Published in final edited form as:

Neuropsychologia. 2010 November ; 48(13): 3855–3867. doi:10.1016/j.neuropsychologia.2010.09.018.

Coordination deficits in ideomotor apraxia during visually targeted reaching reflect impaired visuomotor transformations

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Abstract

Ideomotor limb apraxia, commonly defined as a disorder of skilled, purposeful movement, is characterized by spatiotemporal deficits during a variety of actions. These deficits have been attributed to damage to, or impaired retrieval of, stored representations of learned actions, especially object-related movements. However, such deficits might also arise from impaired visuomotor transformation mechanisms that operate in parallel to or downstream from mechanisms for storage of action representations. These transformation processes convert extrinsic visual information into intrinsic neural commands appropriate for the desired motion. These processes are a key part of the movement planning process and performance errors due to inadequate transformations have been shown to increase with the dynamic complexity of the movement. This hypothesis predicts that apraxic patients should show planning deficits when reaching to visual targets, especially when the coordination and/or dynamic requirements of the task increase. Three groups (18 healthy controls, 9 non-apraxic and 9 apraxic left hemisphere damaged patients) performed reaching movements to visual targets that varied in the degree of interjoint coordination required. Relative to the other two groups, apraxic patients made larger initial direction errors and showed higher variability during their movements, especially when reaching to the target with the highest intersegmental coordination requirement. These problems were associated with poor coordination of shoulder and elbow torques early in the movement, consistent with poor movement planning. These findings suggest that the requirement to transform extrinsic visual information into intrinsic motor commands impedes the ability to accurately plan a visually targeted movement in ideomotor limb apraxia.

Keywords

Ideomotor apraxia; Visuomotor transformations; Parietal lobe; Left hemisphere; Stroke; Motor deficits

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1. Introduction

Ideomotor limb apraxia, a disorder that commonly occurs following left hemisphere damage, has been described as an inability to perform skilled, purposeful movements (Haaland, Harrington, & Knight, 1999, 2000; Ochipa & Gonzalez Rothi, 2000; Pazzaglia, Smania, Corato, & Aglioti, 2008; Rothi, Ochipa, & Heilman, 1991). The cardinal deficits associated with the disorder are spatiotemporal errors (e.g. jerky vertical movements rather than smooth horizontal motion when performing a bread slicing gesture) observed across a variety of movement contexts (Clark et al., 1994; Poizner et al., 1995; Poizner, Mack, Verfaellie, Rothi, & Heilman, 1990). These deficits are commonly identified by errors made during imitation or pantomime of meaningful movements (object-related and intransitive gestures) and/or imitation of meaningless movements. In order to diagnose apraxia, most studies rely upon a composite score that reflects errors across these different types of movements, and relatively few studies have directly examined differences among them. However, because several studies have shown that apraxic patients make more errors in the context of object-related actions (Haaland & Flaherty, 1984; Haaland et al., 2000; Mozaz, Rothi, Anderson, Crucian, & Heilman, 2002) and the view that planning of object-related movements is partially distinct from meaningless movements due to their dependence on previously stored knowledge about objects and their functions (see Frey, 2007 for a review), recent research has focused largely on understanding deficits in object-related motion (see Daprati & Sirigu, 2006 for a review).

However, many studies, including some from our laboratory have demonstrated that spatiotemporal deficits in apraxia are not limited to object-use movements. For example, we have previously shown that apraxic patients make errors that are consistent with impaired integration of spatial and temporal features of movements during reaching (Haaland et al., 1999) and sequencing (Harrington & Haaland, 1992). Importantly, apraxic patients also make more errors than non-apraxic patients and healthy subjects when asked to imitate meaningless movements, such as touching the nose, and also intransitive gestures, such as saluting (Goldenberg, 1999; Haaland et al., 2000; Toraldo, Reverberi, & Rumiati, 2001). In fact, numerous studies have used deficient imitation of intransitive and/or meaningless movements as a basis for classifying patients as apraxic, without considering object-use movements at all (Buxbaum, Johnson-Frey, & Bartlett-Williams, 2005; De Renzi, Motti, & Nichelli, 1980; Pazzaglia et al., 2008). These results have thus demonstrated that deficits in apraxia are evident during movements made in a variety of contexts, and are not simply limited to object-use actions.

More recent studies have focused on elucidating the mechanisms underlying the different types of deficits observed in apraxic patients. Several authors have proposed that these deficits arise from damage to, or impaired retrieval of previously stored representations of learned actions. Accordingly, lesion and imaging studies have shown the involvement of left parietal regions for recognition as well as imitation of object-related actions and meaningful/intransitive gestures, which has led to the conclusion that these parietal regions form the neural substrate for storage of representations for learned actions (Buxbaum et al., 2005; Buxbaum, Kyle, Grossman, & Coslett, 2007; Buxbaum, Sirigu, Schwartz, & Klatzky, 2003; Chao & Martin, 2000; Creem-Regehr, 2009; Swinnen et al., 2010). Damage to these regions would also explain the impairment observed in apraxic patients during the pantomime and command-evoked gesturing of such learned actions. However, Goldenberg (2009) has reviewed extensive evidence supporting the view that damage to left parietal regions adversely impacts imitation of not just highly learned actions, but also meaningless movements and motor performance on other tasks.

A mechanism that could account for these deficits following parietal damage is a failure to convert visual information, such as experimenter actions during imitation, into motor commands necessary to produce the desired motion. This hypothesis is particularly compelling as an explanation for the deficits seen in apraxic patients during the imitation of novel and meaningless movements, for which neural representations may not be developed (Rothi et al., 1991; Tessari, Canessa, Ukmar, & Rumiati, 2007). This view is also consistent with the extensive evidence supporting the role of posterior parietal circuits in the transformation of extrinsic visual information into intrinsic motor commands required to produce the desired motion during visually targeted movements (see Buneo & Andersen, 2006; Fogassi & Luppino, 2005; Jackson & Husain, 2006 for reviews). For visually targeted movements, such visuomotor transformations have been shown to be a key component of the movement planning process (see Sarlegna & Sainburg, 2009 for a review). Moreover, inaccuracies during this transformation process have been shown to adversely impact motor planning (Sarlegna, Przybyla, & Sainburg, 2009; Schlicht & Schrater, 2007; Sober & Sabes, 2005), with more recent results suggesting that movement coordination errors that occur as a consequence of inadequate transformations are larger for movements involving more complex movement dynamics (Sarlegna et al., 2009). It is important to emphasize that this hypothesis does not imply that deficits in apraxia cannot occur due to a loss in stored knowledge of learned actions, or that such actions do not involve visuomotor transformation processes. Rather, we suggest that deficits should be evident due to impaired sensorimotor transformation mechanisms that operate in parallel or downstream to mechanisms involved in the representation of learned actions. If this is true, we predict: (1) planning deficits in patients with ideomotor apraxia should be evident during simple reaching movements to visual targets and (2) these deficits should be magnified as the dynamic requirements of the movement are increased. We test this hypothesis in a task in which healthy control, and non-apractic and apractic left hemisphere damaged subjects reach to three visually presented targets that vary in the degree of interjoint (shoulder and elbow) coordination required. We expect that apractic patients will show planning deficits associated with impaired specification of movement dynamics early in the movement, prior to the time that feedback can influence movement patterns. In addition, we predict that these deficits will be greatest for the movement requiring maximal interjoint coordination.

