occasions error rates of 100% were observed for some patients (Fig. 3). Error results (e.g., failure to reach target, failure to leave home target, etc.; see Experimental procedures) are displayed as error percentages in Fig. 3. A

one-way ANOVA revealed a significant main effect of group on the total number of task errors ($F_{1, 11} = 24.27, P < 0.01$). Results of independent *t* tests displayed significant differences ($P < 0.05$) between groups for all conditions, with the exception of the vertical condition.

We believe that error totals play a key role in distinguishing not only participant groups but also subgroups within the patient population (Fig. 4). In support of this, noticeable differences are readily observed in average error totals when patients are divided based on their Mini Mental State Exam (MMSE) scores. A significant discrepancy was observed between patients who have a questionable impairment (MMSE 25–30) and those who have a mild to moderate impairment (MMSE mild 20–25, moderate 10–20) (Folstein et al., 1975) (one-way ANOVA; $F_{1, 11} = 11.08, P < 0.01$). In addition, independent *t* tests revealed significant error differences ($P < 0.05$) between these patient subgroups for all conditions. Especially noteworthy is the relative difficulty individuals with a mild/moderate cognitive impairment have in even completing the basic standard task. For example, note that there was nearly a 10-fold increase in errors displayed by this group compared to their questionably impaired counterparts in the standard mapping condition (Fig. 4). Mild to moderately impaired individuals began with a 50% success rate, which deteriorated progressively when a spatial plane transformation was introduced. These individuals deteriorated quickly in their ability to successfully complete trials to the extent that, when completing conditions H and L (spatial change only conditions), their error rate increased to a further 85% and 93%, respectively (Fig. 4). When these individuals were faced with both visual feedback and spatial change transformations, their error rates were substantial, 97%, 97% and 99% respectively.

In general, there was a continuous increase in task performance errors in going from the control group to the moderately impaired group. The difference in the average total number of errors for all task conditions between our control participants and individuals with questionable impairments (e.g., MMSE 25–30) was 12.2. When a further decrease in cognitive ability is probable (based on MMSE score of 20–25, “mildly impaired”), the average number of task performance errors jumped by 43 relative to the questionably impaired group. Finally, we found evidence for a further decrease in visuomotor ability between our mild and moderate (MMSE 10–20) group, with the latter group displaying an additional 10.2 errors than the mildly impaired group (see Table 1).

Table 2 – Error totals by error type

Error type	1	2	3	4	5	6
Controls						
Mean \pm SD	7.2 \pm 3.8	7.2 \pm 3.8	1.3 \pm 3.0	2.4 \pm 3.8	2.9 \pm 2.8	5.9 \pm 3.7
Percentage	6	10	2	3	4	9
Patients (MMSE 27/28)						
Mean \pm SD	6.2 \pm 15.6	4.7 \pm 15.6	2.5 \pm 2.2	4.9 \pm 8.8	2.9 \pm 4.0	3.6 \pm 10
Percentage	13	13	2	7	3	8
Patient (MMSE 24–12)						
Mean \pm SD	46.7 \pm 18.7	19.3 \pm 7.6	2.7 \pm 1.9	16.9 \pm 8.1	10.2 \pm 5.3	10 \pm 6.0
Percentage	38	16	2	14	9	7

