Measurement of Reaching Kinematics and Prehensile Dexterity in Non-Human Primates

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Abstract

A modified “Kluver” or dexterity board was developed to assess fine control of hand and digit movements by non-human primates during the acquisition of small food pellets from wells of different diameter. The primary advantages of the new device over those used previously include standardized positioning of target food pellets and controlled testing of each hand without the need for restraints, thereby allowing the monkey to move freely about the cage. Three-dimensional video analysis of hand motion was used to provide measures of reaching accuracy and grip aperture, as well as temporal measures of reach duration and food-pellet manipulation. We also present a validated performance score based on these measures, which serves as an indicator of successful food pellet retrieval. Tests in three monkeys show that the performance score is an effective measure with which to study fine motor control associated with learning and handedness. We also show that the device and performance scores are effective for differentiating the effects of localized injury to motor areas of the cerebral cortex.
Introduction

Tasks that have been commonly used to gain insight into control of dexterous hand and finger movements usually involve a monkey removing food from wells in a "Klüver" or "Brinkman board" (Friel et al. 2005; Lehman 1978a; 1980; Liu and Rouiller 1999; Nudo et al. 1996b; Schmidlin et al. 2005) or threading food samples over shaped rods (e.g., (Darling et al. 2006; Gash et al. 1999)). These tasks are often used in studies investigating issues related to hemispheric dominance or motor recovery following experimentally induced brain lesions. Pioneering designs of such tasks by Heinrich Klüver initially required animal subjects to use two hands for successful retrieval of the food pellet (Klüver 1935), but later revisions involved the use of only one hand to acquire food morsels from a simple paddle board with wells of equal size and depth arranged in a 4 X 3 matrix (Glees 1961; Glees and Cole 1952). Subsequent modifications of this simple dexterity board have varied over the years, in terms of the number of target wells available, specific diameter and depth of the wells (Brochier et al. 1999; Friel and Nudo 1998; Kermadi et al. 1997; Lawrence and Kuypers 1968; Nudo et al. 1992; Nudo and Milliken 1996) and the vertical versus horizontal orientation of slots into which food is placed (Mason et al. 1998). The success/failure rates and temporal measures are the most commonly recorded parameters, although video measures related to the number of finger flexion motions during grasping of the food morsel have also been recorded in a recent study (Friel et al. 2005).

In early work, the dexterity board was presented directly to the subject in the cage, without allowing control over reach distance or requiring consistent use of the desired limb (Cole 1952; Cole 1953; Glees and Cole 1952). Because monkeys exhibit
less hand dominance than humans (Lehman 1978a; 1980; 1978b), it is difficult to ensure repeated reaches with a specific limb in freely-moving monkeys without some type of restraint, such as a jacket to prevent use of one limb (Friel et al. 2005). This is especially important when considering studies of recovery from brain lesions, when it is necessary to study movements by the limb contralateral to the lesioned hemisphere. The use of such restraints requires anesthesia for placement of the jacket on the subject and its presence may also induce stress and attentional distractions.

In this report, we present a novel dexterity board apparatus that controls for reach distance and task difficulty while permitting the study of repeated limb use. Importantly, our method minimizes restrictions and training time of the animal. Furthermore, we have developed and validated a performance score that can be used to quantitatively assess hand motor performance during the acquisition of small food pellets. This score is based on the transport phase (reach duration, accuracy), grip preparation (finger-thumb aperture) and manipulation phase (manipulation duration and number of separate contacts of digits with the food pellet).

**Methods**

Experimental Animals

Three adult rhesus monkeys (Macaca mulatta) were subjects in these experiments. The monkeys were housed, cared for, and maintained in a United States Department of Agriculture (USDA) approved and inspected facility. All behavioral and surgical protocols were approved by the University of South Dakota (USD) Institutional Animal Care and Use Committee (IACUC), and conducted in accordance with National Institutes of Health and Society for Neuroscience guidelines for the ethical treatment of
experimental animals. Prior to enrollment in the study, each monkey was evaluated by a primate veterinarian and judged to be healthy and free of any physical or neurological deficit.

Experimental Apparatus

At present the “Kluver Board” or dexterity board remains a preferred apparatus for testing fine motor abilities of the upper extremity (Kermadi et al. 1997; Mason et al. 1998; Nudo et al. 1992; Nudo and Milliken 1996). A typical dexterity board is a square Plexiglass platform with four tapered wells of different diameter (A - 10 mm, B - 13 mm, C - 19 mm and D - 25 mm) routed (1 cm deep) into the surface, for the purpose of target food-pellet placement which induce the monkey to reach and grasp. Different levels of fine-digit motor control are assumed to be required depending on the size of the well. The board is attached to the animal’s cage and, after pellet placement into one of the wells or onto the flat surface of the platform, a small portal door is opened allowing the monkey to reach with either hand to acquire the food pellet. This is a simple task for monkeys to learn because they are reaching directly for food rather than being rewarded for performing a movement to a target presented on a visual display.

We modified the general design of the dexterity board to permit the controlled study of reaching (by each hand) to the same target locations (Fig. 1). The food pellet ‘targets’ were positioned directly in front of the left or right portal opening depending on the hand studied (Figs. 1A-B, 2). The modified device has a circular plate containing four wells of the same size as in the original design (wells A-D) plus a small 0.2 mm deep “well” (well E) to hold the pellet in place without interfering with grasping (Fig. 1 B).
The plate was rotated about a vertical axis with the well centers arranged in a circle with a radius of 4.7 cm about the axis. The rotating plate design is similar to that used in recent studies by Nudo and colleagues (Friel et al. 2005). However, our device differs in that it accommodates the larger subjects used in our studies, and the rotation of the well plate is not motorized. The rotating platform was centered in front of the two portal openings on a horizontal platform such that the wells and food pellets were always placed in the same location in front of the limb to be tested. A spring-loaded locking mechanism ensures consistent placement of the desired well in the appropriate location, for access through the portal of choice (Fig. 2). Finally, the location of the rotating plate relative to the cage front was adjustable so that the plate could be moved closer to the cage for animals with short arms (see single arrowhead in Fig 1 B) and further away for animals with long arms (see double arrowhead in Fig. 1 B). Once this location was determined for a given monkey, it was used throughout all pre and post lesion tests.