2. Methods

2.1. Participants

Because ideomotor limb apraxia is more prevalent following left rather than right hemisphere damage (De Renzi et al., 1980; Haaland & Flaherty, 1984; Kertesz & Ferro, 1984), we restricted our patient group to 18 left hemisphere damaged (LHD) stroke patients. We compared the performance of these stroke patients with that of 18 age- and education-matched healthy control subjects. Prior to participation, all subjects gave informed consent according to the Declaration of Helsinki. The study was approved by the Human Research Review Committee of the University of New Mexico and the New Mexico Veterans Affairs Healthcare System. All subjects were pre-morbidly right-handed; handedness was determined using a 10-item version of the Edinburgh inventory (Oldfield, 1971). None of the participants had a history of (i) substance abuse within the past 10 years and/or significant psychiatric diagnosis; (ii) any neurological diagnoses for control subjects and non-stroke related neurological problems for stroke patients, or (iii) movement restrictions for peripheral reasons, such as neuropathy or orthopedic disorders. Language comprehension (Kertesz, 1982) and grip strength were assessed in all subjects, and stroke patients were also given the Fugl-Meyer test of motor function in the contralesional arm (Fugl-Meyer, Jaasko, Leyman, Olsson, & Steglind, 1975).

The LHD stroke patients were divided into two groups, apraxic or non-apraxic, determined using a standardized test for limb apraxia (Haaland & Flaherty, 1984). Patients were asked to imitate five meaningless (e.g. index finger on earlobe), five intransitive (e.g. salute) and five transitive (e.g. brush teeth) movements with their ipsilesional (left) arm. When errors in internal hand configuration (e.g. fist versus flat palm), orientation (e.g. vertical versus horizontal) or target (e.g. brushing nose instead of teeth) were made, or when a body part was used as an object (e.g. extend finger to brush teeth), the item was scored as incorrect. Thus, more than one type of error could be made on a single movement, but only one error per movement was scored. Patients were considered apraxic if they made spatio-temporal errors on four or more of the fifteen movements (2 SD greater than normal controls) (Haaland & Flaherty, 1984; Haaland et al., 2000). Movements were videotaped for scoring by two raters. Using this test, 9 of the 18 LHD patients were classified as apraxic, while the remaining 9 were classified as non-apraxic. The average number of errors made by the apraxic group was 4.88 ± 0.35 (mean $\pm$ S.E.), while the non-apraxic stroke subjects made 1.22 ± 0.32 (mean $\pm$ S.E.) errors during apraxia testing. The same battery was given to control subjects, who made 1.7 ± 0.29 (mean $\pm$ S.E.) errors.

MRIs were obtained in 16 stroke patients, while CT scans were done for 2 patients (1 apraxic, 1 non-apraxic) due to medical contraindications for MRI (e.g. cardiac pacemakers). The area of damage for each patient was traced on 11 standardized horizontal sections derived from the DeArmond atlas (DeArmond, Fusco, & Dewey, 1989) using T1-weighted MRI images for anatomical detail and T2-weighted images to specify borders of the damaged tissues. This was done by a board certified neurologist, who was blinded to the behavioral characteristics of the patients. These outlines were retraced on a digitizing tablet for input into a computer program to allow the overlapping of lesions within each stroke group and to calculate lesion volume (Frey, Woods, Knight, Scabini, & Clayworth, 1987).

2.2. Experimental setup and task

The experimental setup (Fig. 1) and task were the same as in our recent study (Schaefer, Haaland, & Sainburg, 2009b). Briefly, subjects sat facing a table with their palms facing downwards and hands supported over the table using an air sled system to eliminate the effects of gravity and minimize friction. A cursor representing the position of the index finger tip, a start circle and targets were projected using a ceiling mounted projector onto a back projection screen, and a mirror was placed beneath this screen. The mirror blocked direct vision of the subjects arm, but reflected the visual display to give the illusion that the display was in the same horizontal plane as the fingertip. Position and orientation of the forearm and upper-arm segments were sampled using a Flock of Birds (Ascension Technology) system. The positions of the index finger tip, the lateral epicondyle of the humerus and the acromion, directly posterior to the acromio-clavicular joint were recorded using a stylus that was rigidly attached to a 6-DOF Flock of Birds (FOB) sensor. This sensor was then attached to the upper arm segment, while another sensor was attached to the air sled. As sensor data were received, the 3D position of the above-mentioned landmarks was computed using custom software, with the *X-Y* plane parallel to the tabletop. We used our computed *X-Y* coordinates of the fingertip to define the projected cursor position. Digital data was collected at 103 Hz. Custom algorithms for experimental control and data analysis were written in REAL BASIC (REAL Software) and Igor Pro (Wavemetrics, Inc.), respectively.

All subjects performed the task with their left arm, which was the ipsilesional arm for the stroke patients. Three targets, all of which were presented in the left hemispace (defined relative to the midline of the body) at a distance of 16 cm from the start position were used. The left hemispace was the ipsilesional workspace for the stroke patients and was chosen to avoid the possibility that subjects' responses in the contralesional hemispace could be

influenced by the possible presence of hemispatial neglect. The targets were oriented 0°, 40° counterclockwise and 40° clockwise from the start position. Subjects were thus required to move medially (towards midline) to the clockwise target, laterally (away from midline) to the counterclockwise target, and to the center (straight ahead). Prior to the start of each trial, the cursor and the start circle were displayed on the screen. To initiate the trial, the subject brought the cursor into the start circle and after a 200 ms delay, one of the three targets appeared on the screen along with an audio-visual “go” signal. Feedback of the fingertip position (the cursor) was removed at this point and subjects were asked to reach to the target with a minimum speed requirement of 0.5 m/s. The speed criterion was used only to emphasize consistent performance, and was not used as a basis for excluding trials. If subjects satisfied the speed criterion, they received “points” based on the location of the index finger at the end of the movement relative to the center of the target, which were also used for motivational purposes only. Following score presentation, the cursor was redisplayed on the screen for the subjects to return their left index fingertip into the start position to begin a new trial. The three targets were pseudo-randomly presented over a session of 99 trials, such that no target was presented consecutively.