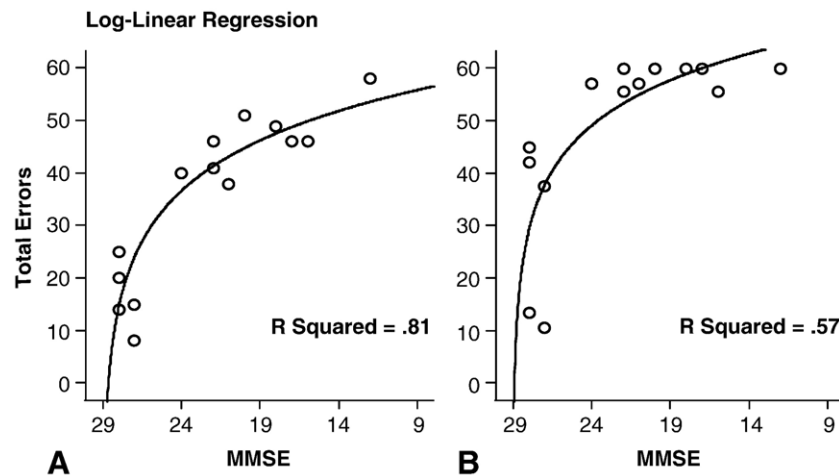


Fig. 5 – Log-linear regression model representing the patients’ level of cognitive impairment (MMSE score) in relation to their errors (errors averaged across spatial locations for each patient, $N = 14$). Panel A represents direct visual feedback and panel B represents rotated visual feedback.

In addition, we also examined the type of errors (see Experimental procedures) both groups were making. We found that the relative proportion of error types made by both groups were similar (Table 2). However, we did observe that the patient group had a greater number of failed trials due to not moving from the peripheral target of the previous trial back to the center “home” target for the next trial within 5 s (type 1 error). Also, the patient group had a greater number of failed trials caused by taking more than 2 s to leave the starting target to move out to the peripheral target upon the “go” signal (type 4 error). As with the overall error results, the total number of error trials within each error type increased steadily as one goes from the control group to the less cognitively impaired patient group to the more cognitively impaired patient group (Table 2).

2.4. Relationship between cognitive rating and task performance

Based on error counts, we hypothesized that there would be a significant relationship between one’s level of cognitive ability (as rated by the MMSE score) and the number of errors they committed. To determine the predictive strength of this relationship while acknowledging the ceiling effect observed in the error count, we applied a curvilinear measurement (log-linear regression) to the data (Tabachnick and Fidell, 1996). Using a log-linear regression fit, we determined that there was an observable relationship between number of errors committed and level of cognitive functioning (i.e., MMSE rating) for both direct (V, H, L) and rotated (VR, HR, LR) conditions.

The log-linear regression displayed a significant relationship between cognitive rating and error total for both direct movement conditions ($r^2 = 0.81$, $P < 0.01$; Fig. 5A) and for rotated visual feedback conditions ($r^2 = 0.57$, $P < 0.01$; Fig. 5B). Thus, we can conclude that for our patient sample, as cognitive functioning declines we can observe significant increase in the number of errors made during the performance of the visuomotor task.

2.5. Hand path formation

Mean hand paths to each target were calculated for each participant group for each task condition. The patient group displayed a larger deviation in their hand paths from an ideal straight line relative to the control group (Fig. 6). Further, patients demonstrated greater hand path variability (note the larger standard error lines in Fig. 6). This variability became more pronounced as the relationship between visual cue and hand movement became more dissociated. In particular, hand paths became more variable as soon as individuals were required to make a nonstandard mapping procedure (i.e., condition V vs. conditions H–LR). Conditions H and LR are overlaid with raw trajectories from an individual subject.

Interestingly, linearity ratio (deviation of the hand path from a straight line) results did not reveal any significant differences between groups. Thus, we observed that if subjects were able to make successful movements to target locations, they then performed these movements using fairly straight hand paths.

