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Jianhong Zhang
Shandong University

Yunling Xiao
Shandong University

Zong-Ming Li
University of Arizona

Na Wei
Shandong University

Leitong Lin
Shandong University

Ke Li (kli@sdu.edu.cn)
Shandong University

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Reach-to-Grasp Kinematics and Kinetics in Early-Stage Alzheimer’s Disease

Jianhong Zhang¹#, Yunling Xiao²#, Zong-Ming Li³, Na Wei², Leitong Lin¹, Ke Li¹*

¹ School of Control Science and Engineering, Shandong University, Jinan 250061, China
² Department of Geriatrics, Qilu Hospital, Shandong University, Jinan 250012, China
³ Department of Orthopaedic Surgery, University of Arizona, Tucson, AZ 85724, USA

* Corresponding author
E-mail: kli@sdu.edu.cn

# These authors contributed equally to this work.
Abstract

This study aimed to investigate the effects of early-stage Alzheimer’s disease (AD) on the reach-to-grasp kinematics and kinetics with different visual feedbacks. Seventeen patients who had been diagnosed with the early-stage AD and the same number of age- and gender-matched cognitive normal (CN) adults participated in the experiment. Each subject was instructed to perform the reach-to-grasp task, and the kinematic and kinetic parameters were collected and calculated to quantify the characteristics for both the AD and CN groups. Results showed that the early-stage AD remarkably decrease the reaching speed, reduce the grasping accuracy and increase the transportation variability. In addition, the early-stage AD extended the preload duration, disturbed the grip and lift forces (GF-LF) coordination, and increased the feedforward proportion in the grasping force control. The AD-related changes in the reach-to-grasp kinematic and kinetic parameters depended on visual feedback conditions and were associated with nervous system function according to correlation analyses with the neuropsychological testing. These results imply that quantifying the reach-to-grasp performance may help us better understand the changes in sensorimotor control in the early-stage AD and may provide novel approach to the early screening and evaluation of AD.

Keywords: Alzheimer’s disease; sensorimotor control; reach-to-grasp performance; kinematics; kinetics
Introduction

Alzheimer’s disease (AD) is one of the most prevalent dementia, and more than 50 million people have been diagnosed with AD and the prevalence will increase twofold in the next few decades worldwide [1]. The AD commonly manifests as insidiously cognitive decline, irreversible memory loss, disorientation and psychiatric symptoms. One of the keys to effective manage AD is early screening and diagnosis, followed by proper interventions to delay its progression.

The preliminary diagnosis of AD is made by a combination of clinical criteria which includes mental status tests, neurological examination and brain imaging [2]. However, even with these clinical tests, the diagnosis of AD remains difficult especially in patients having mild or early-stage AD. For example, mini-mental state examination or clinical dementia rating, the frequently used clinical examinations relying on patients’ self-report and clinicians’ judgement, has limitations in the objectivity and precision [3]. Evaluating Aβ or protein tau from blood serum may serve as a biomarker for early-stage AD, but the sophisticated and invasive operation for analyzing the cerebrospinal fluid keeps it from being widely applied [4]. Brain imaging with functional magnetic resonance imaging, positron emission tomography or diffusion tensor imaging has been applied in probing the early-stage AD, but is inconvenient and costly particularly for mass screening of high-risk populations. Hence, searching for objective, noninvasive, and practical biomarkers would still be an intriguing issue for promoting the early diagnosis and screening of AD.

Converging evidence reveals that the neurodegeneration with AD involves changes of the sensory or motor functions. Abnormities in gait [5], postural equilibrium [6], language and
skilled movement [1, 7] could be early signs for cognitive decline, and associated with
dementing process. Sensorimotor markers are independent of culture background and
educational levels, thereby would be suitable for clinical use. Despite the promising
applications, sensorimotor markers are still facing challenges, such as to find the optimal
sensorimotor tasks and variables for detecting cognitive declines, or to recognize the role of
cognition in a given sensorimotor task. Although sensorimotor markers as an independent
contributor to the cognitive decline remain controversial, growing evidence suggests that
sensorimotor variables incorporating cognitive assessment would improve the evaluation of
eyearly cognitive decline [5]. There is a need to find more sensitive, reliable and easy-to-perform
sensorimotor markers combined with cognitive assessments for early screening and long-term
evaluation of AD.

The unique ability of human and non-human primates to interact with the environment lies
in their skilled use of the hands for dexterous object manipulation [8]. Target-directed reaching
involves the initial stage that requires localization of the target in space, selection of contact
sites for digits, transportation and orientation of hand, and re-shaping and coordination of the
hand and digits relative to the target [9, 10]. As the digits physically contact with the object,
reaching transitions to grasping that can be further divided into lifting, holding and releasing
phases. Multimodal sensory including vision, haptics and proprioception may play a role in
spatial and temporal regulation for the reach-to-grasp behavior. Visual information about the
position and characteristics of the object may facilitate to form appropriate sequence of motor
commands for specific manipulation goals [11, 12]. Tactile sensors in fingertips can detect the
physical properties of the object including the curves and friction of the contact area; and can
encode the information about the weight, moving speed and center of mass of the object [13, 14]. Proprioception encodes the information about limb velocity, load on a limb, body position, movement, and acceleration. The multimodal sensory information continuously and seamlessly integrated with motor commands and memory forms a sensorimotor mechanism that may guarantee a successful reach-to-grasp performance.