2.3. Kinematic data analysis

Elbow and shoulder angles for the arm were calculated from the 2D positions of the finger, elbow and shoulder. All kinematic data were filtered at 8 Hz using a 3rd order dual-pass Butterworth filter and angular data were differentiated to yield velocity and acceleration values. The first 9 trials were considered practice trials and were not analyzed. All remaining trials were included in the analysis, except in the extremely rare case when the subject failed to initiate a movement in response to the “go” signal (a total of 5 trials across all stroke and control subjects). Thus, for almost all subjects, all 90 trials were included for analysis, yielding 30 movements per target direction. Movement onset was determined by first identifying the maximum in the tangential velocity profile and then searching backwards from this point to the time of the first minimum (zero acceleration) below 3% of maximum velocity. Movement termination was defined as the first minimum below 3% of maximum velocity when searching forward from the point of maximum tangential velocity.

Our dependent measures included peak acceleration (maximum tangential acceleration), acceleration duration (time from movement onset to peak velocity), peak velocity (maximum tangential velocity), final position error (absolute value of the distance between the finger position at movement end and the center of the target), reaction time (time from target presentation to movement onset), movement time (time from movement onset to movement end), initial movement direction error and handpath curvature. Initial direction error was calculated relative to the line connecting the start position and the target, and was defined as the angular deviation between the “target line” and the line from the starting location of the hand to the hand location at peak acceleration. Positive values indicate handpaths that were directed lateral (clockwise error: CW) to the target line, whereas negative values indicate trajectories directed medially (counter-clockwise error: CCW) relative to the target direction. Handpath curvature was calculated as the minor axis divided by the major axis of the handpath. The major axis was defined as the largest distance between any two points in the handpath, while the minor axis was defined as the largest distance perpendicular to the major axis. Thus smaller values of this dependent variable indicate straighter movements, while larger values indicate more curved trajectories. To assess movement variability, we also calculated variable direction error at peak acceleration, peak velocity and movement end. This was quantified as the absolute value of the difference between the actual movement direction during a trial and average movement direction for all trials at each of the three points in time. This calculation was performed separately for each target, for each subject.

2.4. Inverse dynamic analysis

In order to understand the kinetic basis of our kinematic results, we used a planar two-segment rigid body model to calculate joint torques at the elbow and shoulder. The terms in the equations of motion were partitioned into three main components: net torque, muscle torque and interaction torque. The net torque is directly proportional to joint acceleration and equal to the sum of the muscle and interaction torques. Interaction torque at a joint represents the rotational effect of forces due to the motion of body segments adjacent to the joint (e.g. torque generated at the elbow because of shoulder motion), while muscle torque primarily represents the rotational effects of muscle forces. Torques were computed for the shoulder and elbow joint as detailed in (Bagesteiro & Sainburg, 2002). Limb segment inertia, center of mass location and mass were computed using subjects body weight and limb segment lengths (Winter, 1990).

We also quantified the contribution of muscle torque to the net torque at the shoulder and elbow joints during the initial phase of motion (until the time of peak tangential acceleration). This was done as follows: time intervals during which the muscle torque component acted in the same direction as the net torque were considered to contribute to a positive impulse. Intervals during which the muscle and net torques were in opposite directions were considered to contribute to a negative muscle torque impulse. All positive and negative impulses were summed to yield a total muscle torque impulse for the initial phase of motion. This value was normalized to the total net torque impulse during the same phase so that comparisons could be made across subjects.

2.5. Statistical analysis

We subjected the means of our kinematic dependent measures to a 2-way group (healthy control, apraxic, non-apraxic) $\times$ target (lateral, center, medial) analysis of variance (ANOVA). Subjects were treated as a random factor for this analysis. For each subject, we also performed linear regressions between initial movement direction and muscle torque contributions to net torque at the shoulder and elbow joints, separately for each target. Comparison of regression coefficients was done by converting r values to z scores (Fisher transform) and then averaging these scores. The mean z scores were subjected to a 1-way ANOVA, with group as the independent factor. When warranted by significant main or interaction effects, post-hoc comparisons were performed using Tukey's HSD test, which corrects for multiple comparisons (Kutner, Nachtsheim, Neter, & Li, 2004). Statistical significance levels were set to 0.05.

3. Results

3.1. Subject characteristics

Table 1 shows the characteristics of each subject in the two patient groups as well as the mean data for the healthy control group. The three groups were not significantly different in age ($F_{1,16} = 0.0023$, $p = 0.9620$) or education ($F_{1,16} = 0.1490$, $p = 0.7045$). As described earlier, the apraxic group made significantly more errors on our apraxia battery relative to the non-apraxic group ($F_{1,16} = 58.8649$, $p < 0.0001$), and this served as a basis for subject classification. The two stroke groups did not differ in time (in years) post stroke ($F_{1,16} = 0.0001$, $p = 0.9938$), lesion volume ($F_{1,16} = 1.3165$, $p = 0.2681$) or contralesional grip strength ($F_{1,16} = 1.9547$, $p = 0.1812$). Marginal differences were found in language comprehension ($F_{1,16} = 3.2926$, $p = 0.0884$) and contralesional arm scores on the Fugl-Meyer test ($F_{1,16} = 3.4432$, $p = 0.0820$) between the two stroke groups, with the apraxic group demonstrating somewhat greater impairment in both. However, we ensured all our participants understood the task well, and their data confirmed that any language comprehension problems did not affect their performance. In addition, the differences in

contralesional Fugl-Meyer scores did not influence our results directly because we tested the left arm, which was the ipsilesional arm for both stroke groups.

