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Impaired movement control in Alzheimer's disease

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Abstract

Movement accuracy in normal subjects depends on feedforward commands based on representation in memory of spatial and biomechanical features. Here we ask whether memory deficits in Alzheimer's disease (AD) interfere with movement planning and execution. Nine AD patients and nine age-matched controls moved a cursor to targets without seeing their limb. Starting and target positions were always visible on a screen, while, during movement, cursor position was either visible or blanked. Patients' paths showed discontinuous segments and prolonged movement time; movement inaccuracy, which increased without visual feedback, correlated significantly with scores of disease severity, working memory and attention.

Keywords: Alzheimer's disease; Bradykinesia; Reaching movements; Humans; Kinematics

Patients with Alzheimer's disease (AD) show significant memory deficits and cognitive involvement. Subtle signs of motor impairment [14] as well as increased reaction time may also be present early in the disease [17]. These patients walk more slowly with significant problems in maintaining stability [2]; they are at higher risk for falls and immobility [6] and their finger tapping and point-to-point arm movements are slower than in normally aging subjects [18]. All studies showed a weak relationship between motor performance and dementia severity.

In normal subjects, accuracy of movements to visual targets depends primarily on feedforward mechanisms that govern the phase covering most of the movement distance; visual feedback (FB) can increase accuracy only modestly once the hand is near the target [13,20]. Feedforward commands are based on representation in memory of different parameters [10,19], including spatial relations of target and hand which are updated by sensory information [10]. For instance, movements performed without visual FB show systematic directional biases depending on the initial hand position with respect to body mid-line [10]. These errors represent a range effect reflecting prior experience: the error-free area includes habitual location of the hand in daily tasks and practice in spaces away from it produces new biases in previously error-free regions [10]. Vision of the hand prior to movement is required to update internal representation of the starting point in the workspace and to plan movement direction. Otherwise, representation in memory of the hand's usual location in the workspace is used, leading to directional bias.

With this study we sought to determine: (1) whether and how trajectory formation is altered in AD patients compared to aged-matched controls; (2) whether memory deficit interferes with movement planning or execution.

Subjects were nine unmedicated patients with 'probable' AD according to NINCDS-ADRDA criteria [16] and nine age-matched neurologically intact controls (three men and six women). All subjects were right-handed with no signs or symptoms of parkinsonism. Neuropsychological evaluation included the tests reported in Table 1 [1,3,5,7]. Subjects performed reaching movements as fully described elsewhere [10–12]. Briefly, they sat facing a computer screen

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Table 1

Patients with AD: scores from neuropsychological tests

Patient	Age (years)	MMSE	Token	Benton	Raven	Cancellation
M.P.	66	14	30.5	12	11	29
D.C.	74	20	29	11	7	29
PL	65	9	20	5	9	12
R.V.	72	9	23	7	15	16
C.G.	61	16	25.5	8	6	24
D.G.	71	21	32	24	13	44
N.G.	70	24	33	19	23	34
G.G.	74	23	32	23	31	39
B.P.	69	21	24	18	15	40

and moved a hand-held cursor with their right arm on a digitizing tablet located at waist level. The screen displayed cursor position on the tablet along with two circles, indicating starting and target location. Subjects were instructed to position the screen cursor in the start circle and then, to move it to the target 'with a single, uncorrected movement, as accurate and as fast as possible'. Twelve targets in equally spaced directions at 7.5 cm from a common starting position (Fig. 1) were presented pseudo-randomly in blocks of 48 trials. Movements initiated from three points: the center position, 30–40 cm in front of the subject's sternum; the right, displaced 25–30 cm to the right on a medio-lateral axis; and the left, 15–20 cm to the left of the center. To study the effect of visual FB screen cursor was blanked during movement in 'no FB' sessions and remained visible during movement in 'cursor FB' sessions [11]. In both conditions, the target was displayed on screen for the entire movement duration, hand path displayed on the screen after each move and vision of the limb blocked by an opaque screen. All subjects underwent two to three training sessions.

Details of data analysis are in previous papers [10–12]. Each path consisted of x and y coordinates sampled at 100 Hz and smoothed using a cubic spline; tangential velocity and acceleration were computed and onset, peak velocity, peak acceleration and end-point were marked. Distance between end point and target was defined as 'linear error' and reflected end point accuracy. Movement extent was the straight line from the starting to the end point of the movement; movement direction was the orientation of this line. Directional error was the difference between target and movement direction at the peak velocity and at the end point: clockwise errors were negative and counter-clockwise errors positive. For the trajectories of each starting point we computed magnitude and direction of the average vector [10–12]: in absence of preferred movement extent and direction, vector's magnitude is zero.

