Functional restitution of manual dexterity in macaque monkeys after a motor cortex lesion assessed with the Brinkman box (BB) task

Eric Schmidlin, **Anne-Dominique Gindrat**; Mélanie Kaeser; Alexander F. Wyss; Cindy Leuthard and Eric M. Rouiller

Domain of Physiology, Department of Medicine, Faculty of Sciences and Fribourg Center for Cognition, University of Fribourg, Fribourg, Switzerland

Introduction

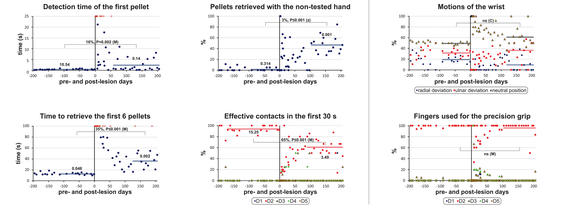
Motor and somatosensory cortical areas are densely interconnected and participate together to the motor control, forming the functional sensorimotor system. The primary somatosensory cortex (S1) sends corticospinal projections and somatosensory inputs to the primary motor cortex (M1), contributing to the control of voluntary movements such as the precision grip. Moreover, the somatosensory system plays a key role in active motor exploration by palpation in the absence of visual feedback.

A behavioural task was initially developed by Brinkman and Kuypers (1973) to test the precision grip ability in non-human primates, and an improved version - the modified Brinkman board task - is currently used in our laboratory. The animal has to retrieve banana pellets contained in 25 vertically and 25 horizontally oriented wells distributed on a rectangular board.

Hypothesis

After a lesion in M1, the sensorimotor system will be affected in parallel with the motor control itself. The resulting impairments can be highlighted with another test derived from the Brinkman board task: the **Brinkman box (BB) task,** which was specifically designed to assess the role of sensory inputs in a precision grip task performed with or without visual feedback before and after a lesion of the hand representation of M1.

The lesion affects differentially some behaviours of the contralesional hand in BB task without vision in a given monkey.



The post-lesion time course and level of recovery in a given monkey (data from Mk-VA) vary according to the analysed parameters.

As a first approach, pre- and post-lesion **mean plateaux** were visually defined for each analysed parameter (need to use more systematic criteria for the post-lesion plateau in the near future) and are displayed in a lighter colour than the corresponding data.

The **percentage of recovery** is defined for appropriate parameters as (mean post-lesion plateau/mean pre-lesion plateau)*100 when a higher plateau value means a better performance and as 1/(mean post-lesion plateau/mean pre-lesion plateau)*100 when a lower plateau value represents a better performance.

Pre- and post-lesion plateaux were statistically compared with t-test (t), Mann-Whitney test (M), z-test (z) or Chi-square test (C), as the case may be. The corresponding p-value or ns (non-significant, P > 0.05) is indicated.

The **performance ratio** (Pizzimenti et al., 2007) is defined for appropriate parameters as mean plateau/SD when a higher plateau value implies a better performance and as (1/mean plateau)/SD when a lower plateau value suggests a better performance. This measure takes into account the variability of the data and, thus, a more stable performance corresponds to a higher performance ratio.

Partially or completely missing values at a given date (mainly task not performed after the lesion) are represented by o.

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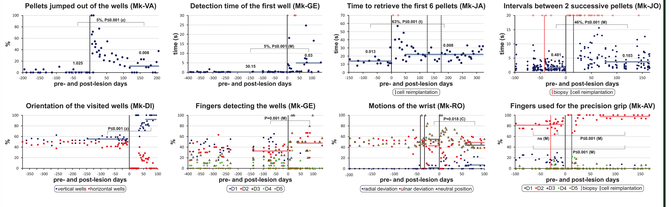
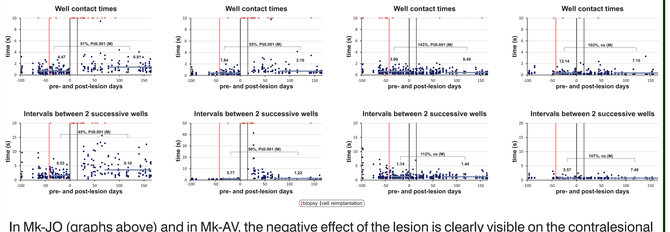
Results

A cortical lesion of the M1 hand representation induces a wide range of deficits of the contralesional hand in BB task without vision across monkeys.