3.2. Lesion characteristics

Fig. 2 shows the superimposed lesion locations for all subjects within each stroke group. 4 out of the 11 template slices are shown; slices 1 through 6 and slice 11 did not differentiate the apraxic and the non-apraxic groups and are therefore not shown. Colors of the shaded regions denote the percentage of subjects in each group with damage in the corresponding area. While overall lesion volume was not significantly different between the two stroke groups (Table 1), as can be seen from slices 7 and 8, a larger number of apraxic patients had damage to frontal areas including motor and premotor cortices (BA 4 and 6) relative to the non-apraxic group. While at least six patients in the apraxic group had lesions in these regions, a maximum of three non-apraxic patients had damage in these areas. Slices 9 and 10 show that more apraxic than non-apraxic patients had damage to posterior parietal regions. As can be seen from slice 10, at least four patients in the apraxic group had damage in the superior and inferior parietal lobes (BA 7, 39 and 40), while only one non-apraxic patient had damage to these areas. These results are consistent with our previous study that showed damage in these frontal and parietal areas in a greater number of apraxic patients (Haaland et al., 2000).

3.3. Kinematics

3.3.1. Task performance—Our experimental design required subjects to reach to three targets that varied in the degree of interjoint coordination required to make the desired movement. Fig. 3A shows the ratio of shoulder joint excursion to elbow joint excursion for the three targets [lateral (L), center (C), medial (M)] for each of our groups. As can be seen from this figure, the joint excursion ratio increased from the lateral to the medial target directions, indicating that the degree of shoulder movement relative to elbow motion increased, thereby reflecting an increase in interjoint coordination from lateral to medial target directions. This was statistically confirmed by a significant main effect of target ($F_{2,33} = 48.0404$, $p < 0.0001$) on this ratio in our ANOVA. Post-hoc tests showed significantly larger shoulder to elbow joint excursion ratio values for the most medial target relative to the center and lateral targets ($p < 0.0001$ in all cases). Fig. 3B–E shows the mean ($\pm$ SE) reaction time, movement time, peak velocity and absolute final position error for each group, separated by target direction. As is evident from Fig. 3B and statistically confirmed by our ANOVA, reaction time was not significantly different among the three groups ($F_{2,33} = 0.6455$, $p = 0.5309$) or the three targets ($F_{2,33} = 0.2836$, $p = 0.7540$), and there was no significant group $\times$ target interaction effect ($F_{4,66} = 1.7434$, $p = 0.1510$) for this measure. In contrast, movement time was significantly longer for the apraxic group. This result, shown in Fig. 3C, was statistically confirmed by a significant main effect of group ($F_{2,33} = 7.0839$, $p = 0.0028$). In addition, movement time varied consistently with target direction for all groups ($F_{2,33} = 26.0424$, $p < 0.0001$), such that the duration of movements made to the medial target was significantly longer relative to the lateral and center targets, consistent with previous reports (Gordon, Ghilardi, Cooper, & Ghez, 1994; Gordon, Ghilardi, & Ghez, 1994). There was no significant group $\times$ target interaction for movement time ($F_{4,66} = 1.7264$, $p = 0.1546$).

In addition to longer durations, the apraxic patients also showed considerably lower movement speeds. Fig. 3D shows that peak velocities were smaller for the apraxic group independent of target direction. This was supported by a significant main effect of group ($F_{2,33} = 7.2053$, $p = 0.0025$), but no significant interaction between group and target ($F_{4,66} = 1.7158$, $p = 0.1570$). Post-hoc tests showed that the apraxic group moved slower than the healthy control ($p = 0.0022$) as well as the non-apraxic ($p = 0.0207$) groups. Moreover, we

observed a significant effect of target ($F_{2,33} = 91.4725$, $p < 0.0001$), such that movements to the medial target tended to be the slower than those to the lateral ($p < 0.0001$) as well as center target ($p < 0.0001$) for all groups. This target dependent effect was also observed for peak acceleration ($F_{2,33} = 55.8663$, $p < 0.0001$) and acceleration duration (normalized to total movement duration) ($F_{2,33} = 18.2845$, $p < 0.0001$). Acceleration amplitude decreased ($p < 0.0001$) while acceleration duration increased ($p = 0.0004$) from the lateral to the medial targets for all groups. However, the lack of a significant group $\times$ target interaction for these measures (peak acceleration: $F_{4,66} = 1.5230$, $p = 0.2057$; acceleration duration: $F_{4,66} = 1.1497$, $p = 0.3411$) suggests that all groups used a similar strategy for achieving peak velocity for a given target. Despite the group differences in peak velocity, we observed no significant differences in the final position error across groups. There was neither a significant interaction effect ($F_{4,66} = 1.4161$, $p = 0.2383$), nor a significant main effect for group ($F_{2,33} = 0.6854$, $p = 0.5109$). These results are shown in Fig. 3E, which demonstrates fairly similar mean errors among groups, as well as analogous target dependent effects within each group. This result is consistent with our previous work that demonstrated no significant differences in positional accuracy between healthy control subjects and left hemisphere damaged stroke patients, during the same task (Schaefer et al., 2009b).

Thus, overall, the apraxic subjects moved more slowly and took longer to reach the target, yet showed final position accuracy similar to the non-apraxic and healthy control group.

3.3.2. Movement trajectory—Fig. 4A shows handpaths from an entire session for a representative healthy control, non-apraxic and apraxic subject for the lateral (L), center (C) and medial (M) targets. As can be seen from these plots, movements made by the apraxic subject showed large irregularities compared to those of the control and non-apraxic subjects. While the control and non-apraxic participants performed fairly straight, smooth movements that were initiated in the direction of the target, the apraxic subject's trajectories were often initiated in the wrong direction, but were corrected later in the movement to bring the arm back towards the target. Large initial direction errors and the subsequent trajectory corrections resulted in highly curved handpaths for the apraxic patients, especially when they moved to the most medial target. The robustness of these results across all subjects is demonstrated in the line plots of Fig. 4B and C, which show the mean ($\pm$ SE) initial movement direction error and handpath curvature across all subjects in the three groups. Fig. 4B shows that while initial movement direction error was similar between the groups for the lateral and the center targets, it was much larger in the apraxic patients for movements to the medial target. Consistent with this observation, our ANOVA revealed a significant group $\times$ target interaction ($F_{4,66} = 5.5429$, $p = 0.0007$) for this measure. Post-hoc analysis confirmed that apraxic subjects made significantly larger initial direction errors when moving to the medial target relative to the control ($p = 0.0149$) and the non-apraxic ($p = 0.0016$) groups. We also observed a strong group $\times$ target interaction ($F_{4,66} = 3.2129$, $p = 0.0180$) for handpath curvature (Fig. 4C), with post-hoc tests showing that the movements to the medial target were significantly more curved for the apraxic patients relative the healthy control ($p = 0.0057$), but not the non-apraxic group ($p = 0.5508$). In addition, as can be seen from Fig. 4C, although mean handpath curvature for movements made to the medial target was larger for the non-apraxic group compared to the healthy control group, this difference was not statistically significant ($p = 0.7780$). Larger handpath curvatures for the apraxic and non-apraxic patients when moving towards the medial target may be reflective of interjoint coordination deficits following left hemisphere damage in general, independent of limb apraxia (Schaefer et al., 2009b).