The characteristics of object manipulation can be examined in kinematics and kinetic. Kinematic parameters, such as the attitude and joint angles of the grasping hands, and the moving speed and trajectory of the target object, have been mostly analyzed during reach-to-grasp [15]. It has been found that the initiation of grasp closure was correlated with the onset of the deceleration phase of transport, the contact points were modulated according to object’s center of mass under visual or tactile feedbacks, and faster movements and decreased grip aperture were achieved with simultaneous availability of vision and tactile sensation [16]. The kinetic parameters, such as the amount and direction of fingertip forces and moments, are subject to a variety of mechanical constraints. For example, the vertical shear force offsets the gravity, the ratio of tangential to normal forces should be smaller (minimally greater?) than the coefficient of friction, the moments applied upon the object satisfy equilibrium condition [17]. To meet all these mechanical constraints, the kinetic parameters should adapt to the objects’ physical properties (e.g. center of mass, friction condition) [18], movement status (e.g. in acceleration, in rotation) [19] and task demands (e.g. lifting, descending) [20].

The sensorimotor integration for reach-to-grasp kinematics and kinetics is under the government of center nervous systems (CNS). Experiment from macaque monkeys suggested that the anterior intraparietal area (AIP) was involved in grasp planning and visuomotor
transformation, the rostral part of ventral premotor cortex (F5) was responsible for the muscle
activation and task execution particularly for precision grip, and the primary motor cortex (F1)
received the motor commands from F5 and plays a role in dynamic adjustment for reach-to-
grasp behavior (REF). Observations from human subjects suggest that superposition of visual
and proprioceptive maps for accurate reaching was the posterior parietal cortex and
corticospinal drive to brachioradialis and anterior deltoid could be strongly excited during
reaching for muscle activations, hand transportation, digit orientation (REF). Cognitive
degenerations or lesions in CNS could disturb the central mechanism, thus potentially
detectable from a reach-to-grasp performance. However, little is known about a functional
decay of kinematics and kinetics of reach-to-grasp movement associated with early-stage AD.

This study aimed to investigate the effects of early-stage AD on the reach-to-grasp
kinematics and kinetics with and without visual supervision of the grasping arm and hand. To
explore the AD-related changes with reduced sensory feedback, the visual information about
the grasping forearm and hand was deprived during reach-to-grasp performance. We
hypothesized that the early-stage AD would affect the kinematic (e.g. accuracy and
coordination of reaching) and kinetic (e.g. force and moment control) performance particularly
without visual feedback on the grasping hand and forearm, and that the abnormal kinematic
and kinetic characteristics would correlate with the status of early-stage AD.

Materials and Methods

Subjects

Seventeen patients who had been diagnosed with the early-stage AD (Age: 64.9±6.5 y, 7
male, 10 female) and 17 age- and gender-matched cognitive normal (CN, Age: 64.9±5.8 y, 7
male, 10 female) adults participated in the experiment. All subjects were right-handed with normal or corrected-to-normal vision. The AD patients were recruited from the Department of Neurology at Qilu Hospital of Shandong Province, China. They were diagnosed as the early stage of AD according to the criteria of National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association by professional therapists. Neuropsychological tests including the Mini–Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Hamilton Anxiety Scale (HAMA) and the Hamilton Depression Scale (HAMD) were performed on each AD patient. The inclusive criteria (1) were over 50 years old, and (2) have clear mental state and could understand the instructions. Exclusion criteria were those had sever stroke, Parkinson’s disease, any history of upper-limb diseases, or any history of upper-limb fractures. Each subject was fully informed the purposes of this study and given informed consent prior to the experiment. The experimental procedures were approved by the Institutional Review Board of Shandong University (KYLL-2020(KS)-340) and were in accordance with the Declaration of Helsinki.

Experimental Setup

A group of retro-reflective markers were affixed to the dorsal surface of the right hand of each subject. The marker set included nail marker-clusters on distal segments of the thumb and index finger [21, 22], hand marker-cluster along the second metacarpal, and single marker proximal to wrist. An optical three-dimensional (3D) motion capture system (OptiTrackTM, USA) was used to track the position of the marker set. The grasping task included two protocols: the grasping kinematics and kinetics. For the kinematic task, the grasping target was a reflective marker installed on a base (Fig 1(a)); and for the kinetic study, the grasping target was a custom-
made apparatus installed with two six-component force/torque transducers (Nano 17, ATI Industrial Automation, Inc., Apex, NC). The transducers were mounted on the apparatus by precisely positioning that the $x$-axis and $y$-axis were along the vertical and horizontal directions in the contact surface of each transducer, and the $z$-axis was in the perpendicular direction to the contact surface (Fig 1(b)). The grip surfaces were oriented in parallel with a pinch span of 50 mm and were covered with 100-grit sandpaper to increase the coefficient of friction. The gross weight of the instrumented apparatus was 172 g. Both the reach-to-grasp kinematics and kinetics were performed under two visual feedback conditions – with visual feedback (VF) and without visual feedback (NVF). In the VF condition, subjects could observe their grasping hand and forearms when approaching and contacting the target (Fig 2(a), Fig 2(b)). By contrast, in the NVF condition, subjects could only observe the target but not their grasping hand and forearms (Fig 2(c), Fig 2(d)). A mirror operating system was designed to deprive the visual feedback of their grasping hand and forearms from the online reach-to-grasp action [15]. The mirror was approximately 50 cm x 49 in height and width, and 1 cm in thickness. After the mirror was in place, the space in front of the subject could be divided into two alleys. The reflective and the coating sides of the mirror are facing the left and right alleys, respectively. A marker-target or an apparatus was placed on the left alley at the symmetric position of the real target with respect to the mirror. The subject was seated facing directly the left alley, and was able to clearly gaze the mirror-reflection of the marker-target or apparatus. Because the subject's reaching right hand was behind the mirror in the right alley, there was no visual feedback about the reaching hand during reach-to-grasp movement. Data was collected using a custom LabVIEW program (National Instrument, Austin, TX). Force signals were amplified and
multiplexed using an ATI interface boxes (ATI Industrial Automation, Inc., Apex, NC) and converged to 16-bit analog-digital converters (PCIe-6343, National Instrument, Austin, TX) at a sampling frequency of 1000 Hz.