The modified dexterity board is attached to the primate cage with rigging and clamps that ensure consistent placement of the board in the front and center region of the cage. This positioning equally accommodates both right and left hand movements, such that each well can be presented at the same location relative to the respective portal (Fig. 1 A). To permit study of reaching by each hand without any restraints placed on the animal (so that it could freely move within the cage), a Plexiglass portal tube, or chute, angled slightly (e.g., 20°) from the portal door toward the center of the cage was developed (Fig. 1 C-see arrow; Fig. 1 D-E). The rotational position of the portal tube is adjustable in 10° increments, to accommodate the natural reaching angle of each animal (Figs. 1E, 2). Once the rotational angle of the chute was established for a given animal, it
was used throughout all pre and post lesion testing sessions. Importantly, if an animal reaches through the portal tube with the “wrong” hand, it is unable to reach the food pellet because the required upper limb configuration cannot be attained due to spatial constraints on elbow motion. However, the portal tube exerts little constraint on reaching with the correct hand. The monkeys in our study thus quickly learned to use the correct limb, depending on which portal door was opened by the investigator. This element was critical during post-lesion tests because injured animals will often defer to the unaffected limb when given the choice, even when it has the capacity to accomplish the task with the affected limb. Therefore, “arm choice” was eliminated from the experimental paradigm and valuable information was collected from the affected limb.

Digital Video Acquisition

Movements of the reaching hand were recorded using four digital video cameras interfaced with the SIMI Motion data acquisition package (SIMI Reality Motion Systems, Unterschleissheim, Germany). The cameras (Basler, model A602fc) were connected to a personal computer (Dell Precision Workstation 650) via standard PCI Firewire (IEEE 1394)-based interfaces. Each camera was powered by the Firewire bus and operated at 100 Hz. The digital video from each camera was automatically synchronized with the SIMI software and streamed directly to independent hard drives. Video resolution from each camera was 656 X 492 pixels, which is adequate to employ standard digitizing procedures.

A custom-built (16 cm X 16 cm X 23 cm) rigid frame (Fig. 1 F) constructed of ½-inch welded rectangular tube steel was designed to calibrate the space through which the
monkey’s hand moved to acquire the pellets. To validate the frame, the relative locations of 41 marked points on the frame were measured using an Optotrak 3020 system (Northern Digital) with its handheld digitizing probe. The probe, with its 6 coplanar mounted IREDs, was sequentially moved to each marked point to determine its relative position. This procedure was repeated 5 times and the average 3D locations of the points were used to compute the locations of each marked point on the frame. These known point locations on the frame were subsequently used to construct a calibrated volume for each experimental session. Prior to experimental data collection, a calibrated volume of the space that spanned the range of possible hand locations during the reaching/grasping movements was acquired to permit three-dimensional (3D) reconstruction of hand and digit movement kinematics from the digital video. The calibration frame construction and its use during experimental procedures are required procedures for any kinematic reconstruction from video (Allard et al. 1995).

Video segments of the calibration frame within the space used for the experiments were recorded using the SIMI system for each side of the USD Dexterity apparatus (right and left) prior to each experimental session and when disruptions in the testing field occurred (e.g., if a camera moved). Direct linear transformation algorithms from the SIMI data collection software system were used to calibrate the camera fields and compute 3D coordinates of landmarks on the monkey’s hand as it moved through the calibrated volume.

Video data collection began when the portal door was opened and continued until the pellet was retrieved into the cage, the pellet was knocked off of the platform, or the
60 s time limit had expired. Video collection was manually triggered and single trial video clips were manually created and verified.

Behavioral Procedures

Prior to an experimental session the monkey was food restricted for 18-24 hours. The initial training and testing sessions used the “standard” dexterity board to assess the preferred hand of each monkey (since the monkey could choose to use either hand with this device) as described previously (Nudo et al. 1992). Training and testing with the new, modified device commenced after hand preference was determined.

Full testing sessions included 5 retrievals from each of the wells (A-E) for both limbs, thereby giving the monkey 50 opportunities to retrieve pellets, 25 with each hand. Pellets were presented in the different wells in a pseudo-random order. After a pellet was placed in a well, the portal door on the side of the arm to be tested was opened, allowing the monkey to reach toward the pellet.

Prelesion data were collected every 0.5-3 weeks. The final five prelesion experiments with Case 1 were conducted over a 5-week period, those for Case 2 were conducted over an 11-week period, and those with Case 3 were conducted over a 6-week period. These testing sessions demonstrated relatively stable levels of performance before lesions were made to cortical motor areas (see Results). Post lesion data were collected from both limbs during weekly experimental sessions after the surgery. It was only during these post lesion experimental sessions that subjects had exposure to the dexterity board.
Surgical Procedure

As part of an ongoing research project to study the effects of lesions to frontal cortical motor areas on fine motor control, data were also collected after ictus. The lesions were limited to the arm areas of primary motor cortex (M1) (category I lesion – Case 1 – female, age 20 years); M1 + the adjacent dorsal lateral premotor cortex (LPMCd) (category II lesion – Case 2 – female, age 18 years); and M1 + LMPCd + the supplementary motor cortex (M2) (category III lesion – Case 3 – male, age 9 years) contralateral to the preferred limb (as determined from hand preference testing sessions) (Fig. 3). The lesions were created by subpial aspiration of the arm areas in the respective motor cortices that were localized using intracortical microstimulation.

All surgical procedures were performed using sterile methods. Preoperatively, each monkey was injected with atropine sulfate (.05mg/kg), immobilized with ketamine hydrochloride (10mg/kg), intubated then placed on a mechanical respirator where it was anesthetized with isofluorane inhalation (1.2-1.5%) and a surgical grade oxygen mixture. The monkey was placed into a head holding device and administered mannitol (1.5g/kg) intravenously. A skin incision, bone flap and dural flap was made over the lateral frontal convexity of the hemisphere and the frontal lobe exposed. Following aseptic cortical exposure, the animal was transferred to intravenous ketamine anesthesia for electrophysiological mapping of the frontal motor cortices. Intracortical microstimulation was used to localize the arm areas of M1, LPMCd and M2 (Morecraft et al. 2002; Morecraft et al. 2001; Morecraft et al. 2007). To accomplish this, a tungsten electrode (impedance 0.5-1.5 MΩ) was inserted 200 µm below the pial surface then advanced at 500 µm intervals. Movements were evoked using a train duration of 50 ms and pulse duration of 0.2 ms.
delivered at 330 Hz. Current intensity ranged between 7 and 90 μA. Threshold currents were determined and the evoked movements were recorded when noted by two observers. Digital images were taken of the surgically exposed cortex using a Cannon EOS 20D 8 megapixel digital camera and Cannon EF17-100 lens with an attached Cannon MR-14EX macro ring flash. A high resolution color print was made using a Hewlett Packard 1220C printer and the precise location of each stimulation point was recorded directly on the print of the cortical surface in the operating room. The borders between the somatotopical regions (i.e., face/head, arm and leg) were also marked on the photograph. After defining the location and borders of the forelimb representation(s) the animal was returned to isofluorane anesthesia. Subpial aspiration was then used to remove the gray matter, avoiding regions controlling face/head and leg function. Following resection, the dura was sutured closed and the bone flap replaced and anchored. The galea aponeurotica, temporalis muscle and skin was closed using standard surgical techniques. Each animal was carefully monitored postsurgically throughout the survival period. Buprenorphin (0.5mg/kg) was administered postoperatively for 48-72 hours. Twenty four hours prior to the surgery, and for 9 days post-surgery, each animal was administered amoxicillin as a preparatory and postoperative antibiotic.