Although the apraxic patients showed larger average initial direction errors and higher curvature primarily when moving to the medial target, their movements showed greater variability irrespective of target direction. Fig. 5A shows the finger positions at peak

acceleration (●), peak velocity (+) and movement end (○) for our representative subjects in each of the three groups, with the density ellipses representing the 95% confidence interval of these finger positions at each of these three time points. Compared to the narrow width and distinct orientation of the ellipses at peak acceleration and peak velocity for our control and non-apraxic subjects, their substantial overlap and rounded shape for the apraxic patient underscores the deficits in this group. These patients failed to consistently initiate their movement in the direction of the target, resulting in a large spread of finger positions early in the movement. However, these contrasting patterns between the apraxic and other two groups at the beginning of the movement did not correspond to variability at movement end. The apraxic patients were able to correct their movement to bring their arm towards the target, resulting in end position distributions comparable to those of the control and non-apraxic patients. In order to quantify these effects across all subjects, we compared the average variable direction error at peak acceleration, at peak velocity and at movement end across the three groups. These results are shown in Fig. 5B, which contrasts this measure across the groups at the different time points. A significant effect of group for variable direction error at peak acceleration ($F_{2,33} = 4.5874$, $p = 0.0175$) and peak velocity ($F_{4,66} = 3.9261$, $p = 0.0295$), with subsequent tests showing larger errors for the apraxic group relative to both the control and non-apraxic groups confirmed how these movements were not initiated in specific directions relative to the target location in these apraxic patients.

In summary, our kinematic analysis showed that the movements of the apraxic patients were slower and highly variable with large directional errors during movement initiation. The following section examines the kinetic basis of these deficits.

3.4. Inverse dynamics

Because we observed the largest deficits in apraxic subjects when they moved to the medial target (movement with the largest interjoint coordination requirement), we focused our kinetic analysis on these movements. Fig. 6A shows handpaths corresponding to the largest negative (black) and positive (gray) errors made when reaching to the medial target by our representative subjects from each of the three groups. Fig. 6B and C shows the shoulder and elbow joint torques for the sample movements of Fig. 6A, corresponding to the first 200 ms of movement. Positive values indicate flexor torque, while negative values reflect extensor torque. Joint torque patterns for the healthy control and non-apraxic subjects were fairly similar to each other and both groups showed little variation between the trials with the largest positive (gray) and negative (black) initial direction errors. These movements were initiated with flexor shoulder net torque, which was driven primarily by flexor shoulder muscle torque. These shoulder torques produced large extensor interaction torques at the elbow that caused the elbow to accelerate into extension. In fact, the extensor net torque at the elbow, a reflection of elbow acceleration and equal to the sum of elbow muscle and interaction torques, was determined completely by interaction torque while elbow muscle torque remained quite small. These torque patterns remained fairly similar across the two movements for the control and non-apraxic subjects (compare black and gray profiles for these two groups). Thus, these subjects were able to exploit intersegmental interactions to drive forearm motion in a seemingly efficient manner (Bagesteiro & Sainburg, 2002).

The apraxic subjects however showed smaller torques at the shoulder and elbow joints (expanded Y-axis for the representative subject in Fig. 6B and C), which corresponded to their lower velocities, as described earlier. In addition, these subjects showed substantial variation in how joint torques were coordinated across the two trials displayed. For instance, for our representative subject, for the movement with the largest negative error (black profile), shoulder net torque at the beginning of the movement remained close to zero, suggesting minimal acceleration of the shoulder. Instead, this movement to the medial target was initiated by the action of elbow muscles: elbow interaction torque was small, while

elbow muscle torque almost completely determined the extensor elbow net torque. This extensor acceleration of the elbow led to the hand trajectory being initiated perpendicular to the target direction, thus resulting in a large initial direction error. For the movement with the largest positive error (gray profiles), an opposite pattern of joint torques was observed. In this case, flexor muscle torque gave rise to flexor net torque at the shoulder. Flexor shoulder acceleration produced extensor elbow interaction torque, which resulted in an extensor net torque at the elbow. The large elbow interaction torque was countered by flexor elbow muscle torque, which presumably acted to prevent excessive extensor motion at the elbow joint in order to correctly direct the hand towards the target. In this case, the absolute direction error was smaller than that of the movement with the largest negative error (black profile). Thus, even though the primary driver for the desired motion was the shoulder joint, for the apraxic subject, movements to the medial target were more closely related to the pattern of torques at the elbow: if elbow muscles contributed to produce elbow net torque, errors were large, but if this contribution was small or if elbow muscle and net torques were in opposite directions, the resulting error was small. Note that we could have also drawn our conclusions based on the contribution of elbow interaction torque to elbow net torque. However, we chose to focus our conclusion on the contribution of elbow muscle torque to elbow net torque because we interpret muscle torque as being under the influence of descending neural commands and accounting for changes in interaction torque (Sainburg, Ghilardi, Poizner, & Ghez, 1995).

To test the consistency of the observation that elbow muscle torque influences initial movement direction across all apraxic subjects, we regressed initial movement direction with the contribution of elbow muscle torque to elbow net torque. Fig. 7A–C show this regression for our representative subjects from the healthy control, non-apraxic and apraxic groups, respectively. For our healthy control (Fig. 7A) and non-apraxic (Fig. 7B) participants, initial movement direction was not predicted by muscle activity at the elbow joint. However, for the apraxic subject (Fig. 7C), we observed a strong relationship between these variables, suggesting that the direction of the trajectory at the beginning of the movement was closely tied to muscle torque at the elbow. When elbow muscle torque contributed minimally or countered the action of the elbow net torque (negative values on X -axes), the resulting initial direction errors were small, and close to those of the control and non-apraxic subjects. However, if elbow net torque was produced by the action of elbow muscles, as reflected by the positive values of the X -axes, large errors in initial movement direction were observed. This effect was robust across all subjects as evidenced in the normalized z value plot of this regression across all subjects (Fig. 7B). This was statistically confirmed with a significant main effect of group ($F_{2,33} = 11.3110$, $p = 0.0002$). Post-hoc tests indicated a significantly larger normalized z for our apraxic group relative to both, the healthy control ($p = 0.0001$) as well as the non-apraxic ($p = 0.0039$) groups. Thus, the apraxic group showed significantly more variable movements that were associated with irregular joint torque patterns across multiple trials, especially at the elbow joint.