Fig 1. Apparatus, experimental protocol, and reach-to-grasp kinematic and kinetic signals.

**Experimental Procedures**

Subjects sat comfortably at a table, with their right elbow flexed approximately 90° in the parasagittal plane, their left hand naturally on the left side of body. The grasping target (eight the reflective point or the apparatus) was rigidly fixed on the testing table, aligned with the subject’s right shoulder and at a distance of 35 cm in front of the subject. The right hand was placed on the start position of the table before each trial.

**Task 1: Reach-to-grasp kinematics**

Both the AD and the CN groups performed a reach-to-grasp kinematic test in the VF and NVF conditions (Fig 2(a), Fig 2(c)). In the VF condition, there was no mirror set on the testing table, so that the subjects could observe their grasping hand and forearms as well as the target. In the NVF condition, the mirror was installed on the testing table, and thus the subjects were able to clearly gaze the mirror-reflection of the marker-target, but were unable to observe their
grasping hand and forearm. For both the VF and NVF condition, subjects were required to reach and grasp the target with the tips of their thumb and index finger following auditory cues for consecutive five times.

Fig 2. The reach-to-grasp kinematic and kinetic testing for two representative subjects. (a) Kinematic testing in VF; (b) kinetic testing in VF; (c) kinematic testing in NVF; (d) kinetic testing in NVF.

Task 2: Reach-to-grasp kinetics

For the reach-to-grasp kinetic test, the marker-target set in the kinematic test was replaced with an apparatus. In the VF condition, subjects could observe the apparatus and their grasping hand and forearm without the visual block of the mirror. An auditory cue initiated each trial and prompted the subjects to reach and grasp the center of the contact surfaces of the apparatus with their thumb and index finger (Fig 2(b)); after touching the apparatus the subjects received a second auditory cue to lift the apparatus vertically about 13 cm above the testing table, and maintain the apparatus in the air as stably as they could for 5 s; after that the subjects received a third auditory cue for the replace phase, and the subjects were instructed to replace the apparatus at the testing table and return back their grasping hand to the initial position. In the
NVF condition, the mirror was installed on the testing table (Fig 2(d)). An apparatus was placed behind the mirror and another apparatus with the exact same size was placed at the symmetric position of the reflective side. Subjects could gaze the target apparatus from the reflection, and reach to grasp the apparatus with their right hand. In this case, their right hand and forearm were at the shading side of the mirror, so that the subjects could not observe either their right hand or forearm, or the real target apparatus. The reach-to-grasp testing protocol in NVF condition was the same as that in the VF condition.

**Data Analysis**

**Reach-to-grasp kinematic metrics**

All the kinematic signals recorded by the motion capture system were filtered with a fifth-order Butterworth digital filter at a cutoff frequency of 5 Hz. The onset of the reaching was determined once the velocity of the moving hand exceeded 5 mm/s. We defined the grasping time \( GT \) as the duration from the onset of reaching to the timepoint when the hand returned back to the initial position.

The spatial localizations of the contact points by the thumb and index finger for each subject were fitted by an ellipsoid, which included 95% of the pinch contact points by a principal component analysis (Fig 3(a)). The volume \( \text{Vol} \) of the ellipsoid was computed as an estimation pinch accuracy \( i \). A mean absolute error \( \text{MAE} \), defined as the Euclidean distance between the pinch contact location and the target, was calculated for each trial as follows:

\[
\text{MAE} = \sqrt{(x_t - x_0)^2 + (y_t - y_0)^2 + (z_t - z_0)^2}
\]  

(1)

where \( x_t, y_t \) and \( z_t \) are coordinates of the pinch contact positions and the \( x_0, y_0 \) and \( z_0 \) are the coordinates of the target.
Fig 3. The reach-to-grasp kinematic performances. (a) Spatial localizations of the contact points by the thumb and index finger from a representative AD patient and a CN subject; (b) reach-to-grasp trajectories in a velocity-position phase diagram; (c) representative minimum-jerk trajectories between the start and end points of the reaching hand.

A movement harmonicity ($MH$) was proposed to quantify the movement variability of reach-to-grasp kinematics (Fig 3(b)). Previous studies have demonstrated that the movement trajectories during a self-paced reach-to-grasp performance normally presents as elliptic curves in a velocity-position phase diagram (the $x$-axis is distance between the reaching hand and the target and the $y$-axis is the velocity of the hand, Fig 3(b)). The MH can be computed as follows:

$$MH = \frac{|R_{\text{ideal}} - R_{\text{measure}}|}{R_{\text{ideal}}}$$

$$R_{\text{ideal}} = \frac{C_{\text{ideal}}}{A_{\text{ideal}}}$$

$$R_{\text{measure}} = \frac{C_{\text{measure}}}{A_{\text{measure}}}$$

where the $C_{\text{ideal}}$ and $A_{\text{ideal}}$ are the circumference and area of an ideal ellipse whose major axis equals to the distance between the initial hand position and the target, and minor axis equals
to the maximum velocity in the velocity-position phase diagram; the $C_{\text{measure}}$ and $A_{\text{measure}}$ are the circumference and area of the fitting ellipse of the movement trajectories in the velocity-position phase diagram.