Estimation of Lesion Volume

It is well known that injury or removal of brain tissue results in atrophic distortion at the lesion site (see Fig. 3, Case 3, left) as well as distally along fiber pathways originating from the lesion site (Bucy 1964; Denny-Brown et al. 1975; Graham and Landtos 2002; Ho 1982; Warabi et al. 1990). Some of the contributing factors include
tissue collapse (cavitation) and Wallerian degeneration which can negatively impact post
mortem quantification of lesion volumes. To minimize these effects, we superimposed
an outline of the lesion site onto the undamaged hemisphere to estimate the total gray and
white matter volume of the lesion.

The lesion site was initially reconstructed using metrically calibrated digital
photomicrographs of the exposed cortical surface taken immediately before and after the
lesion. The surgical exposure was made large enough so that the photomicrographs
contained important anatomical landmarks such as the central sulcus, arcuate sulcus,
posterior tip of the principle sulcus, superior and inferior precentral dimples, and the
cingulate sulcus. These landmarks assisted with the postmortem reconstruction and
transfer of the lesion site boundaries onto a surface image of the non-lesioned hemisphere
(i.e., Fig. 3, right). These boundaries were then verified by microscopic analysis of
matching tissue sections from the lesioned hemisphere (Fig. 4 A, A’, B, B’, C, C’).

To estimate gray matter lesion volume, the boundaries of the lesion site were then
marked on anatomically matched Nissl stained tissue sections through the non-lesioned
hemisphere (Fig. 4 A”, B”, C”). These boundaries were then traced as closed contours
using Stereo Investigator software (Microbrightfield, Colchester, VT) and an Olympus
BX-52 microscope (Leeds Precision, Minneapolis, MN) equipped with a computer
controlled MAC 5000 motorized microscope stage (Ludl Electronic Products,
Hawthorne, NY). The external boundary of the closed contour was defined as the
external surface of layer I. The internal boundary of the closed contour corresponded to
the actual depth of the lesion in the gray matter field. In regions where all six layers of
cortical gray matter were removed, the internal boundary of the closed contour corresponded to the interface between layers VI and the subcortical white matter.

To calculate the gray matter volume of the lesion, we applied the Cavalieri estimator in the Stereo Investigator software (Microbrightfield, Colchester, VT). This stereological probe estimates the total area and volume of a region of interest (ROI), which in our study was the gray matter volume, in a systematic series of tissue samples (Gundersen and Jensen 1987). This stereological method has been shown to reliably calculate the volume of cortical and subcortical brain structures (Jelsing et al. 2005; van der Worp et al. 2001). The systematic random sample was obtained by omitting the first 50-200 μm of tissue from the rostral tip of the frontal pole during tissue sectioning. This was followed by a systematic collection of serial sections that were 50μm in thickness and spaced 500μm apart. We analyzed every other section yielding a series section interval of 1 in every 20. Thus, the analyzed tissue samples were spaced 1mm apart through the entire lesion. The Cavalieri estimator then placed a rectangular lattice of points spaced 120μm apart over the entire ROI (i.e., the area within the gray matter closed contour in Fig. 4 A’’, B’’, C’’) in each tissue section. The number of points that fell within the ROI was then counted by the software using the marquee mode. After determining the number of points within the closed contours for all tissue sections, the software calculated an estimate of total gray matter area and volume associated with the mapped lesion. A coefficient of error (CE) was then determined by the software based upon the distance between tissue sections in our systematic random sample as well as the shape of the ROI (Table 1). The same general method was used to estimate the white matter lesion area and volume. However, the external boundary of the white matter ROI
coincided with the junctional interface layer VI and the subcortical white matter (Fig. 4 A”, B”, C”, see solid closed contour in white matter). Similarly, the internal boundary of the white matter ROI corresponded to the depth of the lesion as determined from Nissl and myelin stained sections through the lesioned hemisphere.

Video Analysis

Temporal characteristics of reaching, manipulation, and 3D locations of the tips of the index finger and thumb were determined from the digital video files. Event time markers recorded from the digital video included: hand exit from portal; first contact of the USD Dexterity board with the index finger or thumb; first touch of the food pellet; end of the first grasp attempt; end of subsequent grasping attempts; beginning of the return toward cage; and re-entry of hand into cage. Multiple grasp attempts were defined if the monkey lost contact with the pellet and initiated a new grasp attempt (similar to the multiple finger flexions described by (Nudo et al. 1996a)). These were used to compute reach duration (time from hand exit of portal to first contact of dexterity board), duration of first manipulation (time from contact with pellet until pellet is acquired in grasp or contact with the pellet is broken), number of manipulation attempts, and total manipulation duration (time from first contact with pellet until pellet is acquired and hand movement toward cage begins).

The locations of the tips of the index finger and thumb were manually digitized, using the SIMI software, from each camera that had an unobstructed view of the hand and digits. Two camera views of each point of interest are required to reconstruct the 3D location of an anatomical point of interest. There were no external markers placed on the
monkeys’ hands because they would not tolerate them. Thus, investigators digitized anatomical landmarks that could be consistently observed on the finger and thumb tips (e.g., border of nail or a skin marking that were consistently observable at the time of touchdown). We tested for consistency of digitizing using 10 selected trials with a large range of reach accuracies and grip apertures at touchdown. Linear correlation coefficients between the reach accuracy and grip apertures from the digitized points of two digitizers were used to assess inter-rater consistency in digitizing. In some cases, automatic digitizing by pattern recognition software (SIMI), combined with visual confirmation, was used to examine paths of the index and thumb tips throughout the reaching and grasping motion. The digitized locations from each camera were then processed through a direct linear transformation algorithm that constructed 3D position data (x, y, and z) of each anatomical location. From these digitized data, measures of grip aperture (as a measure of finger-thumb coordination during the reach) and distance of finger-tip and thumb-tip from pellet (as measures of reach accuracy) were made from when the finger first touched the dexterity board. These measurements, along with temporal data, were then normalized and used to compute an overall performance score (see below) which provides a relative measure of the monkey’s ability to complete the task on each well.

