Assessment of functional recovery of manual dexterity in non-human primates following a motor cortex lesion using the Brinkman box task

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Introduction

Motor areas and somatosensory 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.

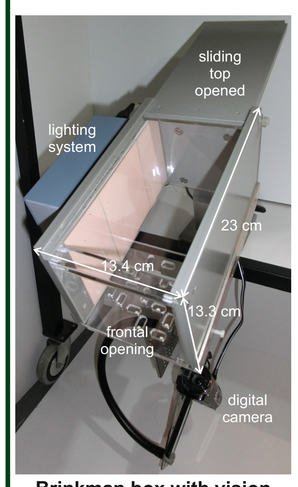
A behavioural task was initially developed by Brinkman and Kuypers (1973) to test the precision grip ability in non-human primates and is currently used in an improved version -the modified Brinkman board task- in our laboratory. The animal has to retrieve banana pellets contained in 25 vertically and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

Hypothesis

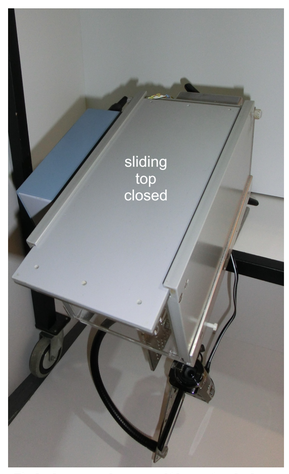
After a lesion in M1, the sensorimotor system will be affected in parallel with the motor control itself. The resulting impairments can be highlighted with another test derived from the Brinkman board task: the **Brinkman box task without vision,** which was specifically designed to assess the role of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

Material and methods

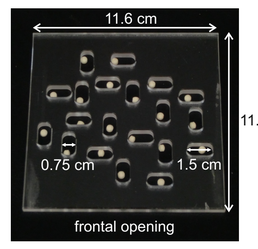
Brinkman box task



Brinkman box with vision



Brinkman box without vision

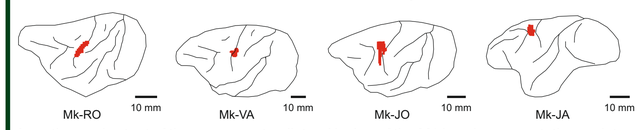


The Brinkman box task consists of a square board containing 10 vertically and 10 horizontally oriented wells, each filled with a banana pellet.
This board is located in a box whose top can be opened or closed. The task can consequently be performed unimanually with or without visual feedback. Without vision, the task is more challenging, relying mostly on tactile inputs from the fingers and on spatial memory.

Monkeys

	Mk-RO§	Mk-VA	Mk-JO	Mk-JA*
Treatment	None	Anti-Nogo-A antibody	Cell therapy	Cell therapy
Age at time of lesion (rounded to 0.5 year)	4	5.5	3.5	4
Weight at time of lesion (kg)	3.2	4.9	3.4	4.3
Volume of ibotenic acid injected (µl)	18	15.5	15	38
Number of ICMS sites injected with ibotenic acid	12	11	10	38
Total volume of lesion (mm³) in the gray matter (motor cortex + post-central gyrus)	14	20	33.6	22.2
Volume of lesion in post-central gyrus (mm³)	0	5.8	3.8	2.5
Volume of lesion spread to subcorticall white matter (mm³)	0	0	23.6	38.4

§ Mk-RO was subjected to three successive cortical lesions because the first two did not produce the expected impairment on the contralesional manual dexterity assessed with the modified Brinkman board task. Day 0 was defined as the time of the 3rd lesion.
* 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.