A mathematic model [23] based on the theory of dynamic optimization [24] was applied to quantify the motor coordination during reach-to-grasp maneuver. Briefly, an objective function for motor coordination can be defined as follows:

$$\arg \min_{(x(t),y(t))} \frac{1}{2} \int_{0}^{t_f} \left[ \left( \frac{d^3 x(t)}{dt^3} \right)^2 + \left( \frac{d^3 y(t)}{dt^3} \right)^2 \right] dt$$

(3)

Where $x(t)$ and $y(t)$ are the real-time coordinates of the hand in a planar motion, $t_f$ is the movement duration. A minimum-jerk trajectory (MJT) algorithm was applied to estimate the $x(t)$ and $y(t)$ that minimize the function (3), by which the $x(t)$ and $y(t)$ can be expressed as fifth order polynomials as follows:

$$\begin{cases} x(t) = x^s + (x^f - x^s)(-10(\frac{t}{t_f})^3 + 15(\frac{t}{t_f})^4 - 6(\frac{t}{t_f})^5) \\ y(t) = y^s + (y^f - y^s)(-10(\frac{t}{t_f})^3 + 15(\frac{t}{t_f})^4 - 6(\frac{t}{t_f})^5) \end{cases}$$

(4)

where the $(x^s, y^s)$ and $(x^f, y^f)$ are the initial and final coordinates of the reaching hand, and $t_f$ is the duration of reach-to-grasp movement. The area between the trajectory of reaching hand and the curve formed by the $(x(t), y(t))$ in equation (4) of each trial serves as an indicator for motion coordination (Fig 3(c)).

**Reach-to-grasp kinetic metrics**

The apparatus was used to measure the forces ($F_x$, $F_y$ and $F_z$) and torques ($T_x$, $T_y$ and $T_z$) of the thumb and index finger, separately. All the force and torque components were recorded
simultaneously and then filtered using a fifth-order Butterworth digital filter with a cutoff frequency of 30 Hz. The grip force, $GF$, applied by the thumb and index finger, were the average of the two perpendicular forces. The load force, $LF$, was the summation of the vertical lifting forces applied by the thumb and index finger (Fig 4(a)). The process of hand-object interaction can be divided into three phases: (a) the preload phase ($T_{pre}$), the period from the moment when index finger and thumb first touched the object (the $GF$ first exceeded 0.1 N for more than 2 s) and the onset of the load phase (the $LF$ first exceeded 0.1 N); (b) the load phase ($T_{load}$), from the onset of the load phase to the moment when the load force overcame the gravity so that the object started to move; and (c) the static phase, when the $GF$, $LF$ and the position of the apparatus maintained stable (Fig 4(b)).

The first derivative of $GF$ versus time during the load phase was computed as grip force rate ($GFR$, Fig 5(a)). A Gaussian function was used to fit the curve of $GFR$ (Fig 5(b)), and the root mean square errors ($RMSEs$) between the normalized $GFR$ and the fitted Gaussian curve were...
calculated to quantify their differences. A continuous wavelet transform (CWT) with slow and fast bell-shaped functions (Mexican Hat waveform) was used to examine the time-frequency characteristics of the normalized GFR (Fig 5(c)). The slow bell-shaped function indicates the components with lower frequency (or higher scale), reflecting the slowly changed GFR components; by contrast, the fast bell-shaped function indicates the components with higher frequency (or lower scale), which reflects the fast changes in GFR. To simply the calculation, the slow bell-shaped component $S(b)$ was defined as the average of the 5 scales of the slow bell-shaped function in formula (6). Similarly, the fast bell-shaped component $F(b)$ was defined as the average of the 5 scales of the fast bell-shaped function. The percentage ratio $R(b)$ was calculated as the division of the slow bell-shaped component to the sum of slow and fast bell-shaped components as specified in formula (6).

$$R(b) = \frac{S(b)}{S(b) + F(b)} \times 100\%$$

where $a_i = 15, 17.5, 20, 22.5, 25$ as $i = 1, 2, \ldots, 5$ for the slow components and $\delta j = 70, 80, 90, 100, 110$ as $j = 1, 2, \ldots, 5$ for the fast components. The average of $R(b)$ during the load phase was calculated as a parameter for the statistical analysis.
Fig 5. The GFR analysis for representative AD and CN subjects. (a) The GSF time series in VF and NVF; (b) normalized GFRs and their fitted Gaussian functions; (c) the time-frequency analysis of the normalized GFR.

The GF-LF coordination was estimated by computing a cross-correlation function based on the rates of change of the GF and LF. For each trial, the maximal coefficient of correlation \((CC)\) and the time shifts \((TS)\) were used to quantify the GF and LF coupling (Fig 6(a)). The coefficient of variation \((COV)\) which was defined as the ratio of the standard deviation of GF to the mean of GF during the first 5 s of the static phase was used to quantify the variation of pinch force control (Fig 6(b)). To determine the index and thumb fingertip positions on the manipulandum, the \(x\) and \(y\) coordinates of the center of pressure \((COP)\) of each fingertip were measured during the static phase. The \(COP\) data were fitted by an ellipse for the thumb and index finger (Fig 6(c)), separately. The area of the ellipses in which 95\% of the \(COP\) were located was computed as an estimate of the \(COP\) variability.
Fig 6. Analyses of the GF-LF coordination and COP areas. (a) The deviations of GF and LF, and the CC and TS for quantifying the GF-LF coupling; (b) the COV defined as the ratio of the standard deviation to the mean of GF of the static phase; (c) distribution of COP and its area estimated by a fitted ellipse.

The validity of reach-to-grasp kinetic and kinematic parameters were examined with neuropsychological tests. Correlations analyses between the reach-to-grasp parameters and the scores of MMSE, MoCA, HAMA and the HAMD were performed for the AD group. Only the correlations fulfilling statistically significance were retained as meaningful results. The degrees of correlations were ranked into four levels according to their Pearson correlation coefficients.