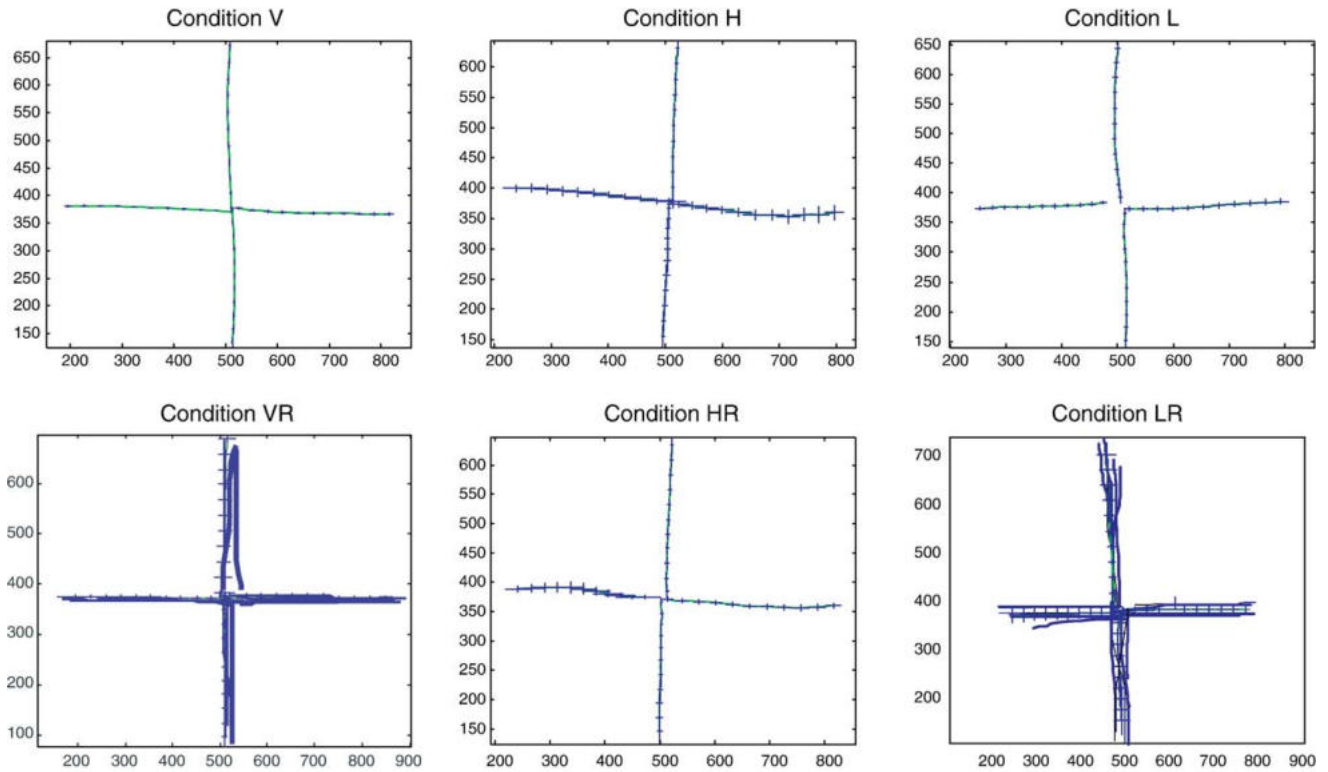
3. Discussion

This study demonstrates a significant decrease in task completion and performance across all participants with the introduction of nonstandard mapping tasks. Notably, a steady decline in visuomotor performance can be seen in relation to declining cognitive status. The resulting slowness and decreased accuracy in reaching to target locations under nonstandard mapping conditions may be linked to Alzheimer’s disease-related structural deficits affecting the PPC region during reaching or pointing.

3.1. Errors and visuomotor ability

Error rates provide insight into the ability of participants to process target locations and respond successfully by generating an effective and timely motor response. Because the

Control Participants Mean Trajectories (mm)



Patient Participants Mean Trajectories (mm)