Performance Score

Performance was assessed by computing a normalized score for each subject based upon the maximum and minimum of each temporal and kinematic measure from individual pre-lesion trials for movements by both hands. We compared performances
across hands, wells, and pre and post-lesion conditions. The measures that contributed to the score include: reach duration (time from cage to pellet or board); manipulation duration (time from initial pellet contact until pellet is acquired or attempt is abandoned); number of ‘contacts’ (defined as 1 + the number of times contact between the digit and pellet is broken during manipulation); accuracy (distance from index finger to pellet at time of contact with the board); grip aperture (distance between the fingertip and thumbtip at time of contact with the board); and whether the trial was a success (pellet acquired and lifted from the board), failure (pellet not acquired), or no attempt (no contact made with pellet or board). We used the index finger to assess accuracy of the reach because all three monkeys first touched and then manipulated the food pellet with the index finger. The lowest performance scores occurred when no attempt was made (i.e., 0) and the highest performance scores occurred when the subject performed with the lowest reach and manipulation durations, highest accuracy (smallest distance between index tip and pellet), smallest grip aperture and fewest numbers of contacts of the digit with the pellet (i.e., 1000 if a single trial had the best score for each component among pre-lesion scores – see equation 1). To ensure discrimination between trials where no attempt was made and where a failed attempt occurred, failed attempts received a minimum score of 50.

\[ PS_t = m_t^* (100^* (Rdur + Gapp + Mdur + Acc + C)) \]  

Where:

\( PS_t \) = performance score on trial t

\( m_t \) = multiplier (0 = no attempt, 1 = failure, 2 = successful retrieval of pellet) on trial t
Rdur = (maximum pre-lesion reach duration – reach duration on trial t) / (maximum – minimum pre-lesion reach duration)

Mdur = (maximum pre-lesion manipulation duration – manipulation duration on trial t) / (maximum – minimum pre-lesion manipulation duration)

Acc = (maximum pre-lesion pellet-index distance at touchdown – pellet-index distance at touchdown on trial t) / (maximum – minimum pre-lesion pellet-index distance at touchdown)

Gapp = (maximum thumb-finger distance – thumb-finger distance on trial t) / (maximum – minimum pre-lesion thumb-finger distance)

C = 1 / (1 + number of times contact is broken between a digit and pellet on trial t)

To assess the validity of the performance scores, we first examined the contribution of each component to the overall performance score using multiple linear regression, and then also compared performance scores with subjective ranking of performances. Nine blinded investigators ranked the performances of ten trials by a single subject for a single well based on video files from a single camera. The ten trials chosen received a range of performance scores from 0 (i.e., no attempt) to 926 (i.e., close to the subject’s best possible performance on that well). A “forced choice” ranking procedure was used such that individual investigators could not rank two trials as equal (i.e., rankings forced to 1 – 10). Rank-order correlation analysis was used to assess the relationship between the scores from individual investigators and the performance score ranks. We also computed a mean ranking of the nine investigators’ scores for each trial and computed a Pearson product-moment correlation coefficient relating the mean rank and performance score.
The PS<sub>t</sub> provides a composite measure of the overall performance for each movement. We also quantified the contributions of the constituent components of reaching and manipulation. The components of the movement reach and manipulation scores are expressed in Equations 2 and 3 respectively.

\[ R_{St} = m_{rr} \times (100 \times (R_{dur} + G_{app} + Acc)) \]  \hspace{1cm} (2)

Where: \( m_{rr} \) = multiplier (0 = no attempt, 1 = dexterity board contacted) on trial \( t \)

\[ M_{St} = m_{r} \times (100 \times (M_{dur} + C)) \]  \hspace{1cm} (3)

Where: \( m_{r} \) = multiplier (0 = no attempt, 1 = failure, 2 = successful retrieval of pellet) on trial \( t \)

Failed attempts received a minimum reach score of 15 and a minimum manipulation score of 25 to ensure discrimination between trials where no attempt was made and where a failed attempt occurred.

Validity and Reliability of Video data

The validity and reproducibility of acquiring kinematic data from the digital videos while using the SIMI software was tested by digitizing points on a mechanical rig. The small rig was constructed of stainless steel, and measures between major landmarks on the rig were determined using high precision calipers (Mitutoyo, Japan). Motion of the rig representing movement of the primate hand within the field of interest was digitally recorded. These recordings were then analyzed independently by two individuals working on the project. Each individual digitized 10 frames from each of six
trials (3 from the left view, and 3 from the right view). In each of the 10 frames, 15 landmark locations on the rig were digitized. Distances between specific landmarks on the rig were calculated (using the SIMI software) for each frame during the motion, and were compared to those measured using the precision calipers.

**Results**

**Validation of the Video Data**

Digitizing by investigators was consistent. When digitizing the rigid frame markers, differences between calculated link lengths made by the investigators were generally within 1 mm of each other. Correlations between the digitized values of the rigid frame markers and the measured distances between markers were very high (r > 0.99) for both investigators. In addition, two investigators digitized the positions of the pellet, fingertip, and thumbtip for computations of reaching accuracy and grip aperture at touchdown. The calculated reaching accuracy and grip apertures for the two digitizers were highly correlated (r > 0.97), on a series of trials from a single primate subject. Reliability of digitized data was ensured by having the same investigator digitize all data for a specific primate subject. Examples of 3D recordings of the fingertip and thumbtip paths for two movements are shown (Fig. 5). The initial paths for the two movements are nearly identical, with the finger and thumb tips moving in a curved path from the cage to the target. It is possible that the angled chute inside the cage necessitated some manipulation of shoulder/elbow kinematics that prevented a straight path to the target. The finding that grip aperture (distance between fingertip and thumb increased after the
hand exited the cage and then decreased as the target was approached, a characteristic of human reach-to-grasp movements (e.g., (Chieffi and Gentilucci 1993)), was observed.

Validation of the Performance Scores

Subjective rankings of the ten sample trials by the nine investigators were highly correlated with the objective performance scores, thereby providing evidence for the validity of the score. Spearman rank-order correlation coefficients for the relationship between subjective and performance score rankings ranged from 0.58 – 0.98 (all p < 0.05; mean r after Z-transformation = 0.91) for the nine investigators. The average rankings by the nine investigators were highly correlated with the performance scores (Fig. 6, Pearson r = 0.97, p < 0.05). In contrast, individual measures of reach duration, accuracy, manipulation duration, number of attempts, and overall duration were only weakly correlated with the performance score (r range = -0.31 to -0.52).