**Statistical Analysis**

All statistical analyses were performed using SPSS 25.0 (SPSS Inc., Chicago, IL). There were two visual conditions: (1) VF and (2) NVF. For each condition, the kinematic and kinetic parameters were at first examined for normality using a Kolmogorov-Smirnov test (K-S test). Analysis of variance (ANOVA) with repeated measures were employed to examine the differences of kinematic and kinetic parameters between the AD and CN groups as the between-subject factor across and the VF versus NVF conditions as the within-subject factor. Independent
samples $t$-tests were applied to examine the difference in the kinematic and kinetic parameters between the AD and CN groups. Paired samples $t$-tests were applied to examine the effects of visual feedback for both the AD and CN groups. Correlation analyses between the neuropsychological test scores, including the MMSE, MoCA, HAMA, and HAMD, and the kinematic or kinetic parameters were further performed. A $p$-value of less than 0.05 was considered statistically significant.

Results

Results of reach-to-grasp kinematics

The $GT$ for the VF and NVF conditions during the reach-to-grasp kinematic task are shown in Fig 7(a). The ANOVA tests showed significant main effects of AD ($F_{(1,32)} = 11.477, p < 0.01$) and visual conditions ($F_{(1,32)} = 26.777, p < 0.001$) on the $GT$. Specifically, in the VF condition, the $GT$ were $2.42 \pm 0.53$ s for CN and $3.07 \pm 0.87$ s for AD ($t = -2.512, p < 0.05$); in the NVF condition, the $GT$ were $2.93 \pm 0.83$ s for CN and $4.17 \pm 1.23$ s for AD ($t = -3.428, p < 0.01$).

Compared with the VF conditions, relatively higher $GT$ was found in the NVF for both the AD ($t = -5.038, p < 0.001$) and CN ($t = -2.240, p < 0.05$) groups. The distribution of grasping contact locations and its fitting ellipsoid in the NVF condition are demonstrated in Fig 3(a). The AD patients showed a larger volume of the fitting ellipsoid than the CN subjects ($0.0933 \text{ m}^3$ for AD vs. $0.0266 \text{ m}^3$ for CN). The $MAE$ of the AD patients were $10.5 \pm 0.8$ cm, significantly higher than those of the CN group in the NVF condition ($5.9 \pm 0.3$ cm, $t = 8.728, p < 0.01$, Fig 7(b)).

Results of the $MH$ and $MJT$ are shown in Fig 7(c) and Fig 7(d), respectively. Repeated measures ANOVA showed significant main effects of group (AD vs. CN) on both the $MH$ ($F_{(1,32)} = 4.239, p < 0.05$) and $MJT$ ($F_{(1,32)} = 5.822, p < 0.05$). The $MH$s of AD were $0.39 \pm 0.09$ in VF and $0.41\pm$
0.15 in NVF, and those of the CN were 0.37 ± 0.16 in VF and 0.29 ± 0.12 in NVF. The MHs of AD were significantly higher than those of the CN group in NVF (t = -2.828, p < 0.05). No effects of visual conditions (p = 0.310) or the visual × group interaction (p = 0.116) were found for the MH. By contrast, significant differences was found between the VF and NVF conditions for the MJT (F(1,32) = 9.375, p < 0.01); but no significant interaction between the group and visual conditions was observed (p = 0.097). Specifically, the MJTs were 10.50 ± 3.03 cm² for AD and 2.74 ± 0.08 cm² for CN in VF (t = -3.341, p < 0.01); and the MJTs were 16.80 ± 4.85 cm² for AD and 12.43 ± 3.58 cm² for CN in NVF (p = 0.743). Compared with the VF conditions, relatively higher MJTs were found for both the AD (t = -3.335, p < 0.01) and CN (t = -4.101, p < 0.01) groups under the NVF condition.

![Fig 7](image)

**Fig 7.** Statistical results of the reach-to-grasp kinematics, including (a) the GT, (b) the MAE, (c) the MH, and (d) MJT for both AD and CN. * p < 0.05; ** p < 0.01; *** p < 0.001.

### Results of reach-to-grasp kinetics

Results of the T_{pre} and T_{load} during the grasping kinetic task are shown in Fig 8(a) and Fig 8(b), respectively. The repeated measures ANOVA showed significant main effects of group (F(1,32) = 10.152, p < 0.001) and visual conditions (F(1,32) = 47.620, p < 0.01) on the T_{pre}, with significant interaction observed between the group and visual conditions (F(1,32) = 5.191, p < 0.05). Relatively higher T_{pre} was found in NVF than in VF for both the AD (t = -8.922, p < 0.001)
and CN ($t = -2.979, p < 0.01$) groups. In VF, the $T_{pre}$ values were $0.202 \pm 0.038$ s for AD and $0.163 \pm 0.036$ s for CN, without significant differences between groups ($p = 0.095$); in NVF, the $T_{pre}$ values were $0.713 \pm 0.119$ s for AD and $0.420 \pm 0.09$ s for CN, with significant difference between groups ($t = 3.090, p < 0.01$). The repeated measures ANOVA showed significant main effects of visual conditions on the $T_{load}$ ($F_{(1,32)} = 6.807, p < 0.05$). No significant difference was found between the AD and CN groups for the $T_{load}$ ($p = 0.664$). The $T_{load}$ values of AD were $1.362 \pm 0.149$ s in VF and $2.200 \pm 0.317$ s in NVF ($t = -2.554, p < 0.05$); and those of the CN were $1.580 \pm 0.142$ s in VF and $1.660 \pm 0.191$ s in NVF ($p = 0.538$).