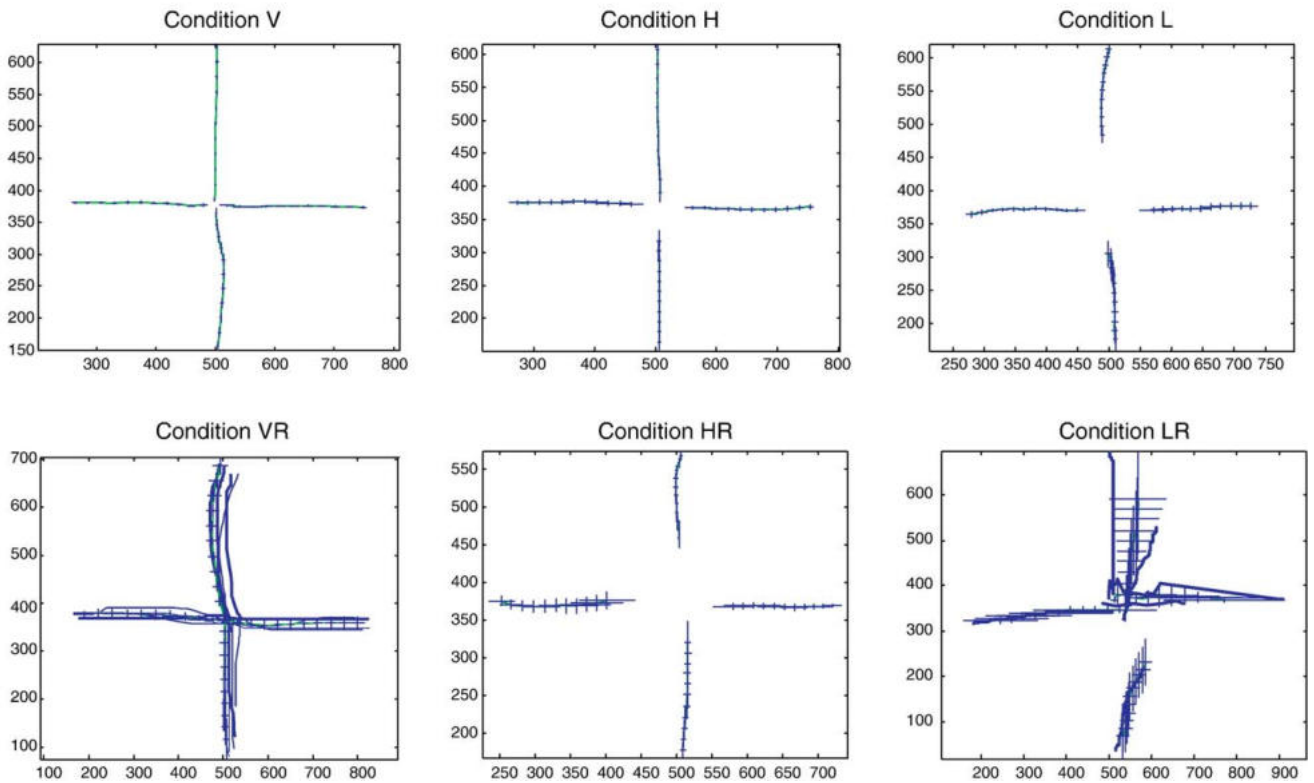


Fig. 6 – Mean trajectory results for the patient and control participants for all six conditions (for condition abbreviations, see Experimental procedures). Raw trajectories (thick lines) are overlain for conditions VR and HR.

spatial location of the visual cues was invariant between task conditions, and the movements themselves were roughly equivalent, we deduce that participants with large error rates were struggling with the relationship between the two. Four important observations can be made with regards to our error rate findings.

First, an overall increase in errors was observed in both patient and similarly aged control participants as the task required the integration of more information to plan and execute an appropriate motor response to a given visual target (Fig. 3). These results are not only seen for the older participants examined in the current study, but have also been seen in younger populations (Tippett and Sergio, 2004). The decline in motor performance under all of the nonstandard mapping conditions may reflect additional processing by the brain to accommodate the arbitrary relationship between the visual target and the required limb movement. The greater difficulty observed for the “rotated” visual feedback conditions suggests that the neural substrate underlying the integration of cognitive information needed for these conditions may be, in part, distinct from that substrate processing the postural coordination required for the plane change conditions.

Second, errors in our visuomotor integration task are readily observable even between our control sample and the putative high functioning patients with a diagnosis of “questionable impairment”, which suggests that AD is substantially affecting visuomotor performance even in its very early stages. It may be that regions of the brain that are affected early on in AD may not strongly affect what are traditionally considered cognitive abilities but do appear to affect the cortical networks required to process movements that require the integration of rule-based information. This type of skill testing could thus be useful for alerting clinicians about a potential AD diagnosis in its very early stages.