In summary, our findings indicate substantial deficits in the movements of apraxic patients. Not only were their movements slower, but they also showed a large variation in how movements were initiated. These deficits were associated with an inability to specify qualitatively and quantitatively similar joint torque patterns across multiple trials, particularly during the early phase of movement.

4. Discussion

We hypothesized that deficits in ideomotor limb apraxia evident during movements made in response to visual stimuli are reflective of impaired transformation processes that convert extrinsic visual information into intrinsic motor commands that specify the dynamics

required to produce the desired motion. We therefore predicted that apraxic patients would show deficits during simple visually targeted reaching, and that these deficits would be magnified as the dynamic requirements of the task increased. In this study, healthy control subjects and non-apraxic and apraxic left hemisphere damaged patients reached to three targets that varied in the degree of interjoint coordination required. Apraxic patients failed to consistently *initiate* their motion in the direction of the target and as a result, showed large initial direction errors and greater trajectory curvature. These deficits were the largest for the target requiring maximum shoulder and elbow coordination, and were associated with impaired specification of intersegmental dynamics.

While the task and some of the analyses used in the current study are similar to our recent paper (Schaefer et al., 2009b) it is important to emphasize that our recent work has investigated differences in performance following left or right hemisphere stroke, without explicit reference to any hemisphere-specific clinical syndromes such as ideomotor limb apraxia. Thus, while this study uses methods similar to those previously utilized by our group, the question examined in this study is completely novel relative to our recent research reports. Moreover, the kinematic and kinetic analyses used in this manuscript bridge a large gap in the apraxia literature associated with the knowledge about behavioral manifestations of the disorder and the neural mechanisms that give rise to the behavioral deficits. Thus, it is the use of these methods that has enabled us to describe the potential mechanisms that give rise to spatiotemporal deficits seen in ideomotor apraxia and to demonstrate that these deficits are not isolated to object-use movements and other highly learned actions.

Poizner and colleagues (Clark et al., 1994; Poizner et al., 1995, 1990) first quantified intersegmental coordination deficits kinematically in apraxic patients. However, because they did not include non-apraxic left hemisphere damaged patients, it could not be conclusively determined whether these deficits were related to apraxia or left hemisphere damage in general. Moreover, these studies did not address the underlying cause of the observed kinematic deficits. Our study is the first to our knowledge that uses inverse dynamic analyses to examine the kinetic basis of the deficits seen in apraxia. We show that the large initial direction errors were related to poor control of intersegmental dynamics, such that for the apraxic patients, when movements required primarily shoulder motion, initial movement direction was predicted by action of the elbow muscles. The fact that these deficits occurred early (by the time of peak acceleration) in the movement is consistent with the notion that they are related to impaired movement planning. Movement patterns up to the time of peak acceleration have been shown to be good indicators of movement planning processes. Support for this idea has come from studies in healthy individuals showing that the amplitude of the initial acceleration pulse scales with the intended movement distance and is resistant to changes in peripheral feedback prior to and during movement onset (Gordon & Ghez, 1987; Sainburg & Schaefer, 2004). In addition, studies have shown that the earliest changes in electromyographic activity occurs ~30 ms following changes in sensory input through the application of a perturbation (Evarts & Tanji, 1974, 1976; Ghez & Shinoda, 1978). Because of an additional ~30 ms excitation-contraction delay (Della-Santina, DeAngelis, & Lehman, 1989; Mutha, Boulinguez, & Sainburg, 2008), changes in muscle force and acceleration due to changes in sensory feedback require at least 50–60 ms, roughly the time of peak acceleration from movement onset. Thus, the errors observed at or before peak acceleration in our apraxic patients reflect inadequacies in their planning of the desired motion. Moreover, these deficits were associated with impaired coordination of intersegmental dynamics, which have been shown to be largely dependent on feedforward control processes (Gribble & Ostry, 1999; Sainburg, Ghez, & Kalakanis, 1999).

Buxbaum and colleagues have also suggested that apraxic deficits arise from impaired planning. However, their studies have primarily emphasized planning based on previously

stored representations of object-related actions (Buxbaum et al., 2005, 2007, 2003; Jax, Buxbaum, & Moll, 2006). In one such study, they (Buxbaum et al., 2005) required subjects to specify by pressing a button, which end of certain objects their thumb would contact if they were to reach out and grasp the objects. This task presumably involves planning of the grasp even though its overt execution is not necessary (Johnson, 2000; Johnson et al., 2002). These authors showed that apraxic subjects made more errors when making judgments about hand postures, compared to when they were asked to actually execute the same motion, and suggested that this deficient planning was related to a disruption in representations of object-related hand postures. Similar to Roy and Square's (Roy & Square, 1985) model, Buxbaum and colleagues have classified such deficits as "representational ideomotor apraxia", and have distinguished them from deficits arising primarily due to impaired execution of movements ("dynamic ideomotor apraxia"). Further, these authors have suggested that patients exhibiting dynamic apraxia are deficient in "spatiomotor coding", i.e. specifying the positions of body parts relative to each other ("intrinsic coding"), or relative to external visual stimuli (e.g. external objects, "extrinsic coding"), a process emphasized to develop "online" and combined with previously learned representations, based on task demands (Buxbaum, 2001; Buxbaum et al., 2007).

Our results are consistent with the idea of impaired transformation of extrinsic visual information into an intrinsic coordinate frame to specify dynamic variables to produce the desired motion. However, in contrast to Buxbaum's view that these processes emerge online and are related to movement execution, we argue that such transformations are part of the movement planning process. This notion is consistent with the large body of research that has suggested that the planning of a movement to visual targets involves multiple stages (see Sarlegna & Sainburg, 2009 for a review). First, the spatial location of the target is remapped from extrinsic to body (eye, head or shoulder) centered coordinates (Carrozzo, McIntyre, Zago, & Lacquaniti, 1999; McIntyre, Stratta, & Lacquaniti, 1997). This information is then combined with hand position information (Bagesteiro, Sarlegna, & Sainburg, 2006; Sober & Sabes, 2005; Vindras, Desmurget, Prablanc, & Viviani, 1998) to plan the movement as a vector with an amplitude and direction in extrinsic space (Gordon, Ghilardi, & Ghez, 1994; Vindras & Viviani, 1998). Ultimately, this kinematic plan is transformed into variables specifying muscle forces or joint torques required to produce the desired kinematics (Sarlegna et al., 2009; Sarlegna & Sainburg, 2007, 2009). Errors in this transformation process have been shown to adversely affect movement planning (Schlicht & Schrater, 2007; Sober & Sabes, 2005; Soechting & Flanders, 1989). More recent evidence has suggested that performance deficits due to such inadequate sensori-motor transformations are larger for movements requiring greater intersegmental coordination (Sarlegna et al., 2009). In our study, apraxic patients showed the greatest initial directional errors when moving to the medial target, and these errors were associated with impaired specification of joint torques during the beginning of the movement, prior to the time that sensory feedback could impact movement patterns. This pattern of results suggests that the deficits in the apraxic patients were a consequence of impaired planning associated with an inability to transform external visual information of target location into the appropriate neural commands that predict accurate task-specific dynamics, although which exact stage of the visuomotor transformation process is impaired cannot be conclusively determined from the current data.