Following training, end points of movements with cursor FB from the centered position were consistently accurate in both groups: accuracy was not statistically different in patients and controls (Fig. 1A–D). However, while controls' hand paths were straight with bell-shape velocity as previously shown [11], patients' trajectories had multiple curves with discontinuous segments and fragmented velocity profiles and movement times significantly higher than controls' (Fig. 1B,D). Similar results were obtained when targets were presented directly on the tablet. Without cursor FB, accuracy of normal subjects did not change significantly and their straight trajectories showed bell-shape velocity profiles (Fig. 1C). Mean movement time slightly decreased compared to 'cursor FB' condition. In all patients, linear error and movement time were significantly higher than in controls; velocity profiles showed fragmented movements (Fig. 1C,D).

As previously reported [10], without visual FB, movements of all controls showed systematic biases depending on the starting point. Mean directional error was positive for

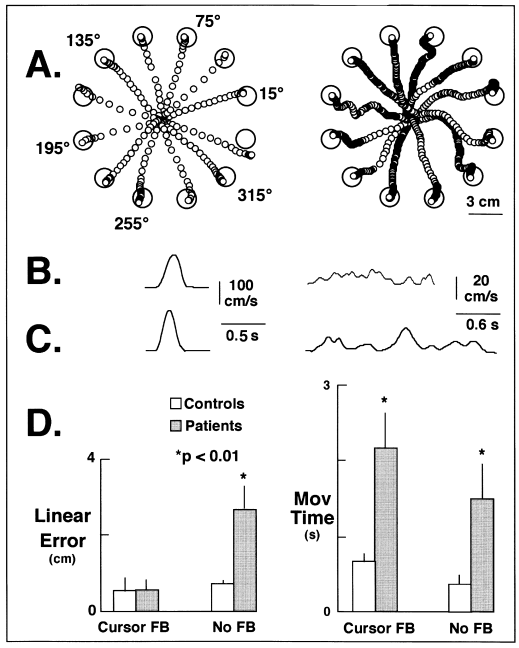

Fig. 1. (A) Hand paths of normal control R.M. [left] and patient R.V. [right] with visual FB to 12 targets. (B,C) Velocity profiles for both subjects for movements to the 15° target with (B) and without visual FB (C). Both time and amplitude scales are different for the two subjects. (D) Mean linear error and mean movement time +SE for patients' and controls' movements with and without visual FB.

left starting position, negative for right and close to zero for centered position. The combined data of the nine controls showed that 80% of the variance (r^2) in mean directional error was accounted for by the distance of the starting point from the body midline (Fig. 2C) [10]. This trend was already present at the time of peak acceleration ($r^2 = 0.85$) and peak velocity ($r^2 = 0.85$). Mean extent error was close to zero for all starting points. In all controls the magnitude of the average vectors was always less than 1 cm but was higher for the displaced starting points (Fig. 2B).

As shown in Fig. 2A for one of the more impaired patients (R.V.), hand paths in AD were hypermetric and curved towards specific directions accordingly to the starting position. For the centered starting point, movements clustered directly in front of the patients' mid-line where they were generally hypermetric and curved towards the axis centered on the 90° direction. For left starting positions, end point clustered in the right upper quadrant; for the right in the upper left quadrant (Fig. 2A). This is reflected by the direction of average movement vectors: for the centered starting position the mean vector direction is about 90°, for the left is about 30° and for the right is about 135° (Fig. 2A). When the screen was moved to the right, the direction of the vectors for the centered position changed accordingly towards the new screen position. Magnitude of average vectors were always more than 1 cm and were significantly different from controls (Fig. 2B). Directional bias was not found in two patients with the lowest Mini-Mental State Examination (MMSE) score. The combined data of the nine patients showed that only 20% of the variance in mean directional error at the end point was accounted for by the distance of the initial hand position from body mid-line. However, mean directional error at the time of the first peak velocity showed a significant dependence ($r^2 = 0.40$) from the initial position of the hand (Fig. 2C). These data suggest that patients plan and initiate movements similarly to the controls, but are not able to sustain the motor plan. Since directional bias was not detectable in the two most impaired patients it is possible that, as the disease progresses, the learned representation of the spatial relations of target and hand can be degraded also.