Third, the disruption in visuomotor ability is severely progressive in nature. Although the task complexity increased at the same rate for both participant groups, error rates increased exponentially in the AD patients. Also, moving from AD patients that showed a diagnosis of a questionable impairment to AD patients with a diagnosis of mild/moderate impairment revealed substantial differences – indeed, a ceiling effect – in completing tasks that required both types (i.e., spatial plane and visual feedback) of visuomotor transformation. Although Alzheimer’s disease progression may result in a steady decline on traditional measures of cognitive performance, it may be that the brain networks involved in the performance of movements that require the processing of arbitrary visuomotor relationships are particularly affected by the advancement of AD. Therefore, these types of nonstandard eye–hand coordination skills may only be sensitive measures of functional decline in early stage Alzheimer disease.

Fourth, an analysis of the types of errors that patients were making revealed an inability to “task switch”. That is, they had the most difficulty when they had to conclude one trial and begin the next, or conclude one phase of the task (home target hold) and respond to a “go” signal. Such a difficulty may reflect reduced interactions between anatomically and functionally distinct frontal and parietal lobe systems engaged in the performance of different components of the task (see Section 3.6).

3.2. Hand trajectories

Both groups had greater difficulty producing movement trajectories when the element of manipulated visual feedback was introduced, regardless of the spatial plane that the movements were made in. Specifically, direction reversals (seen as thickened lines in the trajectory plots) were more prevalent on rotated visual feedback conditions. This is not entirely surprising, given the well-known effect of altered visual feedback on movement accuracy in the elderly (Seidler-Dobrin and Stelmach, 1998). However, to have a direction reversal recorded in the current study meant that the participants were aware of their error, made a corrective movement and still arrived at the target successfully within the allotted time. When a participant was unaware that they were moving in the wrong direction, or was unable to correct the movement using on-line feedback, the trial would be counted as an error. Therefore, the trajectories shown do not fully reflect the difficulties that those patient groups with large error totals had in making the movements.

A prominent characteristic displayed by the patient group is the gap between the center of the start target and the start of the trajectory (Fig. 6b, open area in the middle of each plot). A change in the spatial plane of motion relative to the visual guidance increased the size of the gap, and an additional change in the direction of visual feedback increased the size of the gap further. Gaps in the trajectories can occur for a number of reasons. If the individual hesitated, lifted their finger, or was very slow in starting the movement, the scored movement onset would be delayed. Making one or a combination of these errors indicates that the patient population needed more time to acquire the target and plan a reach. The need for additional processing time is supported by the significantly longer reaction times seen in the patient group. Such effects on the movement trajectory across different levels of task complexity and across subject groups further demonstrate the reduced ability to plan and execute visually guided movements in AD patients.

3.3. Movement time and movement execution

The inability of patients to complete movements where the direction of hand motion is dissociated from the direction of both the cued visual target and the online visual feedback may be due to their reduced ability to apply sustained effort to the task. With the introduction of a new, more complex visuomotor program, consolidation can be remarkably reduced and the generation of an effective response compromised (Chong et al., 1999). Indeed, in the present study the majority of successful trials were in the nonrotated conditions, suggesting the possibility that patients were tapping into a stored movement program (Shadmehr, 2004).

3.4. Reaction time and movement planning

As with movement time, the introduction of nonstandard mapping conditions resulted in an increase in reaction time across all participants, and patients took significantly longer than controls to initiate movements in the nonstandard

mapping conditions. This suggests that when task complexity was increased, participants were undoubtedly required to enlist more cognitive resources to plan and initiate the appropriate hand movement (Hamzei et al., 2002).

Recently, it was reported that individuals in the early stages of AD were successful in planning movements but did not retain the ability to control the ongoing movement effectively (Ghilardi et al., 1999). In that study, AD patients had limited or no visual feedback of the limb, and as a result they were not as accurate in completing the movement as they were in starting the movement. The authors concluded that the patients were able to plan but were unable to maintain their current motor objective, relying heavily on memory components and visual sensory monitoring to maintain limb control (Ghilardi et al., 1999).