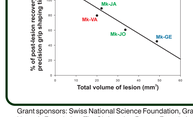
Different behaviours and strategies are observed across the monkeys to retrieve the pellets. The analysed parameters are differentially affected by the cortical lesion, with a large variability across the animals.

The post-lesion deficits of contralesional hand are counterbalanced by a significant improvement in the performance of the ipsilesional hand in some animals.



In Mk-JO (graphs above) and in Mk-AV, the negative effect of the lesion is clearly visible on the contralesional hand performing the BB task with and without vision. It goes with a significant improvement in the performance of the ipsilesional hand in the BB task without vision. Conversely, this improvement in the dexterity of the non-lesioned hand is not observed in Mk-DI.

The post-lesion recovery of the contralesional precision grip shaping time in BB task without vision is negatively correlated with the volume of M1 lesion, irrespective of the treatment.



Mk-AV was excluded from this Pearson correlation analysis because the cortical lesion affected more the premotor cortex than M1 and Mk-DI was excluded as well because the lesion volume is not known yet.

The percentage of pellets successfully retrieved as well as the time needed to successfully collect the first 6 pellets are also inversely correlated with the lesion volume, irrespective of the treatment, but these are only trends ($r = -0.864$, $P = 0.0591$ and $r = -0.851$, $P = 0.0673$, respectively).

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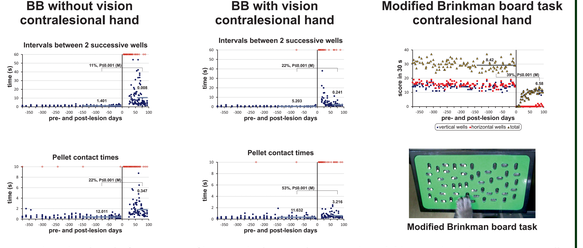
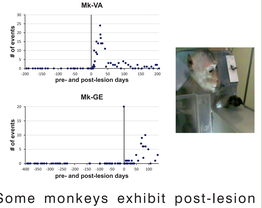
The BB task without vision is much more challenging than other tasks performed with visual control.



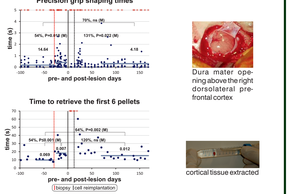
As expected, the level of recovery of the contralesional hand in the BB task without vision is usually lower than the one in the BB task with vision or in the modified Brinkman board task, given that the former is more difficult to perform than the latters. Moreover, the pre-lesion performance is better with visual control than without (data from Mk-DI).

Somatosensory-related deficits of the contralesional hand



Some monkeys exhibit post-lesion somatosensory-related deficits comparable to a sensory agnosia: in several trials (*# of events* above), they did a precision grip but failed to grasp the pellet, withdrew the hand from the well to the mouth, then visually inspected the empty palm and only at that time realised that they did not retrieve any pellet.

Adverse effect of a prefrontal cortical biopsy on the ipsilesional hand



In Mk-AV, there is an obvious adverse effect of a large prefrontal cortical biopsy (red line), inducing among others an increase in the time needed to shape the precision grip and in the time needed to successfully collect the first 6 pellets, both deficits remaining persistent after the post-lesion recovery. Conversely, the functional recovery from the lesion is excellent.

Conclusion and prospects

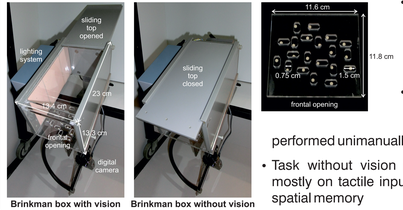
The Brinkman box (BB) task is very sensitive and relevant to test the exploratory ability and tactile sense in a lesional context. It allows detecting subtle impairments and highlights the importance of somatosensory feedback, especially in tasks performed without visual control.