![Fig 8](image)

**Fig 8.** Statistical results of the reach-to-grasp kinetics, including (a) the duration of preload phase, (b) the duration of load phase, (c) the CC, (d) the TS, (e) COV, (f) COP areas, (g) the RMSE and (h) $R(b)$ of GFR. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Results of the CC and TS are shown in Fig 8(c) and Fig 8(d), respectively. Repeated measures ANOVA showed significant differences of CC between the AD and CN groups ($F_{(1,32)} = 31.172, p < 0.001$). Significant differences was found on visual condition ($F_{(1,32)} = 7.962, p < 0.01$), without significant interactions between group and visual condition ($p = 0.478$). The CC
values in VF were 0.636 ± 0.092 for the AD and 0.760 ± 0.078 for the CN ($t = -4.067, p < 0.001$); and in NVF were 0.547 ± 0.101 s for the AD and 0.707 ± 0.127 s for the CN ($t = -3.856, p < 0.01$). Compared with the VF conditions, relatively lower CC was found in the NVF for the AD ($t = 2.829, p < 0.05$). There was significant difference in TS between the AD and CN groups ($F_{(1,32)} = 10.359, p < 0.001$). The AD showed relatively lower TS than the CN in NVF ($t = 2.409, p < 0.05$). No significant interaction was found between group and visual conditions for TS ($p = 0.613$).

Results of COV and COP are demonstrated in Fig 8(e) and Fig 8(f), respectively. Repeated measures ANOVA showed significant main effects of visual conditions for the COV ($F_{(1,32)} = 9.415, p < 0.01$) and COP ($F_{(1,32)} = 5.573, p < 0.05$). No significant difference was found between the VF and NVF conditions for either the COV ($p = 0.786$) or COP ($p = 0.410$). For the AD groups, the COV and COP in NVF (COV: 0.083 ± 0.028; COP: 0.544 ± 0.203 cm²) were significantly greater than those in VF (COV: 0.049 ± 0.004, $t = -3.636, p < 0.01$; COP: 0.320 ± 0.150 cm², $t = -2.500, p < 0.05$). For the CN, however, no significant difference between the VF and NVF conditions was found for the COV ($p = 0.252$) or COP ($p = 0.287$).

The time course of normalized GFR and the fitting curves with Gaussian functions for the grasping kinetic task are shown in Fig 8(g), respectively. The repeated measures ANOVA showed significant main effects of groups ($F_{(1,32)} = 10.303, p < 0.01$) and visual conditions ($F_{(1,32)} = 21.764, p < 0.001$) on the RMSE. The AD showed significantly higher RMSE values than CN only in VF condition ($t = 3.279, p < 0.01$). The RMSE of AD in VF (0.090 ± 0.005) was significantly lower than in NVF (0.110 ± 0.007, $t = -4.074, p < 0.01$); and the RMSE of the CN
in VF (0.067 ± 0.005) was significantly lower than in NVF (0.095 ± 0.006, \( t = -2.922, p < 0.05 \)).

No significant visual \( \times \) group interaction was found in \( RMSE \) (\( p = 0.811 \)).

Results of \( R(b) \) are shown in Fig 8(h). No significant difference was found in \( R(b) \) between the AD and CN groups (\( p = 0.785 \)). Visual conditions could affect the \( R(b) \) (\( F(1,32) = 4.132, p < 0.05 \)). For the AD group, the \( R(b) \) values in VF were 0.712 ± 0.019 and in NVF were 0.701 ± 0.006, with significant differences between the two visual conditions (\( t = 2.495, p < 0.05 \)). No significant difference was found between the two visual conditions for the CN group (\( p = 0.407 \)).

**Results of correlations between reach-to-grasp parameters and neuropsychological tests**

The neuropsychological tests showed the MMSE, MoCA, HAMA, HAMD scores for the AD patients were 24.2 ± 5.2, 20.2 ± 7.7, 18.4 ± 7.2, and 15.8 ± 8.1, respectively. In VF, the MMSE was negatively correlated with the \( GT \) (\( r = -0.506; p < 0.05 \), Fig 9(a)) and the \( MJT \) (\( r = -0.598; p < 0.05 \), Fig 9(b)), and the MMSE was positive correlated with the \( CC \) (\( r = 0.678; p < 0.05 \), Fig 9(c)). The MoCA was correlated with the \( GT \) (\( r = -0.547, p < 0.05 \), Fig 9(a)) and \( CC \) (\( r = 0.540, p < 0.05 \), Fig 9(c)). In NVF, no similar correlation was observed between the \( GT \) and neuropsychological tests (Fig 9(d)), or between the \( MH \) and neuropsychological tests (Fig 9(e)).

The \( MAE \) showed negative correlations with the MMSE (\( r = -0.691; p < 0.01 \), Fig 9(f)) and MoCA (\( r = -0.626, p < 0.01 \), Fig 9(f)). The \( T_{pre} \) was negatively correlated with the MMSE (\( r = -0.653; p < 0.01 \), Fig 9(g)) and \( MOCA \) (\( r = -0.558; p < 0.05 \), Fig 9(g)); and the \( R(b) \) was negatively correlated with the HAMA (\( r = -0.514; p < 0.05 \), Fig 9(h)) and HAMD (\( r = -0.506; p < 0.05 \), Fig 9(h)). In addition, the \( TS \) was correlated with the MMSE (\( r = -0.528; p < 0.05 \), Fig 9(i)).
Discussion

