Effects of permanent or reversible inactivation of primary motor (M1) hand area on precision grip performance in various motor tasks.

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Introduction:

Behavior and its different parameters are differently affected by motor cortical injury, depending on its size and its location. Precision grip is an example of sophisticated motor control (and a specialty of primates) and therefore macaque monkey is a pertinent model to elucidate the mechanisms involved in motor recovery from cortical lesion, as well as to refine therapies aimed at improving rehabilitation using different motor tasks. This study aimed at quantitatively assessing different motor attributes of grasping and precision grip movements in adult monkeys, based on a palette of manual dexterity tasks: a modified version of the "*Brinkman board*" task, a modified version of the "*Klüver board*" task and the "*reach and grasp drawer*" task. These complementary approaches compare in the same macaque monkey the effects of a unilateral lesion in the left primary motor cortex targeted to the hand area on differents parameters assessed with these different tasks.

Discussion:

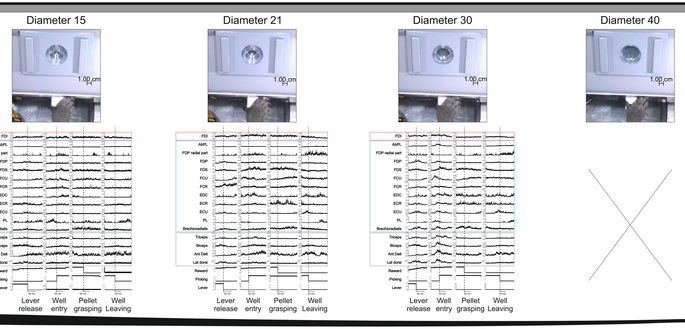
Precision grip is a complex combination of fine, precise and highly controlled motor parameters differently affected by motor cortical injury. Study of the recovery of the fine manual dexterity could not be assessed using only one parameter of these behavioral tasks, each one highlighting several aspects of the movement differently affected and recovered after M1 hand area lesion: 1) modified "Brinkman board" task: precision grip performed with a wrist deviation and pro-supination position was more affected following the lesion than when performed in a vertical position; 2) modified "Klüver board" task: strategy and efficiency to retrieve small object using precision grip and gross manual dexterity involving several fingers, the last one recovered earlier with less error but with a lower percent of recovery; the corresponding preshaping recovered later than the grasping itself; 3) "reach and grasp drawer" task: the maximal and duration value of the grip force applied in a supination position of the hand.

These differences observed on behavioral tasks were associated with SSEP waveform and topography modification on the lesioned hemisphere.

Further investigations will include EMG and intracortical chronic recordings in behaving monkey to correlate behavioral observations with electrophysiological data.

Modified Kluver board:

Pellets retrieved from four slots of different size, allowing pellet retrieval with one finger in the 15 cm diameter slot, two fingers in the 21 cm diameter slot, three fingers in the 30 cm diameter slot and four fingers in the 40 cm diameter slot. Pellets were delivered pressing by hand positioning on a lever.



Waveform average of chronic electromyographic (EMG) recording in 16 upper right limb muscles in behaving monkey during the reach and grasp modified Kluver board task in one daily pre-lesion session:

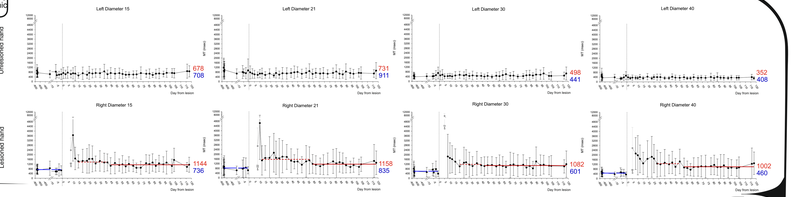
- one intrinsic hand muscle: FDI (*First Dorsal interosseus*),
- 10 forearm muscles: AbPL (*Abductor Pollicis Longus*), FDP (*Flexor Dorsal Profundus*), FDS (*Flexor Dorsal Superficialis*), FCU (*Flexor Carpi Ulnaris*), FCR (*Flexor Carpi Radialis*), EDC (*Extensor Digitorum Communis*), ECR (*Extensor Carpi Radialis*), ECR (*Extensor Carpi Ulnaris*), PL (*Palmaris Longus*), Brachioradialis,
- 4 arm muscles: Triceps, Biceps, Ant. Delt. (*Anterior Deltoid*), Lat. Dorsi. (*Latissimus Dorsi*).

Waveform of chronic EMGs averaged on four precise events: lever release, entry of fingers in the well, pellet grasping at the bottom of the well and the output of the hand out of the well.

Graphs below: Time course of behavioral recovery of four parameters in the manual dexterity modified **Kluver board** task, in a macaque monkey subjected to M1 hand area permanent lesion (microinfusion of Ibotenic acid) in the left hemisphere.