Analysis could be improved by computing a composite performance score (Pizzimenti et al., 2007) including all parameters studied as a global indicator of the ability of the monkeys to perform the task.

Complementary information about the cortical mechanisms underlying the functional recovery after the lesion can be obtained from EEG mapping of somatosensory evoked potential from the scalp (Gindrat et al., 2014).

Material and methods

Brinkman box task



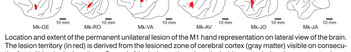
Brinkman box with vision — Brinkman box without vision

- Square board with 10 vertically and 10 horizontally oriented wells, each filled with a banana pellet
- Board located in a box whose top can be opened or closed → task performed unimanually with or without vision
- Task without vision more challenging, relying mostly on tactile inputs from the fingers and on spatial memory

Monkeys

	Mk-DI	Mk-GE	Mk-RO§	Mk-VA	Mk-AV*	Mk-JO	Mk-JA*
Treatment	None	None	None	Anti-Nogo-A antibody	Sham cell therapy	Cell therapy	Cell therapy
Age at time of lesion (rounded to 0.5 year)	9.5	5	4	5.5	3.5	3.5	4
Weight at time of lesion (kg)	3.6	2.8	3.2	4.9	4.3	3.4	4.3
Volume of ibotenic acid injected (µl)	39.7	13	18	15.5	15	15	38
Number of ICMS sites injected with ibotenic acid	21	13	12	11	10	10	38
Total volume of lesion (mm³) in the gray matter (motor cortex + post-central gyrus)	NA	48.7	14	20	33.2	33.6	22.2
Volume of lesion in post-central gyrus (mm³)	NA	7.6	0	5.8	0	3.8	2.5
Volume of lesion spread to subcortical white matter (mm³)	NA	0	0	0	69.8	23.6	38.4
Volume of prefrontal cortical biopsy (mm³)	-	-	-	-	44	20.3	8.8

§ Mk-RO was subjected to 3 successive cortical lesions because the first two did not produce the expected impairement on the contralesional manual dexterity assessed with the modified Brinkman board task. Day 0 was defined as the time of the 3rd lesion.
* The cortical lesion in Mk-AV affected more the premotor cortex than M1.
* Mk-JA was treated post-operatively with an anti-epileptic drug, producing a neuroprotective effect against the cortical lesion performed with excitotoxic drug (ibotenic acid). This resulted in a small volume of lesion in relation to the volume of ibotenic acid injected.
NA Data not available yet.



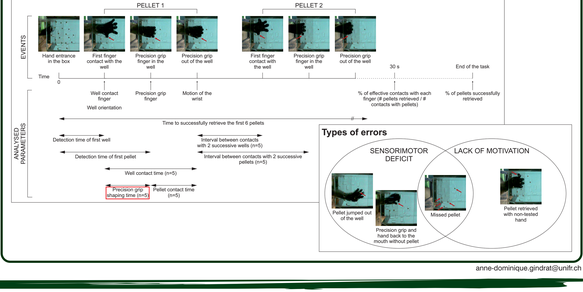
Location and extent of the permanent unilateral lesion of the M1 hand representation on lateral view of the brain. The lesion territory (in red) is derived from the lesioned zone of cerebral cortex (gray matter) visible on consecutive frontal histological sections. Spread of the lesion to the subcortical white matter below the gray matter is not represented here.

modified from Bashir et al., 2012

- 7 adult *Macaca fascicularis*
- At behavioural plateau in manual dexterity tests, unilateral permanent cortical lesion in the hand representation of M1 by microinfusion of ibotenic acid
- Post-lesion:
  - control group
  - anti-Nogo-A antibody treatment protocol (Hamadjida et al., 2012; Kaeser et al., 2010; Wyss et al., 2013)
  - adult neural progenitor cell therapy protocol (prefrontal cortical biopsy) (Kaeser et al., 2011)

Data analysis

BB data **with** and **without vision** obtained from the **contralesional hand** and the **ipsilesional hand** were analysed frame by frame (25 frames/s) with the software Kinovea. The following parameters were measured:



anne-dominique.gindrat@unifr.ch