Estimation of Lesion Volume

The area and volume of gray (Table 1) and white (Table 2) matter lesions increased as a function of the number of motor areas involved in the lesion increased. The category II and III gray matter lesions were respectively 3 and 4 times larger than the volume of the category I lesion (Table 1). The volume of damaged white matter increased by similar proportions with lesion category. Importantly, the coefficients of error (CEs) for the volumes were extremely low for the gray matter lesions (i.e., less than 2 mm$^3$ in each case) reflecting a consistent and valid assessment of gray matter lesion area and volume.
CEs were larger for the white matter lesions because some sections showed no white matter damage and were therefore omitted from the calculations.

Microscopic evaluation of the tissue sections through each lesion demonstrated extensive removal of the cortical gray matter including layers I to VI through the main body of the lesion. At some edges of the gray matter lesion, the depth gradually diminished where the lesion only involved the supragranular layers (i.e., layers I-III) (Fig. 4 A’, A’’, B’, B’’). The M2 lesion involved all cortical layers on the medial wall of the hemisphere but spared the cortex lining the upper bank of the cingulate sulcus (Fig. 4 C’’).

In terms of white matter, the lesion in Cases 1 and 2 involved minimal parts of the subcortical white matter that was restricted primarily to the adjacent fiber bed located immediately below layer VI. The adjacent fronto-occipital fasciculus and the superior longitudinal fasciculus (area SLF II of Schmahmann and Pandya 2006) were completely spared in both cases. In Case 3, the lesion to LPMCd and M2 resulted in damage involving the adjacent fiber bed located below layer VI. In this case there was additional involvement of the dorsal part of the superior longitudinal fasciculus (area SLF I of Schmahmann and Pandya 2006) which contains fibers emerging from and ending within the frontal areas ablated. However, the adjacent fronto-occipital fasciculus and part of the superior longitudinal fasciculus underlying the lateral surface of the hemisphere (area SLF II of (Schmahmann and Pandya 2006)) were spared. In general, all lesions resulted in some tissue distortion and collapse with the most severe lesion (category III – Case 3) demonstrating the most extensive evidence of cavitation (Fig. 3, bottom left; Fig. 4 C-
Microscopic inspection also revealed complete sparing of all subcortical gray matter structures such as the underlying basal ganglia.

Kinematics of Reaching

The monkeys participated in training sessions to learn to use the “standard” dexterity board prior to handedness testing. A single session introduced the subjects to the modified dexterity board before the start of formal testing. As subjects became familiar with the task over the 6-16 week pre-lesion time period, performance scores tended to increase and/or became less variable (Fig. 7, pre-lesion data) due to improvements in the score components (e.g., decreased and less variable reach and manipulation durations, etc.). For the data from case 1 in Fig. 7, the average pre lesion scores for well B increased about 30% (i.e., from about 500 at experiment -9 to about 650 at experiment -3) over the testing period. Also observed was a concomitant decrease in variability. In contrast, for the smaller well A the initial scores (experiment -9) were much lower (about 250) and less variable (due to floor effects because all attempts were unsuccessful). Average scores almost doubled to 450 at the last pre-lesion experiment, but variability increased. Scores were much lower for well A than well B even after 9 sessions primarily because of a greater number of contacts between the index and pellet resulting in higher manipulation durations.

Each subject demonstrated better retrieval skills on at least one of the five test wells with the preferred limb, as determined by a high performance score and low trial-to-trial variability. We quantitatively determined the best well for each subject to be the one for which the ratio of average performance score to variability (S.D. of performance
scores) was highest in the last 5 pre-lesion experiments. On this measure, Cases 2 and 3 performed best with the preferred hand on well E (Fig. 8). In contrast, Case 1 performed best on well D (Fig. 8). Case 1 also performed almost equally with the non-preferred hand on well C (ratio = 7.7 – Fig. 8). Surprisingly, Case 3 performed much better with the non-preferred than with the preferred hand on wells C and D. Not surprisingly, the poorest performances were consistently on the smallest well (A).

Larger lesions of cortical arm motor areas produced greater initial deficits in contralesional hand reaching and manipulation followed by progressive recovery. A category I lesion limited to the M1 arm area caused no attempts on wells A and B (Fig. 7) and decreased overall performance scores on the best well (Fig. 9 A) due to lower reach and manipulation scores at one week post-lesion (Fig. 10 A, A'). This finding was followed by recovery of reach and manipulation scores to pre-lesion levels by four weeks post-lesion for the best well (Fig. 10 A, A'), but performance on the smaller wells (A, B) only recovered to 1/3-1/2 of pre-lesion performance scores. In contrast, category II (M1 + LPMCd) and category III (M1 + LPMCd + M2) lesions resulted in no attempts to retrieve the food pellet at week 1 and a more variable recovery (Fig. 10 B, B’). Unsuccessful attempts to acquire food pellets associated with low reach and manipulation scores occurred on week 2 post-lesion in the category II lesion case (Fig. 9B, 10B). This was followed by the reach scores improving to pre-lesion levels by week 3 and manipulation scores continuing to improve over post-lesion weeks 3-5. The monkey that received the category III lesion made very few attempts to acquire the food with the contralesional hand on weeks 2 and 3 post-lesion (performance scores were zero on the best well - Fig. 9 C, 10 C). During weeks 4 and 5 performance scores improved and approached pre-
lesion levels (Fig. 9 C). A similar pattern was observed in the reach and manipulation scores for this monkey (Fig. 10 C, C’). Overall, these data show that the performance, reach and manipulation score measures are sensitive to lesion volume and differentiate recovery of gross (reach score) and fine (manipulation score) motor skills.

Ipsilesional hand movements were also affected by lesions of cortical motor areas, but in a more variable manner. The lesion limited to M1 produced very small reductions in ipsilesional hand performance (Fig. 9 A) and reach scores (Fig. 10 A). Manipulation scores for this monkey were slightly lower but demonstrated large variability as in the pre-lesion experiments (Fig. 10 A’). In contrast, the category II lesion (M1+LPMCd) resulted in decreased performance (Fig. 9 B) at week 1 post-lesion which was primarily reflected in less coordinated manipulation and more variability in reach score (Fig. 10 B, B’). By week 2 post-lesion the reach scores attained pre-lesion levels, while manipulation scores recovered to pre-lesion levels by the 3rd post-lesion week, but remained quite variable (Fig. 10 B, B’). Surprisingly, the category III lesion (M1+LPMCd+M2) resulted in decreased reach scores during the first two post-lesion weeks while manipulation scores were similar to pre-lesion values, although more variable (Fig. 10 C, C’). Reach scores then recovered to pre-lesion levels by week 3 post-lesion but manipulation scores decreased (Fig. 10 C, C’).