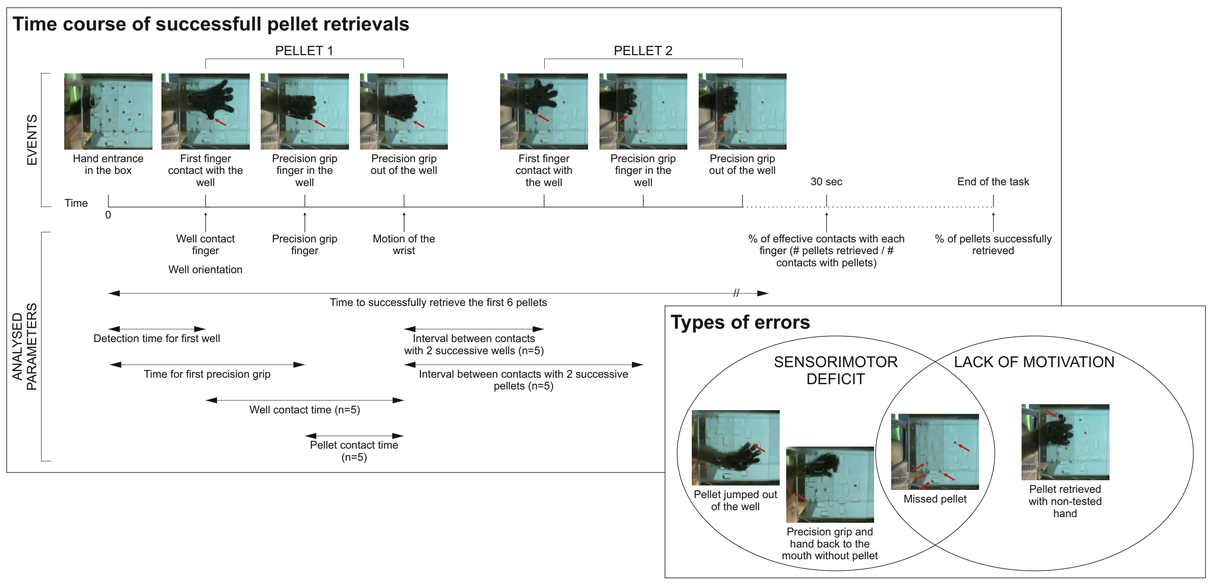


Location and extent of the permanent unilateral lesion of the M1 hand representation on lateral view of the brain. The lesion territory (in red) is derived from the lesioned zone of cerebral cortex (gray matter) visible on consecutive frontal histological sections. Spread of the lesion to the subcortical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

Experiments were conducted on four adult *Macaca fascicularis*.
When the monkeys reached a behavioural plateau in manual dexterity tests, they were subjected to a permanent cortical lesion, performed unilaterally in the hand representation of M1 by infusion of ibotenic acid.
One animal was a control subject (Mk-RO), one was treated with anti-Nogo-A antibody (Mk-VA)(Hamadjida et al., 2012; Kaeser et al., 2010) and two received an adult neural progenitor cell therapy (Mk-JO and Mk-JA)(Kaeser et al., 2011).