Importantly, despite clear difficulty initiating their movement, our apraxic patients were able to reach the target accurately. Final position errors, as well as directional variability at the end of movement, were comparable across all three groups. This suggests that apraxic patients were able to correct their trajectory online in order to bring their arm to the target. Because visual feedback of hand position was occluded during the trial, these corrections reflect an intact ability to utilize proprioceptive feedback that evolves during the course of

motion to modify the ongoing trajectory. This result is consistent with other studies that have shown that errors made by apraxic patients are reduced when increased feedback is available, such as increased tactile feedback when actually manipulating or grasping objects (Buxbaum et al., 2005) or vision of the arm when reaching (Haaland et al., 1999). In fact, this intact capability might also explain why a patient whose characteristics matched the “dynamic apraxia” definition as described earlier, made no final position errors when reaching to a visual “slot” (Buxbaum, Giovannetti, & Libon, 2000). While these authors emphasized that this patient had intact “extrinsic coding” and was therefore able to place the hand correctly relative to the target, they did not analyze the trajectory of the hand while reaching to the slot. Our results show that trajectory deficits associated with impaired visuomotor transformations occur early during the movement and final position errors are small, consistent with poor planning, but intact online control of final position.

The deficits in planning trajectory, but not online control of final position in our apraxic group are consistent with studies that have advocated that these processes are mediated by distinct neural mechanisms (Ghez, Scheidt, & Heijink, 2007; Krakauer, Pine, Ghilardi, & Ghez, 2000; Kurtzer, Herter, & Scott, 2005; Scheidt & Ghez, 2007). Previous results from our laboratory have suggested that these processes might in fact be lateralized in different hemispheres of the brain (in right handers): the left hemisphere appears to be specialized for controlling trajectory features through anticipatory mechanisms, while the right hemisphere appears to be specialized for feedback mediated control of final position (see Sainburg, 2005 for a review). We have recently shown that following unilateral stroke, left but not right hemisphere damage produces deficits in the control of trajectory features of a movement, whereas right but not left hemisphere damage produces errors in final position accuracy (Schaefer, Haaland, & Sainburg, 2007; Schaefer et al., 2009a, 2009b). Given this left hemisphere specialization for feedforward control and other research emphasizing the role of the left hemisphere for storing movement representations, it is not surprising that movement planning deficits in apraxia are more commonly seen after left hemisphere damage. However, the novelty of the current results is the finding that the deficits seen in the apraxic group are not simply a general consequence of left hemisphere damage, but are rather related to impairment of specific processes within the left hemisphere. Although our non-apraxic patients also had left hemisphere lesions, they did not show the initial direction deficits seen in our apraxic group. Thus, these findings significantly expand our current understanding of the neural mechanisms that underlie the deficits seen in apraxic patients. These limitations in planning for our apraxic patients are reflective of visuomotor transformation deficits and most likely related to the larger degree of left parietal involvement in this group (see Section 4.1). Further, it is also plausible that our apraxic subjects relied on their intact right hemisphere’s final position control mechanisms in order to accurately reach the target location. This might also explain why others have observed more accurate responses in left hemisphere damaged apraxic patients under conditions of enhanced feedback.

4.1. Neural correlates

Goodale and Milner (Goodale & Milner, 1992) reworked the early proposal by Ungerleider and Mishkin (1982) of a dual pathway model for goal-directed actions. According to this scheme, a ventral pathway from primary visual areas to inferotemporal cortex underlies the recognition of objects, whereas a dorsal pathway from the same visual areas to posterior parietal cortex mediates the control of object-oriented actions. Converging evidence has shown that this dorsal pathway is also activated when pictures of tools are shown (Chao & Martin, 2000), suggesting a key role of these circuits in the representation of object-function. Accordingly, Buxbaum and colleagues have emphasized left inferior parietal regions as the site for object-related action representations (Buxbaum et al., 2005, 2007,

2003). However, other studies attempting to differentiate between imitation of meaningful object-related movements and meaningless movements, although based on very small sample sizes, have implied that the dorsal portion of the angular gyrus along with memory-related structures, such as the hippocampus, might form the substrate for representations of meaningful movements (Tessari et al., 2007). Further, studies of mirror neuron systems have also implicated inferior frontal brain circuits in the neural basis for stored knowledge of actions (Grafton, Arbib, Fadiga, & Rizzolatti, 1996; Iacoboni et al., 1999; Rizzolatti et al., 1996). The differential role that each of these areas plays in the storage and retrieval of stored representations of skilled movements remains unclear.

It is important to also note however, that the same brain areas are critical during other actions, suggesting that the role of these areas might not be limited to storing or retrieving knowledge of highly skilled movements. For example, Kolb and Milner (1981) showed that left parietal regions are critical for the imitation of meaningless arm movements, a result consistent with several other studies (Muhlau et al., 2005; Peigneux et al., 2000; Rumiati et al., 2005; Tanaka & Inui, 2002; Tessari et al., 2007). Previous theoretical models (Rothi et al., 1991) and newer experimental results (Tessari et al., 2007) have suggested that such actions might be based upon a “direct route” involving transformation of the visual input into task specific dynamics. This view agrees with the large number of studies that have emphasized a critical role of posterior parietal regions in this visuomotor transformation process from extrinsic to intrinsic reference frames during visually targeted movements (see Buneo & Andersen, 2006; Fogassi & Luppino, 2005; Jackson & Husain, 2006 for reviews). Our current experimental results and the lesion characteristics of our patients are consistent with this suggestion. Relative to our non-apraxic patients, a larger number of apraxic patients had lesions in superior parietal (Brodmann Area 7) and inferior parietal regions (angular gyrus, Brodmann Area 39 and supramarginal gyrus, Brodmann Area 40) and showed movement deficits consistent with impaired visuomotor transformation processes. These results must be interpreted with some caution however, because lesion overlap images, as used in the current study, do not provide a clear-cut association between area of damage and observed deficits (Karnath, Himmelbach, & Rorden, 2002). While other techniques such as lesion subtraction between the two patient groups would have provided a more direct assessment of the relationship between areas uniquely damaged in the apraxic group and their deficits, our aim in the current study was to focus on the kinematic and dynamic deficits seen in the apraxic patients and address the potential underlying mechanism rather than focus on the detailed neuroanatomical correlates of apraxia. Nevertheless, the parietal involvement and the nature of the deficits seen in our apraxic patient groups provide preliminary support to the idea that the deficits revealed in this study might be associated with damage to parietal regions.