This study aimed to investigate the effects of early-stage AD on the reach-to-grasp kinematics and kinetics. Two visual conditions (VF vs. NVF) were provided, in order to examine the AD-related changes under sensory modulation. Results showed that the early-stage AD could remarkably decrease the reaching speed (e.g. the increased GT in AD vs. CN), reduce the grasping accuracy (e.g. the greater MAE in AD vs. CN) and augment the transportation variability (e.g. the increased MH and MJT in AD vs. CN) for reach-to-grasp kinematics. In addition, the early-stage AD extended the preload duration (e.g. the increased $T_{pre}$ in AD vs. CN), disturbed the GF-LF coordination (e.g. the decreased CC and increased TS in AD vs. CN), and increased the feedforward proportion in the grasping force control (e.g. the higher RMSE and lower $R(b)$). It is noteworthy that most of the AD-related changes highly relied on the visual...
conditions. Specifically, the grasping errors (MAE), transportation variability (MH), preload duration ($T_{pre}$) and time shifts of the $GF-LF$ coordination ($TS$) showed significantly higher values in AD than in CN under the NVF rather than the VF condition (Fig 7, Fig 8). The AD-related changes in the grasping kinematic and kinetic parameters were associated with nervous system function, which could be demonstrated from the moderate to strong correlations of the reach-to-grasp parameters with the MMSE, MoCA, HAMA or HAMD scores in AD (Fig. 9).

The decreased reaching speed (increased $GT$) associated with the early-stage AD suggests more time to initiate and execute the goal-directed reaching movement. Previous studies found that the risk for cognitive impairment could be associated with slower gait in locomotion [25, 26] and slower initiation and execution of goal-directed pro-tapping task [27]. Individuals with early-stage AD demonstrated slower, clumsy, uncoordinated, and inconsistent handwriting movements than the healthy subjects [28, 29]. Considering the motion speed is associated with the coordination of multiple joints, evidence from the $GT$ suggests that the early-stage AD might lead to deficits or difficulties in coordination of multiple joints while executing reach-to-grasp task [30]. Reduced structural and functional integrity of prefrontal cortex and hippocampus, or dysfunction of the basal ganglia in the patients with AD could be potential reasons for the slower actions [31]. In addition, motor planning and execution are considered to be related to the interconnection of multiple cortical regions [32, 33], the increased $GT$ may also reflect a potential linkage between the systemic disorders across cortical regions and the behavioral manifestation [34].

The decreased grasping accuracy reflected by the greater $MAE$ in the early-stage AD than in CN suggests that the neurodegeneration associated with the AD would impair the fine motor
control for grasping kinematics. This change could be resultant from the decreased localization associated with AD specifically when the visual feedback for the grasping hand was blocked [35]. Several cortical areas, such as Brodmann area 5 of the superior parietal lobe, the parieto-occipital junction and the premotor areas, may play a role in positioning or localizing an object in a 3D space [36]. The structural or functional changes in these cortical areas due to AD potentially lead to the decreased grasping accuracy. In addition, the poor spatial localization performance observed in the early-stage AD may be associated with the trans-neuronal spread of pathological tau within the entorhinal cortex-hippocampal circuit [37]. Accumulation of amyloid-β pathology in the retro splenial cortex associated with AD may also attribute to the decreased grasping accuracy [38].

The higher $MH$ and higher $MJT$ describe transportation variability during reach to grasp an object. The $MH$ is an indicator of movement harmonicity; the values of $MH$ closer to 0 indicate more harmonic movements [39]. The $MJT$ describes ideal trajectories potentially existing in any target-oriented hand motions according to the minimum-jerk principle. The higher $MJT$ implies augmented deviations between the hand transportation to the minimum-jerk trajectory [40]. Results of $MH$ and $MJT$ confirm our hypothesis that the neurodegeneration associated with AD may remarkably increase the movement variability for hand transportation during reach-to-grasp an object, suggesting potentially altered central or peripheral neuroregulatory control in the early-stage AD.

**Grasping kinetic metrics**

The increased $T_{pre}$ associated with AD suggests a longer transition from the kinematic control for reaching to the kinetic control for precision grip. The increased $T_{pre}$ in AD was
probably due to the difficulty increased with degraded neural function in switching the subgoals of a consecutive motor program, resulting in decreased smoothness of the reaching to grasping transitions. Another potential reason for the increased $T_{pre}$ with AD would be the deficits in sensorimotor integration that is responsible for the feedback control of grasping forces according to the real-time tactile afferent information [41]. This finding would be in line with the observations from force tracking tasks that the AD patients showed prolonged reaction time and slower motion due to the deficits in precisely control the force according to the visual feedback [42].

The lower $CC$ and higher $TS$ may suggest decreased $GF$-$LF$ coordination associated with AD. During the load phase of grasping and lifting an object, the $GF$ and $LF$ are found to be simultaneously increased to prevent slips [43]. This $GF$-$LF$ coordination is considered to be a capacity of scaling of the ratio between $GF$ and $LF$, reflecting the consistency between the internal representation for the digit force prediction and the external adaptation of digit forces according to the tactile feedbacks [44, 45]. Previous studies have found that the $GF$ and $LF$ are related to the activation of the right intraparietal cortex, revealing the involvement of the premotor and posterior parietal cortex in the $GF$-$LF$ coordination during precision grip [46]. Loss of synaptic contacts and neuronal cell apoptosis in the premotor, posterior parietal cortex associated with AD therefore may lead to the compromised $GF$-$LF$ coordination for precision grip.

Results further showed that the patients with AD exhibited non-bell-shaped force-rate profiles with higher $RMSE$ compared with the CN during precision grip. Previous studies from arm motion [47] and isometric force production [48] found that the bell-shaped force-rate
profiles would be related to feedforward control strategy, whereas the non-bell-shaped force-rate profiles indicate feedback-driven correction. The $GFR$ peak has been found to be scaled to object mass and occurs before subjects can sense the object’s mass, indicating subjects’ predictions for the object’s weight [49] or sensorimotor memory about the knowledge of the object’s physical properties (e.g. weight or mass distribution) through previous manipulations [50]. Patients with AD may thus exhibit more feedback-driven force corrections instead of feedforward control, implying potential degradation of their sensorimotor memory and motor planning.