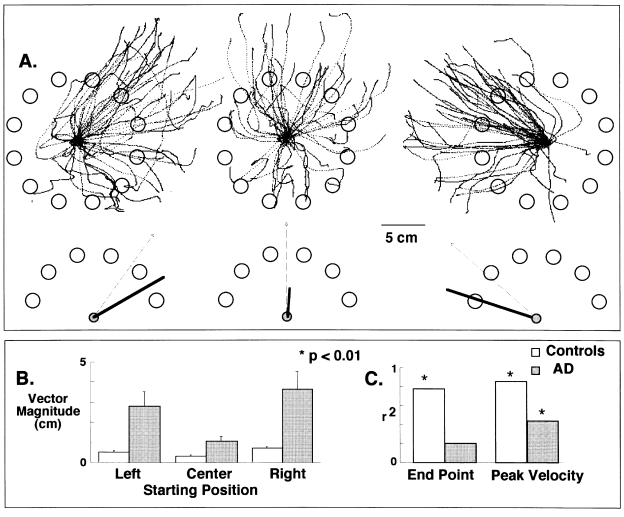

Fig. 2. (A) Top: hand paths of an AD patient (R.V.) to 12 targets from left, center and right starting points. Bottom: Dark heavy lines represent average vectors for the three starting positions in the same patient. The light dashed lines indicates the direction of the position of the screen relatively to each starting point. (B) Mean and standard errors of average vectors of controls and patients for the three starting positions. (C) Variance in mean directional error at the end point and at the peak velocity accounted for by the distance of the initial hand position from the body mid-line.

In the patients' group there was a significant correlation ($P < 0.05$) between the magnitude of mean vector and the scores of MMSE ($r = 0.84$), Token ($r = 0.75$), Cancellation ($r = 0.71$), Corsi Span ($r = 0.68$) and logical memory ($r = 0.75$). No significant correlation was found with scores of Benton and Raven tests. Briefly, MMSE is a global index of disease severity; Token measures language comprehension and short-term memory; cancellation test evaluates attention and concentration, Corsi and logical memory, test short-and long-term memory. Benton's lines orientation measures visuospatial abilities and Raven evaluates global intelligence. With cursor FB, accuracy and vectors' magnitude were similar to the controls' and no correlation was found with neuropsychological scores.

This study shows that movements of AD patients performed under visual guidance are slow with a discontinuous temporal profile; without visual FB, movement inaccuracy increases. As first suggested by Woodworth [20], movements of normal subjects involve two successive phases, 'initial adjustment' and 'current control'. Initial adjustment phase, which quickly transports the hand towards the target, covers 90% of the total movement [13] and results from the programmed scaling of a stereotyped bell-shaped velocity profile. This phase is independent of continuous visual monitoring and, thus, relies on preexisting internal models requiring integrity of mnemonic function. Visual FB is used only in the 'current control', i.e. in the last 10% of the movement, to correct the trajectory once the hand is close to the target. The fragmented velocity profiles and the increased movement times suggest that, in reaching the target, AD patients strongly rely on continuous sensory monitoring of their moving hand. These conclusions are in agreement with the results of a study with cued and non-cued targets [4] as well as of a pilot study on tracking movements (Andrew Schwartz, personal communication). Without visual FB, movements of AD patients are highly inaccurate and deviate progressively towards the location of the display screen. The fact that movements' initial directions are more accurate than at the end point suggests that even at the early stage of the disease, patients can plan but cannot sustain the motor plan throughout its course. As a consequence, the reference frame for specifying the intended direction changes in the course of movement from the learned screen coordinates to a default reference in natural space which is easy to recognize visually.

The high correlation between vector magnitude and per-

formance in memory- and attention-loaded neuropsychological tests suggests that the deterioration of the transport phase is linked to impairment in attention and memory as well as to global cognitive decline. In their study of finger tapping in AD, Ott et al. [18] found a significant correlation between slowness and cognitive tests requiring attention and executive functions. Their findings and ours suggest that frontal lobes, in particular area 46, may be one of the sites responsible for the motor dysfunction of AD patients. In fact, the dorsolateral prefrontal cortex is involved in processes requiring spatial working memory and attention [15]. Parietal cortex, one of the sites involved in sensory-motor transformations required to produce movements [9], is another likely candidate for this type of impairment. Hypoperfusion of the parietal area is a hallmark of AD that strongly correlates with disease severity and clinical evidence of apraxia [8]. Apraxia in AD first disrupts the objective euclidean space, then the body-centered space and, finally, the concrete space of object manipulation. Our patients' motor performance may reflect initial and clinically undetectable impairment of praxic functions which becomes evident only later in the disease.

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