Finally, it is critical to emphasize that our results do not imply that deficits in apraxia cannot arise from damaged representations of skilled actions, or that visuomotor transformation mechanisms are not recruited during these skilled movements. Rather, it is our view that visuomotor transformation processes operate in parallel or downstream to mechanisms for representation of object-related and other highly learned actions.

Acknowledgments

We would like to thank Jennifer Hogan and Lee Stapp for data collection; Dr. Robert Knight for MRI tracings; Drs. John Adair and Sally Harris, and HealthSouth Rehabilitation Hospital and Lovelace Medical Center for patient referral.

Funding: This work was supported by the Department of Veterans Affairs Medical Merit Review and Rehabilitation Research and Development Merit Review (B4125R) grants to K.Y.H. and the National Institutes of Health (NICHD) grant (R01HD39311 and R01HD059783) to R.L.S.

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Fig. 1. Experimental setup. (A) Lateral view of the experimental apparatus. Subjects sat facing a mirror onto which the start position and targets were projected using a back projection screen, and rested their arms in an air-sled system placed on a glass tabletop. (B) Top view of the setup showing the air sled, attachment of the FOB sensors on the subject's arm and a typical screen display. The mirror has been "removed" for display purposes.

Fig. 2.

Lesion overlays. Lesion locations based on MRI or CT scans were superimposed on axial slices separately for the apraxic (top) and non-apraxic (bottom) groups. Colors of the shaded areas denote the percentage of patients in each group with a lesion in the corresponding area.

Fig. 3. Task performance. (A) Mean shoulder to elbow joint excursion ratio, (B) mean reaction time, (C) mean movement time, (D) mean peak velocity and (E) mean final position error for the lateral (L), center (C) and medial (M) targets for each group (control, non-apraxic and apraxic). Bars indicate standard error of mean.

Fig. 4.

Movement trajectory. (A) Handpaths for each trial of a session for a representative subject from each group. Trials are separated by lateral (L), center (C) and medial (M) targets. (B) Mean initial direction error and (C) mean handpath curvature for each group separated for each target. Bars indicate standard error of mean.

Fig. 5. Movement variability. (A) Finger positions at peak acceleration (●), peak velocity (+) and movement end (○) for each trial for our representative subjects from each group for movements made to the lateral (L), center (C) and medial (M) targets. (B) Mean variable direction error collapsed across targets for each group (healthy control, C; non-aprasic, NA; and apraxic, A) at peak acceleration, peak velocity and movement end. Bars indicate standard error of mean.

Fig. 6.

Inverse dynamics. (A) Handpaths for two trials to the medial target are shown for the same representative subject as in earlier figures. These handpaths are for trials with the largest negative (black) and positive (gray) initial direction errors. (B) Net (thin line), muscle (thick line) and interaction (dotted) torque profiles for the shoulder (top) and elbow (bottom) joints for movements with the largest negative error (black handpaths in A). (C) Torque profiles for movements with the largest positive error (gray handpaths in A). Torque data is shown for the first 200 ms of movement.

Fig. 7. Prediction of initial movement direction. Initial movement direction plotted as a function of initial elbow muscle torque contribution to net torque for our representative subjects from the control (A), non-apraxic (B) and apraxic (C) groups for movements made to the medial target. (D) Mean normalized z score for the regression across all subjects in each group. Bars indicate standard error or mean.

Table 1

Summary of participant information.

Subject	Age (years)	Education (years)	Post-stroke (years) ^a	Lesion volume (cm ³) ^b	Language comp. ^c	UE Fugl-Meyer ^d	Right arm grip strength ^e	Apraxia score ^f
Apraxic group								
1	44	14	7.0	147.2	46	22	0	10
2	69	20	8.8	86.3	80	62	50	11
3	61	14	17.2	125.2	66	27	12	11
4	59	16	7.0	187.1	30	59	36	11
5	81	18	1.9	39.7	80	57	53	10
6	55	14	0.7	24.1	44	10	0	9
7	76	12	12.0	114.3	80	33	14	11
8	69	18	1.5	32.5	80	56	32	10
9	70	13	0.6	43.3	80	57	43	8
Mean ± SD	64.9 ± 11.3	15.4 ± 2.7	6.3 ± 5.8	88.8 ± 58	65.1 ± 19.8	42.5 ± 19.56	26.6 ± 20.6	10.1 ± 1.0
Non-apraxic group								
1	68	18	18.6	78.4	80	65	61	14
2	60	14	16.8	28.8	80	45	12	14
3	46	17	5.1	152.9	80	61	27	14
4	71	14	2.5	13.4	80	65	68	14
5	64	12	10.8	177.0	60	64	48	12
6	69	18	1.0	14.0	80	52	25	13
7	71	8	0.5	17.9	80	43	38	13
8	68	18	0.6	12.5	80	57	40	15
9	65	15	1.0	1.7	80	50	35	15
Mean ± SD	64.6 ± 7.8	14.9 ± 3.3	6.3 ± 7.2	55.1 ± 66	77.7 ± 6.6	55.7 ± 8.6	39.3 ± 17.6	13.7 ± 0.97
Healthy control group								
Mean ± SD	63.6 ± 8.7	15.1 ± 2.3	N/A	N/A	79.5 ± 1.9	N/A	49.6 ± 6.5	13.3 ± 1.2

^aYears post-stroke are calculated as time between incidence of stroke and day of data collection.

^bLesion volume is computed from MRI or CT.

^cLanguage comprehension was assessed using the Western Aphasia Battery.

^dMaximum upper extremity (UE) motor subscore of the Fugl-Meyer Motor Assessment is 66.

^eGrip strength from dynamometer is expressed as a standardized *t*-score.

^fApraxia is designated as mean number correct out of 15 items using a validated apraxia battery.