Monitoring limb control is an essential part of reaching to targets effectively. In the present study, we allowed continuous visual feedback throughout the testing procedures in order to reduce the confound of memory involvement. This gave the participants an opportunity to reach target locations as they were presented. We observed nonsignificant differences in linearity ratio, suggesting intact hand path formations in both patients and controls. Therefore, we suggest that impaired performance (i.e., errors, slowing of movement) was directly related to planning and completing motor responses exclusively and did not rely on visual motor memory components related to body position. Our research indicates that AD participants are not only limited in their ability to plan a motor movement, but also have trouble sustaining an effective motor plan even after it has been initiated. Therefore, whether visual feedback is present or absent, these results suggest that even mildly affected AD patients can display a severe disability in both planning and executing visuomotor transformations.

3.5. The role of different motor areas and parietofrontal networks in the visuomotor dysfunction of AD patients

The present behavioral study can only provide indirect evidence concerning the neural substrate affected by AD underlying impaired visually guided movement. Nonetheless, the performance deficits observed in the present study may be related to early neuropathology of motor associate areas and the connections between them. AD is noted to be a global deficit affecting a multitude of cortical regions in the cerebral cortex. Although structural deficits may not initially affect distinct cerebral regions, what may occur is an ineffective integration of information being transmitted from various regions (such as the motor cortices, the frontal lobe and occipital areas) to a site in the cerebral cortex noted to be involved in visuomotor transformations: the posterior parietal cortex (Andersen, 1987; Caminiti et al., 1998; Kalaska and Crammond, 1995). The PPC is reported to be an essential area involved with high-level cognitive functions involving action, which includes intention for action and the ability to generate early movement programs (Andersen and Buneo, 2002). Further, the PPC is known to play a role in the spatial updating of targets, which was required throughout the experimental procedure (Snyder et al., 1998). It is thought that the majority of visuomotor transformations are ob-

served exclusively within the PPC (Andersen and Buneo, 2002), thus requiring this area to be fully intact and operating for accurate and effective reaching/pointing movements.

One of the primary regional connections from the PPC is the frontal cortex, which is implicated in reaching, grasping and oculomotor control (Goodale, 1993). These precentral areas are also involved in the integration of rule-based information into the motor act (Wise et al., 1996). In the present study, patients were slower to respond, had difficulty with both switching to a new phase of the task and with incorporating rule-based information in order to produce the required movement accurately. These performance deficits may arise from a breakdown in the parietofrontal networks required to transform visual information into an appropriate pattern of muscle activity for limb motion. This suggests that, in addition to frontal lobe areas known to be affected in AD patients, the PPC and the connection between them is also compromised. The primary deficits observed in this study could be a result of information that is initially encoded in the PPC being transferred ineffectively (Wise et al., 1996) to frontal regions, a network which is essential for understanding spatial relationships between the eye and hand.

3.6. Conclusion

The impaired AD patients' reaction and movement times that were unmasked by our visuomotor assessment tool revealed an inability to effectively plan and carry out a motor act in response to visual information that required rule-based information processing. Notably, our results indicate that reduced performance can be related to the level of one's cognitive impairment. Characterizing task completion rates allowed us to distinguish differences not only between control and the patient groups but also differences within the patient group itself.

AD patients displayed a compromised ability to effectively complete certain visuomotor tasks. When decisions requiring the immediate integration of vision and rule-based action were needed, AD patients were diminished in their capacity to respond. Limited visuomotor ability of these individuals may have profound functional implications in situations where successful visuomotor transformations are needed (i.e., climbing a set of stairs, crossing the street or operating a motor vehicle). The current study emphasizes the utility of a progressively challenging visuomotor assessment procedure in providing a sensitive measure of early stage functional disability in these patients.

4. Experimental procedures

4.1. Participants

The performance of twelve older participants (6 male, 6 female, mean age 71.2 ± 7.3) was compared to that of fourteen patients with a diagnosis of probable AD (2 males, 12 females, mean age 79.7 ± 4.6). Control participants were recruited from both the university population and the general community.

Patient participants were recruited from a local hospital. Participants were excluded if they reported any visual difficulty completing the task. As well, subjects were instructed to disclose/report any medical condition that would hinder their task performance in any way (i.e., vision difficulties, arthritis). Neither participant group had extensive computer experience, although we believe that computer experience should not affect our simple reaching task. To ensure that experience with computers did not have an effect, we conducted a *t* test on movement time results between subjects that reported computer experience and those who reported limited computer experience within our control sample. Results were not significant, supporting the contention that computer experience does not effect performance on this task.