Discussion

The modified (USD) dexterity board with digital video acquisition of movement kinematics can be used to obtain reliable and meaningful data for a reaching and fine motor-control task performed by non-human primates. The three subjects demonstrated
different performance scores across wells, which may be due to differences in retrieval strategy and digit dimensions. Regardless of the particular retrieval strategy, subjects demonstrated more skill retrieving pellets from one well. Thus, this task can be used quantitatively to study issues such as manipulation ability (to obtain food pellets from different-sized wells), progress of recovery from nervous-system lesions, and differences in digit coordination of preferred and non-preferred hands.

There are many advantages to using the USD dexterity board versus other devices for the study of fine-motor control, handedness, and monitoring the recovery process after brain injury. First, use of the food pellet as the target obviates the need for extended training and acts as a strong motivating force for the subject. Second, consistent placement of the food pellet target relative to the portal opening allows for kinematic analysis and the comparison of performances across wells for a particular subject. Third, chutes projecting into the cage from the test-limb portal ensure that the subject can only succeed by using the desired limb, without the need to impose a physical restraint on the subject. This last point is especially important because it eliminates stress imposed by restraints such as primate jackets and mitts. Furthermore, when animals are lesioned they typically will not use the impaired limb when given the choice, even when some level of ability has returned. The chute, however, requires the animal to make the attempt with the impaired limb if they want to acquire the food, providing key data relevant to the process of recovery.

Perhaps most important is that the design allows the collection of quantitative kinematic and temporal data from each reaching trial, and this can be used to calculate a composite score of performance for each well in each experimental session.
Quantification and normalization of the components of reach (i.e., reach duration, manipulation duration, number of pellet contacts, grip aperture) provides relevant information about how the task is performed. Our overall performance score ($P_{St}$) factors in all of these components to effectively reflect the movement outcome during each reach, regardless of whether pellet retrieval was successful. The performance score also allows more effective monitoring of progress following a brain lesion than is possible through observation of independent single measures. For example, our use of the index finger distance from the food pellet at touchdown to measure accuracy stemmed primarily from observations of subjects using this finger to explore and navigate the wells. The index finger most often made first contact with the dexterity board and pellet, regardless of the well condition or lesion status. This may differ from prehension in humans where the thumb is aimed at relatively large objects during transport (Galea et al. 2001). However, given the small size of the target object (food pellet) and the nature of the task, the index finger position at contact with the dexterity board provides a reproducible indicator for reach accuracy. Almost all monkeys tested in these tasks use (or learn to use) the index finger to first contact the dexterity board, manipulate the pellet within the well, or move the pellet. Thus, our analysis reflects the strategies used in both pre- and post- lesion experiments. In our hands, sample performance scores correlated well with subjective evaluations by nine separate investigators, demonstrating that these scores are an accurate indicator of overall performance. In contrast, each of the temporal, accuracy and grip aperture measures, taken individually, did not provide a consistent indicator of performance or recovery.
The performance score appears to be sensitive not only across well size, but also in the pre- and post-lesion conditions. For example, scores tended to be lower and more variable in well A when compared with well B (Fig. 7), which is verified by the respective performance ratios (Fig. 8). Sensitivity of the score is further demonstrated by its progress through the reported recovery period (Fig. 7). Performance scores during recovery from this subject’s best well (D) were higher (Fig. 9) than those of wells A and B (Fig. 7). Indeed, scores from the smaller well (A) lagged behind those of a larger well (B). Taken across well and lesion conditions this score appears to provide a sensitive measure of performance level.

We also found it useful to separate the performance score into separate reach and manipulation scores reflecting, respectively, proximal and distal muscle function in controlling arm and finger movements. The manipulation scores were more sensitive to learning the task and both scores were affected differently by cortical lesions of different size. Notably, the contralesional arm reach scores were relatively unaffected by a lesion limited to the M1 arm area but showed progressively greater effects due to a progressively larger lesion that included M1 + LPMCd or M1 + LPMCd + M2. It is also noteworthy that reaching ability recovered to pre-lesion levels sooner than manipulation ability in all cases. The manipulation scores showed progressively greater deficits with greater lesion volumes. Future studies will present data for recovery of motor function for longer time-periods (up to one year post-lesion). Clearly, the reach and manipulation scores are useful for characterizing recovery of motor function following brain injury, but more detailed analyses of finger movements will be needed to assess whether motor strategies change following the various lesion categories.
Overall, our results at one week post-lesion interval are consistent with the effects of chemical lesions of M1, primary somatosensory cortex (S1) and ventral premotor cortex on hand movement control. Muscimol applied to reversible inactivate sensorimotor areas (e.g., M1, S1, ventral premotor cortex) has been shown to impair finger movements, grasp force control (Brochier et al. 1999) and hand shaping/grip aperture (Fogassi et al. 2001). Such findings are consistent with our observations of impaired reaching and manipulation performance. In contrast, permanent lesions induced by applying ibotenic acid to M1 and S1 abolished successful food pellet retrievals in a dexterity board task for one month post-lesion and recovery to only 30% of pre-lesion success rates by 7 months post-lesion (Liu and Rouiller 1999). However, it is likely that the severe impairment and poor recovery of fine motor performance, which contrasts with the recovery we observed over 5 weeks following surgically induced lesions, was due to the sensory impairment caused by the additional involvement of S1 in the lesion site in the previous work.

We have also demonstrated inter-digitizer reliability for the video data, and face validity of the performance score. Moreover, we have observed performance score trends that reflect the functional capabilities of the subjects through extended periods of time. The consistent performance scores under the pre-lesion conditions after initial learning (Figs. 8 and 9) demonstrate reliable performance over several weeks. The post-lesion data, characterized by lower average performance scores and higher variability, reflect a general trend of decreased skill by the limb most affected by the lesion compared to the limb ipsilateral to the lesion. Thus, our improved design of the dexterity board, when coupled with quantitative measures of movement, makes possible behavioral
observations that can be linked to motor recovery and, potentially, to measures of CNS reorganization that occur during recovery.