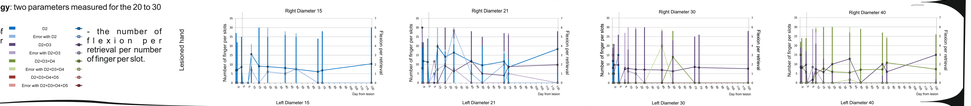
Intracortical microstimulation under light sedation to target digit area of left M1. Microinfusion of Ibotenic acid in 12 fingers sites, 1µL per site.

Retrieval time: mean value of the time spent to correctly retrieve pellets from the slot per session. Each session represents 30 to 50 trials for each well.
(—Prelesion plateau and mean; ---- Postlesion first plateau; — Postlesion second plateau and mean).

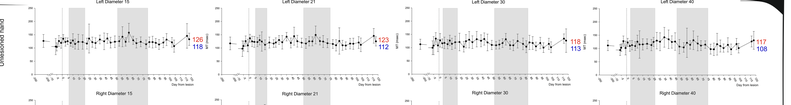


Retrieval strategy: two parameters measured for the 20 to 30 first trials:

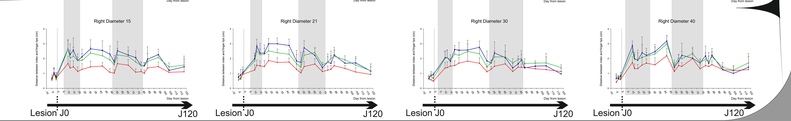
- the number of trials per number of finger in slot.
- the number of flexion per retrieval per number of finger per slot.



Reaching time: time between the lever release and finger entrance in the well. Each session represent 30 to 50 trials for each well.
Pre-lesion and post-lesion mean at plateau.



Preshaping strategy: measure of the distance between the tip of the index and the tip of the thumb during the reaching period. Average of the finger distances of the 5 first correctly retrieved pellets distributed in 3 groups corresponding to areas based on the distances from the lever to the bottom border of the well: the **leaving area**, the transfert area and the entry area.

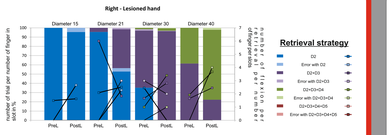


Behavioral task - Results:

Klüver board task:

- **Retrieval**:
  - Subtle short-term recovery for large diameters suggesting early recovery for gross manual dexterity.
  - Paradoxically, the percentage of recovery for the fine manual dexterity was higher in small diameters than in large diameter wells.
  - Modification of the retrieval strategy by privileging, post-lesion, the use of gross manual dexterity as compared to pre-lesion precision grip, as observed for large diameters.

- **Reaching**:
  - Subtle increase of the time needed to reach the targeted well.
  - Distance between index tip and thumb tip indicated a loss of preshaping as compared to pre-lesion period where the hand appeared already prepared from the lever release time.
  - Late tendency of preshaping reappearance around 50 days for the larger diameter wells delayed up to 105 days post-lesion for the smaller diameter wells, however never comparable to pre-lesion level.



Brinkman board task:

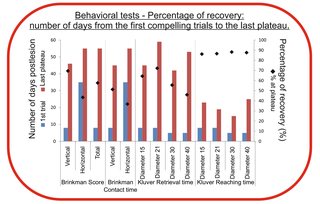
- Permanent M1 hand area ibotenic acid lesion induced a dramatic decrease of **score** and increase of **contact time** of fine manual dexterity.

- Fine manual dexterity requiring wrist deviation and pro-supination movement was more affected, as exhibited by lower percentage of recovery and later recovery for the horizontal slots.

Drawer task:

- **Permanent lesion** :
  - As a consequence of permanent lesion, monkey was unable to perform fine precision grip to open drawer post-lesion.
  - Increase of grip duration and decrease of maximal grip force applied on the knob to open drawer due to opening strategy modification post-lesion.

- **Reversible inactivation** :
  - No modification except at the highest resistance, grip duration increase and maximal grip force decrease tendencies slightly more pronounced due to rTMS inactivation than rTMS sham.



Percentages of recovery: mean values at pre-lesion (PreL) and post-lesion (PostL) plateaux:
- for score and retrieval time = PostL/PreLx100;
- for contact time and reaching time = PreL/PostLx100.

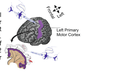
Electroencephalogram (EEG): Right median nerve SSEPs

Method:

- 33-channel EEG mapping of somatosensory evoked potentials (SSEPs) (Gindrat et al, 2014).
- Electrical stimulation to the right median nerve at the wrist.
- k-means cluster analysis
- Fitting of the clustering maps back to the raw data and statistical analysis on several topographical parameters.