4.2. Procedure

Participants slid their finger (note, no stylus or tool was used to manipulate cursor, reducing the chance of performance confounds) over a clear touch-sensitive screen in order to displace a cursor between visual targets under one of three different levels of spatial correspondence, and one of two different levels of visual feedback correspondence, for a total of six conditions. A laptop computer was used in conjunction with a clear touch-sensitive panel (Keytec Magic Screen: Model KTMT-1315) that was placed over the screen of the computer (vertical), in front of the keyboard (horizontal) or horizontally to the right of the computer (lateral). Participants sat at a fixed distance from the screen to ensure a consistent visual angle and were instructed to place their hand in a location that would ensure visibility of all target locations. There were also two levels of visual feedback or cognitive compatibility: cursor reflected finger position veridically or cursor was rotated 180° from finger position (rotated; Fig. 7). Thus, there were two types of mapping categories: spatial correspondence and

feedback correspondence. Note that only the vertical unrotated condition in which the subject was sliding their finger directly over the computer monitor, with the cursor moving in the same direction, could be considered “standard mapping”. This condition was used as the control measure (or baseline) for this experimental design, in that it displayed initially how groups functioned on a standard task before the experimental procedure was manipulated. The five other conditions required the use of nonstandard mapping rules for successful completion, with the “lateral rotated” condition having the greatest amount of dissociation between visual stimulus and motor action.

To begin a trial, participants fixated on a central start location on the monitor and brought their finger to the start location in space, touching the central target (all targets were 4 cm diameter) as indicated by the cursor on the monitor. The participants kept their finger within the central target for a variable time period (2000 ± 500 ms). At the end of the central hold period, the central target disappeared and one of four peripheral targets, arrayed around the central target at locations of 0°, 90°, 180° or 270° (0° being directly to the right, increasing angles are counter clockwise) were presented. The centers of the central and peripheral targets were 9.5 cm apart. The task required the participants to fixate the peripheral target and slide their finger to the appropriate location in space, within specified time period. Participants held the cursor at the peripheral target for another 1000 ms before returning to center target. Real-time continuous visual feedback from the cursor was available throughout the experiment.

Five trials to each target were presented in a randomized block design for each of the six conditions, for a total of 120 trials per participant. The order of conditions was varied randomly across participants. Participants were given explicit instructions on how to complete the trials in each condition and were asked to move as quickly and accurately as possible.

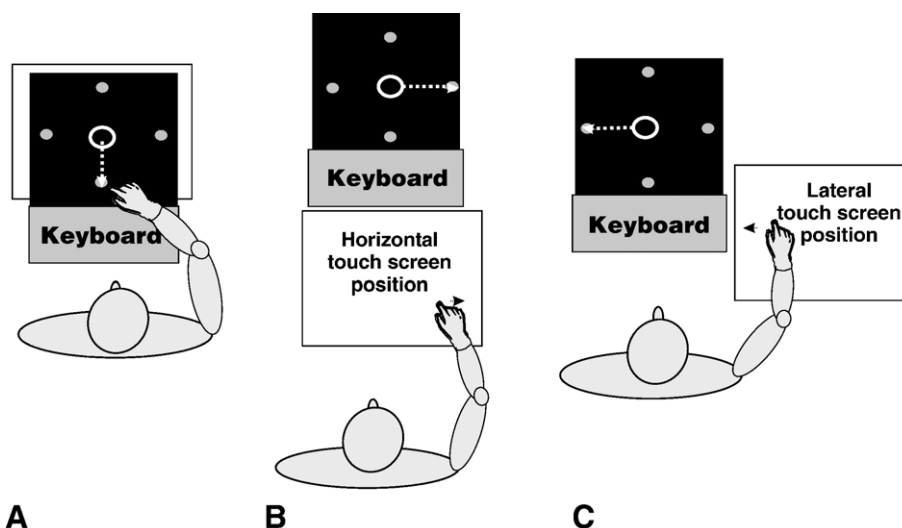


Fig. 7 – Task apparatus and experimental conditions. The black square represents a vertically positioned computer monitor. (A) Subjects make movements directly to targets on the touch screen placed directly over the monitor (vertical condition). (B) Subjects make movements using the touch screen placed horizontally in front of the computer (horizontal condition). (C) Subjects make movements horizontally and to the right of the computer (lateral condition). “Rotated conditions” follow the same three conditions with the visual feedback of the cursor rotated 180° from hand position.