An interesting feature of the dexterity board described here is that it required the animal to use the more-affected limb to reach toward the food target, thereby somewhat resembling the constraint-induced, or forced-use therapies used with humans who experience hemiplegia due to stroke (Taub et al. 2002). Forced-use has been suggested to contribute to better and faster recovery outcomes (Ro et al. 2006; Schaechter et al. 2002). Since our testing schedule provides opportunities to monitor a small number of movements, our measures appear to reflect the severity of the brain injury and the early progress of recovery. Indeed, we were surprised by the recovery of reach and manipulation scores observed in Cases 2 and 3 over a 5-week period following large lesions affecting hand/arm areas of M1 and premotor areas. Although Case 2 made no attempts to acquire the food pellets at one week post-lesion, by week five average performance scores nearly equaled pre-lesion scores, although variability remained high. Similar observations were made during recovery for Case 3. In contrast, Case 1 had a much smaller performance deficit in the testing session one week following the lesion, but did exhibit lower average performance scores and higher variability post-lesion. Inter-subject differences in response to the lesion may be related to age, gender and motivation to perform the tasks as well as lesion extent.

In conclusion, we have demonstrated that a modified Kluver board coupled with 3D digital video acquisition and composite performance evaluation provides a novel method to quantitatively study recovery of arm and hand function following brain lesions in non-human primates. The primary advantages of this method for measuring fine motor
performance include minimal training to learn the task with both hands in cooperative subjects, minimal constraints during the task, a useful measure of overall performance even when the animal is unsuccessful at the task, and high sensitivity to performance changes after neurological injury.

Acknowledgements

Supported by National Institutes of Health Grant NS 046367 and The South Dakota Spinal Cord and Traumatic Brain Injury Research Council. The authors also thank Angela Viaene and Grant Headley for assistance with digitizing video data and Patrick Cline for assisting with video acquisition.
Figure 1: Composite views of the University of South Dakota Dexterity Board. Panel A is a front view of the food retrieval platform with pellet wells (A-E) and portal chutes that permit testing of either the right or left limb. With the (orange) portal door in place, movement to the food pellet target can be accomplished only with the right hand. The dashed line represents the location of the angled chute that protrudes into the cage (also see arrow in panel C). Panel B illustrates a close-up view of the moveable platform from which the pellets were retrieved. The single headed arrow represents the position used for animals with short arms and the double headed arrow the position used for animals with long arms. The diameter and depth of each well are described in the text. Panels C - E illustrate different views of the portal tube, or chute (black arrow in panel C) through which the subject's upper limb must pass to gain access to the platform and food pellets. The adjustable chute is interchangeable to accommodate right and left limbs, and while attached to each portal, is slightly angled (panel D) such that the subject must use the ipsilateral limb to successfully gain access to the food pellet. In panel E the portal door is removed to show the optional rotational angles (i.e., +1, +2, +3, + 4 for example) that can be used to adjust the position of the chute to accommodate the natural reaching path of the animal. The use of the angled chute obviates the need for any type of restraint to ensure that only the desired limb is used for the reaching task. Panel F demonstrates the rigid frame used to calibrate the space volume for each limb. Identifiable markers (1-41) were digitized and used in the direct linear transformation process to reconstruct the 3D movement kinematics from the digitized anatomical markers during reaching and grasping.
Figure 2: Detailed schematic illustration of the testing device. Linear (cm) and angular (°) measures are indicated for major components of the design. Views of individual components are provided in Figure 1.

Figure 3: Line drawings of the lateral surfaces of the hemisphere in Cases 1 and 2 and the lateral and medial surfaces of the hemisphere in Case 3. Depicted on the left is a drawing of the lesion from the fixed tissue preparation. On the right is the non-lesioned hemisphere with the surface area of the lesion mapped onto the cortical surface.

Abbreviations: cc, corpus callosum; cf, calcarine fissure; cgs, cingulate sulcus; cs, central sulcus; ecs, ectocalcarine sulcus; ilas, inferior limb of the arcuate sulcus; ios, inferior occipital sulcus; ips, intraparietal sulcus; lf, lateral fissure; LPMCd, dorsal lateral premotor cortex; ls, lunate sulcus; M1, primary motor cortex; M2, supplementary motor cortex; ots, occipital temporal sulcus; poms, medial parietal occipital sulcus; ps, principle sulcus; rs, rhinal sulcus; slas, superior limb of the arcuate sulcus; sts, superior temporal sulcus.
Figure 4: Plate of photomicrographs showing representative myelin and Nissl stained sections through the lesion site in Case 1 (panels A and A’ respectively), Case 2 (panels B and B’ respectively) and Case 3 (panels C and C’ respectively). The third panel to the right in each row (A’’, B’’ and C’’’) represents a matching Nissl stained section from the non-lesioned hemisphere that has been reflected 180° to match the orientation of the lesioned hemisphere. Cortical layers I-VI are demarcated on the lateral surface of each panel. The dashed closed contour outlines the estimated gray matter region involved in the lesion and the solid closed contour outlines the white matter region estimated to be involved in the lesion. The unlabeled arrow indicates the medial extent of the lesion site and the unlabeled double-headed arrow the lateral extent of the lesion site. In panel C’’ the lesion extended in the lateral dimension beyond the field of view (see asterisk) to a level just above the spur of the arcuate sulcus. Abbreviations: cgs, cingulate sulcus; cs, central sulcus; LPMCd, dorsal lateral premotor cortex; M1, primary motor cortex; M2, supplementary motor cortex.
Figure 5: 3D trajectories of finger- and thumb-tip paths during the reach portion of the task for two movements by Case 2. The food pellet target is indicated by the black dot (●) located at coordinates (0,0,0).

Figure 6: Averaged subjective ranking (± SE) by nine investigators versus performance scores for 10 individual pre-lesion trials by Case 2.

Figure 7: Performance scores for a single subject (Case 1) over the pre and post-lesion experiments for wells A and B using the preferred hand. Performance tends to increase and then stabilize throughout the course of the pre-lesion experimental sessions. Increased performance is indicated by higher averaged scores and lower variability (e.g., well B, experiment -9 and -2). Progression of recovery can be tracked and assessed (e.g., experiment 1-5) using this composite score.
Figure 8: Performance indices for Cases 1-3 at each well. Each bar represents the average performance score divided by the S.D. of performance scores for a single well during the last 5 pre-lesion test sessions (i.e., 25 trials for each well over a 12-16 week period) for each subject. The well for which the subject performed best using the preferred hand is indicated (*).

Figure 9: Average performance scores for the best well (the well with the highest pre-lesion performance ratio) in both the preferred and non-preferred hands of Cases 1-3 (panels A-C). Each symbol shows the average performance score for 5 trials in a pre- or post-lesion test session. Error bars on each symbol are +/- 1 S.D. of performance scores for the 5 trials in a test session. Post-lesion experiments were conducted weekly.