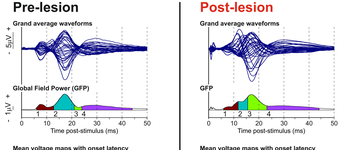
- SSEPs were recorded before and after M1 hand area permanent lesion with ibotenic acid microinfusion.

Intracortical microstimulation under light sedation to target digit area of left M1. Microinfusion of Ibotenic acid in 12 fingers sites, 1µL per site.



Result:

Same sequence of 4 maps before and after the lesion but statistically significant differences in several topographical parameters from the fitting for the maps 2 and 3.

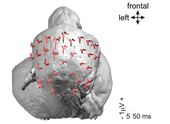


Unpaired *t*-tests between pre- and post-lesion fitting topographical parameters

	map 2	map 3
Latency at first onset	ns	***
Latency at last onset	ns	ns
Duration	***	***
Latency of centroid	**	***
Mean correlation	***	*
Global explained variance	***	***
Best correlation	***	**
Latency at best correlation	***	***
GFP of latency at best correlation	***	***
Maximum of GFP	***	***
Latency at maximum of GFP	***	***
Mean GFP	ns	***

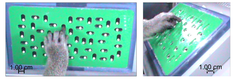
ns: statistically non-significant; * : p≤0.05; * : p≤0.01; * : p≤0.001

Projection of pre-lesion and post-lesion SSEP waveforms on MRI head surface



Modified Brinkman board:

Pellets retrieved from 25 horizontal slots and 25 vertical slots randomly distributed on the board.



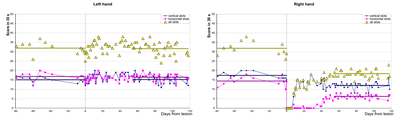
Brinkman board.

Top view — Lateral view

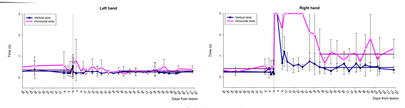
Time course of behavioral recovery in the manual dexterity **modified Brinkman board** task, in a monkey subjected to a M1 hand area permanent lesion (microinfusion of Ibotenic acid) in the left hemisphere.

Intracortical microstimulation under light sedation to target digit area of left M1. Microinfusion of Ibotenic acid in 12 fingers sites, 1µL per site.

Score: number of pellets retrieved from vertical and horizontal slots during the first 30 sec of the task, before and after the lesion.



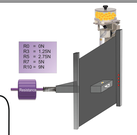
Contact time: mean of the 5 first horizontal and the 5 first vertical correctly retrieved pellets. It represents the time between entry of finger in the slot and the output of pellet out of the slot.
For unsuccessful trials (when less than 5 pellets retrieved), a maximum contact time was fixed at 3 seconds.



— Straight line represent plateau

Drawer:

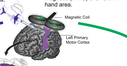
Open a drawer by grasping knob and against four increasing resistances (0, 1.25, 2.75, 5 and 9 Newtons) to retrieve pellets from the well of the drawer.



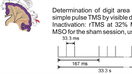
Modification of two parameters of the grip (maximum and duration) in the reach and grasp **drawer** task, in a monkey subjected to reversible inactivation (rTMS) and permanent lesion (microinfusion of Ibotenic acid) targeting M1 hand area over the left hemisphere.

Permanent inactivation with Ibotenic acid microinfusion in left M1 hand area.

Reversible inactivation with repetitive Transcranial magnetic (rTMS) over left M1 hand area.

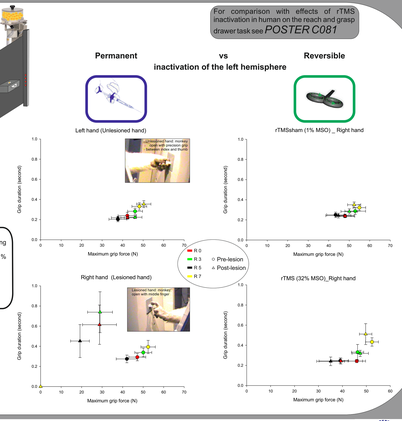


Intracortical microstimulation under light sedation to target digit area of left M1. Microinfusion of Ibotenic acid in 12 fingers sites, 1µL per site.



Determination of digit area of left M1 coordinates and threshold using simple pulse TMS by visible digit muscles contraction (33%).
Inactivation: rTMS at 32% MSO (Maximal Stimulation Output) and 1% MSO for the sham session, using following parameters of stimulation:
33.3 ms
167 ms
33.3 s

For comparison with effects of rTMS inactivation in human on the reach and grasp drawer task see *POSTER C081*



Measure of **duration** and **maximum grip** force applied by monkeys on the knob to open drawer against the four increasing levels of resistances and represented by mean and standard deviation on bi-directional error bar plots.
- permanent inactivation: 5 sessions pre-lesion and 5 sessions of the acute post-lesion period (from J0 to J24).
- reversible inactivation: one daily session before and after rTMS.

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