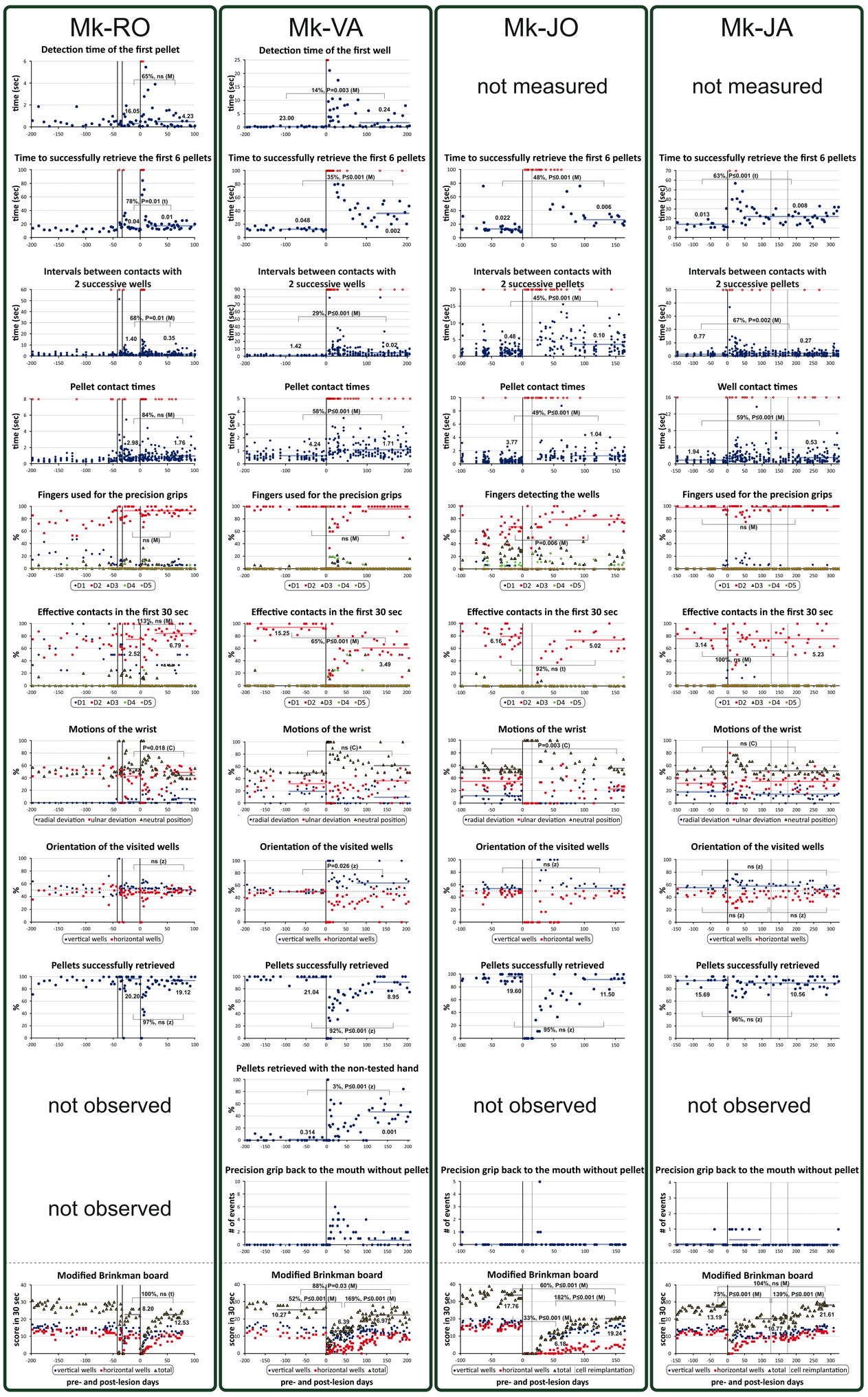
Data analysis

Brinkman box data **without vision** obtained from the contralesional hand were analysed frame by frame (25 frames/sec) with the software Kinovea. The following parameters were measured:



- Different behaviours and strategies were observed among the tested monkeys to retrieve the pellets before and after the lesion. Therefore, the relevant parameters vary among the animals.
- After the cortical lesion, the time course of recovery in a given monkey is different according to the analysed parameters. For example in Mk-JA, whereas the pre-lesionpreferentially used orientations of the wrist and finger for the precision grip are quickly regained after the lesion, the animal can no more successfully retrieve the first 6 pellets as fast as before the lesion.
- As expected, the level of recovery for the Brinkman box task without vision is usually lower than the one for the modified Brinkman board task, given that the former is more difficult to perform than the latter (e.g. Mk-RO and Mk-VA).
- Using a detailed analysis, it appears that this task is relevant to test the exploratory ability and tactile sense in a lesional context. It highlights the importance of the somatosensory feedback without visual control.

Results



As a first approach, pre- and post-lesion **mean plateaux** were visually defined for each analysed parameter (need to use more systematic criteria 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 is indicated by a higher performance ratio.
Partially or completely missing values at a given date are represented by o.

Prospects

- Inclusion of additional animals in each treatment group
- Computation of a composite performance score (Pizzimenti et al., 2007) taking into account the different parameters studied as an global indicator of the ability of the monkeys to perform the task
- Study of the reorganisation of the sensorimotor system following a M1 lesion with somatosensory evoked potentials

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