**Effects of visual feedback on reach-to-grasp performance**

Visual and somatosensory feedback is processed and integrated with motor commands and guarantees successful reach-to-grasp movements [47]. The current study observed altered reach-to-grasp kinematic parameters under different visual conditions. For example, both the AD and CN groups showed increased $GT$ and $MJT$ after the removal of visual feedback, suggesting slower motion speed and increased motion variability without visual guidance of the grasping hand. In addition, according to the results of MAE, the AD groups showed more deteriorated grasping accuracy compared to the CN group after removing the visual feedbacks for the grasping hand and arm, suggesting that the patients with AD may suffer from lack of proprioception, relying more on the visual correction for locating their grasping hands relative to the target and for planning and executing goal-directed movements.

Visual condition could also affect the kinetic parameters of reach-to-grasp performance. The effects of visual condition were more significant in AD than in CN. Patients with AD showed much higher values of $T_{load}$, $T_{pre}$, CC, COP area and RMSE, and much lower values of
R(b); by contrast, the CN group showed significant differences between the visual and non-
visual conditions only in $T_{pre}$. Previous studies found that visual feedback of hand and object
motion contributes to estimation of digit forces and the coordination between $GF$ and $LF$ [51].
Consistent with these findings, the current study further revealed that the effects of AD could
more obviously exhibited without visual feedback, suggesting a more reliance on visual
information when controlling and coordinating kinetic parameters for reach-to-grasping
performance. In addition, this study found that the AD and CN exhibited non-bell-shaped fore-
rate profiles in NVF. The digit force under different visual conditions is possibly due to a higher
level sensory-based control in the CNS that supports the spatiotemporal coordination of both
digit forces. For the VF, the central processes integrate visual, tactile, and proprioceptive
information into a close-loop feedback control. This feedback control allows the two-digit
motor system to coordinate flexibly in order to minimize the overall error of the force output.
By contrast, the withdrawal of visual information may transfer the feedforward control
mechanism to somatosensory feedback dominated by tactile and proprioceptive information.
This study thus confirmed that visual feedback plays a role in feedforward and feedback control
of precision grip and that the AD subjects may rely more on somatosensory feedback for force
and torque control in NVF.

Correlation analyses between the reach-to-grasp parameters and the neuropsychological
testing confirmed that the kinematic and kinetic changes in the early-stage AD could be
attributed to the degradation of neural function. In VF, the $GT$ was negatively correlated with
MMSE and MoCA, indicating the reduced motion speed may reflect the decline of cognitive
function in the early-stage AD; the $MJT$ was negatively correlated with the MMSE, suggesting
that the early-stage AD patients with reduced cognitive status may have difficulties in planning of motion trajectories; the CC was negatively correlated with MMSE and MoCA, revealing that the cognitive impairment could significantly affect the GF-LF coordination during precision grip due to the central or sensory dysfunction. It is noteworthy that the significant correlations between the reach-to-grasp parameters and neuropsychological assessments were highly relied on the visual feedback, and much more significant correlations were found in NVF than in VF conditions. Specially, in NVF the MAE was negatively correlated with the MMSE and MoCA, and the TS was negatively correlated with the MMSE, which indicates that more compromised cognitive status of AD could be associated with reduced grasping accuracy and disturbed GF-LF coordination. The $T_{pre}$ was negatively correlated with HAMA and HAMD, revealing the prolonged preload duration in AD could reflect the cognitive deficits in executive function. These results support the hypothesis that cognitive function could be associated with complex motor behavior, and that the reach-to-grasp kinematic and kinetic maneuver could potentially serve as a novel tool for non-invasive screening or evaluation of the early-stage AD.

**Conclusion**

This study investigated the effects of early-stage AD on the reach-to-grasp kinematics and kinetics with different visual feedbacks. Results showed that the early-stage AD could remarkably decrease the reaching speed and grasping accuracy and increase the transportation variability for reach-to-grasp kinematics; and could extend the preload duration, disturb the GF-LF coordination, and increase the feedforward proportion in the grasping force control. The AD-related changes in the grasping kinematic and kinetic parameters were dependent on visual feedback conditions and associated with nervous system function, which could be demonstrated
from the moderate to strong correlations of the reach-to-grasp parameters with the MMSE, MoCA, HAMA or HAMD of AD. This study shed light on the effects of early-stage AD on fine motor control during reach-to-grasp behavior and may provide a novel approach to the non-invasive screening or evaluation of AD.

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Authors’ contributions

K.L. and N.W. conceived the idea. K.L., J.Z. Z.L. and L.L. designed the systems. J.Z. and L.L. performed the experiments. Y.X. and Z.L. provided guidance and resources. J.Z. K.L. L.L and N.W. analyzed the results. J.Z. wrote the original manuscript and prepared all figures. All authors reviewed and edited the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.
Declarations

Ethics approval and consent to participate

The experimental procedures were approved by the Institutional Review Board of Qilu Hospital, Shandong University (KYLL-2020(KS)-340) and were in accordance with the Declaration of Helsinki.

Consent for publication

Participants give their consent for publication of their image if require.

Competing interests

The authors declare that they have no competing interests.

Author details

1 School of Control Science and Engineering, Shandong University, Jinan 250061, China. 2 Department of Geriatrics, Qilu Hospital, Shandong University, Jinan 250012, China. 3 Department of Orthopaedic Surgery, University of Arizona, Tucson, AZ 85724, USA

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