Figure 10. Average reach and manipulation scores for the best well (the well with the highest pre-lesion performance ratio) in both the preferred and non-preferred hands of Cases 1-3 (panels A-C). Each symbol shows the average performance score for 5 trials in a pre- or post-lesion test session. Error bars on each symbol are +/- 1 S.D. of performance scores for the 5 trials in a test session. Post-lesion experiments were conducted weekly.
Table 1. Computed area and volume of the gray matter lesion in three cases.

<table>
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<tr>
<th>Case</th>
<th>Lesion Category</th>
<th>Grid size (μm)</th>
<th>Block advance (μm)¹</th>
<th>Number of Sections</th>
<th>Shape Factor</th>
<th>Area (mm²) (CE)²</th>
<th>Volume (mm³) (CE)²</th>
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<td>12</td>
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<td>511.79 (0.6)</td>
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</table>

¹ Tissue thickness immediately following sectioning
² Coefficient of error (Gundersen), m=1 (refers to new CE estimate formula by Gundersen, 1999).

Coefficient of error is also shown for each lesion category. Also included are the main parameters used to design the Cavalieri estimator in Stereo Investigator. Category I lesion included only the arm area of M1, Category II included the arm areas of M1+LPMCd and a category III lesion encompassed the arm areas of M1+LPMCd+M2.
Table 2. Computed area and volume of the white matter lesion in three cases.

<table>
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<th>Case</th>
<th>Lesion Category</th>
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<th>Block advance (μm)¹</th>
<th>Number of Sections</th>
<th>Shape Factor</th>
<th>Area (mm²) (CE)²</th>
<th>Volume (mm³) (CE)²</th>
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¹ Tissue thickness immediately following sectioning
² Coefficient of error (Gundersen), m=1 (refers to new CE estimate formula by Gundersen, 1999).

Coefficient of error is also shown for each lesion category. Also included are the main parameters used to design the Cavalieri estimator in Stereo Investigator. Compared to the gray matter analysis, the number of sections decreased because some sections that had gray matter damage but showed no white matter damage had to be omitted when calculating the white matter estimate. Thus, the increase in the CE is the result of decreased sample size.

\[
CE = \sqrt{\frac{\text{Total var}}{\text{nugget}}}
\]

\[
nugget = 0.0724 \frac{b}{\sqrt{a}} \sqrt{n \sum_i P_i}
\]

\[
Var_{sr} = \frac{3(A - \text{nugget}) - 4}{240}
\]

\[
A = \sum_{i=1}^{n} (Q_i)^2
\]

\[
B = \sum_{i=1}^{n} Q_i Q_{i+1}
\]

\[
C = \sum_{i=1}^{n} Q_i^2 Q_{i+2}
\]
References


Composite views of the University of South Dakota Dexterity Board. Panel A is a front view of the food retrieval platform with pellet wells (A-E) and portal chutes that permit testing of either the right or left limb. With the (orange) portal door in place, movement to the food pellet target can be accomplished only with the right hand. The dashed line represents the location of the angled chute that protrudes into the cage (also see arrow in panel C). Panel B illustrates a close-up view of the moveable platform from which the pellets were retrieved. The single headed arrow represents the position used for animals with short arms and the double headed arrow the position used for animals with long arms. The diameter and depth of each well are described in the text. Panels C - E illustrate different views of the portal tube, or chute (black arrow in panel C) through which the subject's upper limb must pass to gain access to the platform and food pellets. The adjustable chute is interchangeable to accommodate right and left limbs, and while attached to each portal, is slightly angled (panel D) such that the subject must use the
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Detailed schematic illustration of the testing device. Linear (cm) and angular (°) measures are indicated for major components of the design. Views of individual components are provided in Figure 1.

190x187mm (600 x 600 DPI)
Line drawings of the lateral surfaces of the hemisphere in Cases 1 and 2 and the lateral and medial surfaces of the hemisphere in Case 3. Depicted on the left is a drawing of the lesion from the fixed tissue preparation. On the right is the non-lesioned hemisphere with the surface area of the lesion mapped onto the cortical surface. Abbreviations: cc, corpus callosum; cf, calcarine fissure; cgs, cingulate sulcus; cs, central sulcus; ecs, ectocalcarine sulcus; ilas, inferior limb of the arcuate sulcus; ios, inferior occipital sulcus; ips, intraparietal sulcus; lf, lateral fissure; LPMCd, dorsal lateral premotor cortex; ls, lunate sulcus; M1, primary motor cortex; M2, supplementary motor cortex; ots, occipital temporal sulcus; poms, medial parietal occipital sulcus; ps, principle sulcus; rs, rhinal sulcus; slas, superior limb of the arcuate sulcus; sts, superior temporal sulcus.

181x236mm (600 x 600 DPI)
Plate of photomicrographs showing representative myelin and Nissl stained sections through the lesion site in Case 1 (panels A and A' respectively), Case 2 (panels B and B' respectively) and Case 3 (panels C and C' respectively). The third panel to the right in each row (A'', B'' and C'') represents a matching Nissl stained section from the non-lesioned hemisphere that has been reflected 180° to match the orientation of the lesioned hemisphere. Cortical layers I-VI are demarcated on the lateral surface of each panel. The dashed closed contour outlines the estimated gray matter region involved in the lesion and the solid closed contour outlines the white matter region estimated to be involved in the lesion. The unlabeled arrow indicates the medial extent of the lesion site and the unlabeled double-headed arrow the lateral extent of the lesion site. In panel C'' the lesion extended in the lateral dimension beyond the field of view (see asterisk) to a level just above the spur of the arcuate sulcus. Abbreviations: cgs, cingulate sulcus; cs, central
sulcus; LPMCd, dorsal lateral premotor cortex; M1, primary motor cortex; M2, supplementary motor cortex.
207x268mm (600 x 600 DPI)
3D trajectories of finger- and thumb-tip paths during the reach portion of the task for two movements by Case 2. The food pellet target is indicated by the black dot ( ) located at coordinates (0,0,0).

85x70mm (600 x 600 DPI)
Averaged subjective ranking (± SE) by nine investigators versus performance scores for 10 individual pre-lesion trials by Case 2.
Performance scores for a single subject (Case 1) over the pre and post-lesion experiments for wells A and B using the preferred hand. Performance tends to increase and then stabilize throughout the course of the pre-lesion experimental sessions. Increased performance is indicated by higher averaged scores and lower variability (e.g., well B, experiment -9 and -2). Progression of recovery can be tracked and assessed (e.g., experiment 1-5) using this composite score.
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