Participants were also instructed to focus on the screen and cursor movement and not to look at their hand. Participants received verbal feedback throughout the testing procedure to eliminate any confusion about their objective. In addition, a familiarization phase was also conducted at the onset of each new visual feedback condition to ensure that participants understood what was required of them to generate a successful response. Once participants demonstrated knowledge of how to achieve a successful response, the familiarization phase was terminated and experimental testing would begin. Familiarization phases never exceeded 8 discrete trials. Participants signed a consent form outlining the procedures, approved by the University Ethics Committee, prior to participating in the experiment.

4.3. Data analysis

4.3.1. Error counts

Experimental errors were monitored and recorded. An inability to complete a trial correctly could occur in several ways. The different types of errors were as follows: failure to touch center (home) target within 5000 ms of its appearance, failure to hold center target for at least 1000 ms, leaving center target too early (less than 150 ms after central target extinction), leaving center target too late (more than 2000 ms after central target extinction), exceeding time duration to target (4000 ms) and failure to remain at the peripheral target (1000 ms).

4.3.2. Movement trajectories

Individual movement paths were first low-pass butterworth filtered at 10 Hz (filtfilt function; Matlab, Mathworks Inc.). Movement onset and endpoints were automatically scored as the point of 10% peak velocity for each trial individually, using a custom-written computer algorithm. Each point was verified visually to ensure that the endpoint chosen was the first point at which the movement slowed. It is important to note that, for the purposes of this study, the point in the trajectory that was scored as movement end was often not the final position of the individual's finger. Individuals completing this task had full visual feedback throughout the trials, and some were able to correct their movements to ultimately place their finger in the middle of the peripheral target. Movement trajectories were then cropped at the start and endpoints and divided into 10 equidistant segments in order to calculate the mean and standard deviation at each point. The standard deviations were calculated relative to spatial variability in the direction orthogonal to the direction of movement (e.g., along the y axis for 0° and 180° targets, along the x axis for 90° and 270° targets).

4.3.3. Linearity ratio

Linearity ratio is determined by the maximum deviation of the path from a straight line drawn between endpoints divided by the length of that straight line (Atkeson and Hollerbach, 1985). A value of 0.5 corresponds to a semicircle, whereas a value of 0 corresponds to a perfectly straight line between the start and endpoints.

4.3.4. Timing

The reaction time epoch started when the peripheral target was presented and ended at the scored movement onset.

Participants who were unable to move in the appropriate direction or moved off home target location prematurely (less than 150 ms) did not receive a reaction time score, but rather the trial was scored as an error trial (see above). The movement time epoch began from movement onset and ended at the first point when the subject slowed to below 10% peak velocity, as mentioned above. If a subject passed through the outer target or could not reach the outer target in the appropriate time, then these individuals received a maximum movement time score of 4000 ms, in addition to the trial being counted as an error.

4.4. Interpretation of MMSE scores

The Mini Mental State Exam (MMSE) is a standardized cognitive test for assessing one's cognitive state (Folstein et al., 1975). Cognitive performance can vary depending on age and education level, which can influence one's assessment rating (Crum et al., 1993). The standard cognitive ratings are normally reported as the following: 25–30 is identified as questionably significant; 20–25 as mild impairment; 10–20 as moderate impairment; and 10 or less is considered severe impairment (Folstein et al., 1975). The role of the MMSE is to help determine the level of dementia an individual is experiencing. The MMSE is not intended to be used as a singular diagnostic tool, rather its role is to complement the comprehensive mental status exam.

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