Parallel assessment of behavioral consequences on manual dexterity of a lesion of the primary motor cortex and of the nigrostriatal system in two groups of macaque monkeys.

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INDTRODUCTION

Cortical and subcortical structures contribute in a very different way in the control of fine finger movements involved in a particular aspect of manual dexterity, the precision grip, which consists in the opposition of the thumb and the index finger, as a specific motor behavior restricted to primates. To precisely distinguish the role played by the primary motor cortex (M1) or by the nigrostriate system in manual dexterity, the motor changes in non-human primates (NHP) subjected to M1 lesion or nigrostriatal lesion were compared. All animals have been tested with the same behavioral task challenging both proximal and distal control of hand movements.

METHODS

Two macaque monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and one monkey subjected to a lesion of the hand representation area of the primary motor cortex (M1) were involved in this study (**Figure 1**). MPTP lesion was produced by an acute treatment involving intramuscular injections of MPTP, until a certain severity of the symptoms mimicking Parkinson's disease (PD) were observed.
Hand representation in M1 area was identified as the area where intracortical microstimulations elicited single joint movements of the hand muscles at low threshold of stimulation. Consequently, the NHP was submitted to the lesion of the primary motor cortex by several intracortical microinfusion of ibotenic acid (an excitotoxic drug) (Figure 2).

In the “reach and grasp drawer” task the animal have to pull the drawer unimanually against increasing resistances in order to retrieve a small food pellet. The force required to grip the knob is recorded (grip force). In one typical behavioral session, the animal performed a total of 60 to 80 trials at several levels resistance to the opening, inducing the animal to increase his grip force to perform the task (R0 = 0 Newtons and R5 = 2.75 Newtons) (**Figure 3**).

Analysed motor parameters were: 1) the maximal grip force, which is needed to open the drawer, 2) the grip force duration, being the time interval between the onset and the offset of the grip force and 3) the trial duration, consisting in the time interval between the start of the drawer's opening and the time when the animal retrieved the food reward from the drawer.

The motor strategy was defined as the percentage of trials performed by the animal using the precision grip versus non precision grip (using only one finger).

Types of lesion

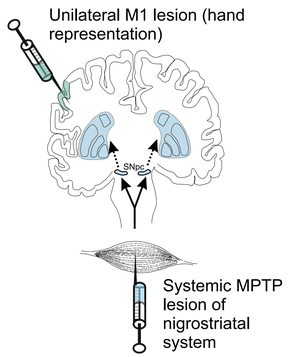

Figure 1: Illustration representing both motor cortex (M1) lesion and nigro-striatal lesion. M1 lesion was produced by infusion of ibotenic acid into the hand area of the primary motor cortex, which led to an instantaneous and permanent loss of manual dexterity of the contralateral limb. The nigro-striatal lesion was made by an acute MPTP treatment consisting of a set of intramuscular MPTP injections. The neurotoxin crosses the blood-brain-barrier and destroys specifically dopaminergic neurons of the Substantia nigra pars compacta (SNpc), which projects to the striatum. This loss of dopaminergic input from the SNpc causes PD-like symptoms. This process is progressive and can be partly reversed through compensatory mechanisms.

Area of the cortical lesion (Mk-DG)

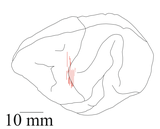

Figure 2: Ibotenic acid lesion performed in Mk-DG in M1 in the left hemisphere

Reach and grasp drawer task

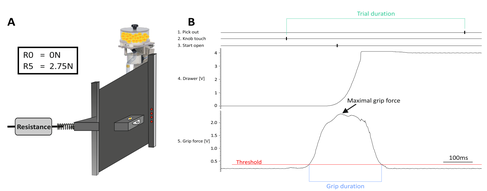

Figure 3: **(A)** Drawing illustrating the “reach and grasp drawer” task setup with adjustable resistances (N). **(B)** Typical traces of the grip force and drawer displacement as a function of time. 1) The “tic” represents the time point when the pellet is retrievd. 2) The “tic” represents the time point when the monkey touches the knob of the drawer. 3) The “tic” represents the time point when the drawer starts opening. 4) The displacement of the drawer. 5) The grip force (the force applied on the knob with the thumb and the index finger).

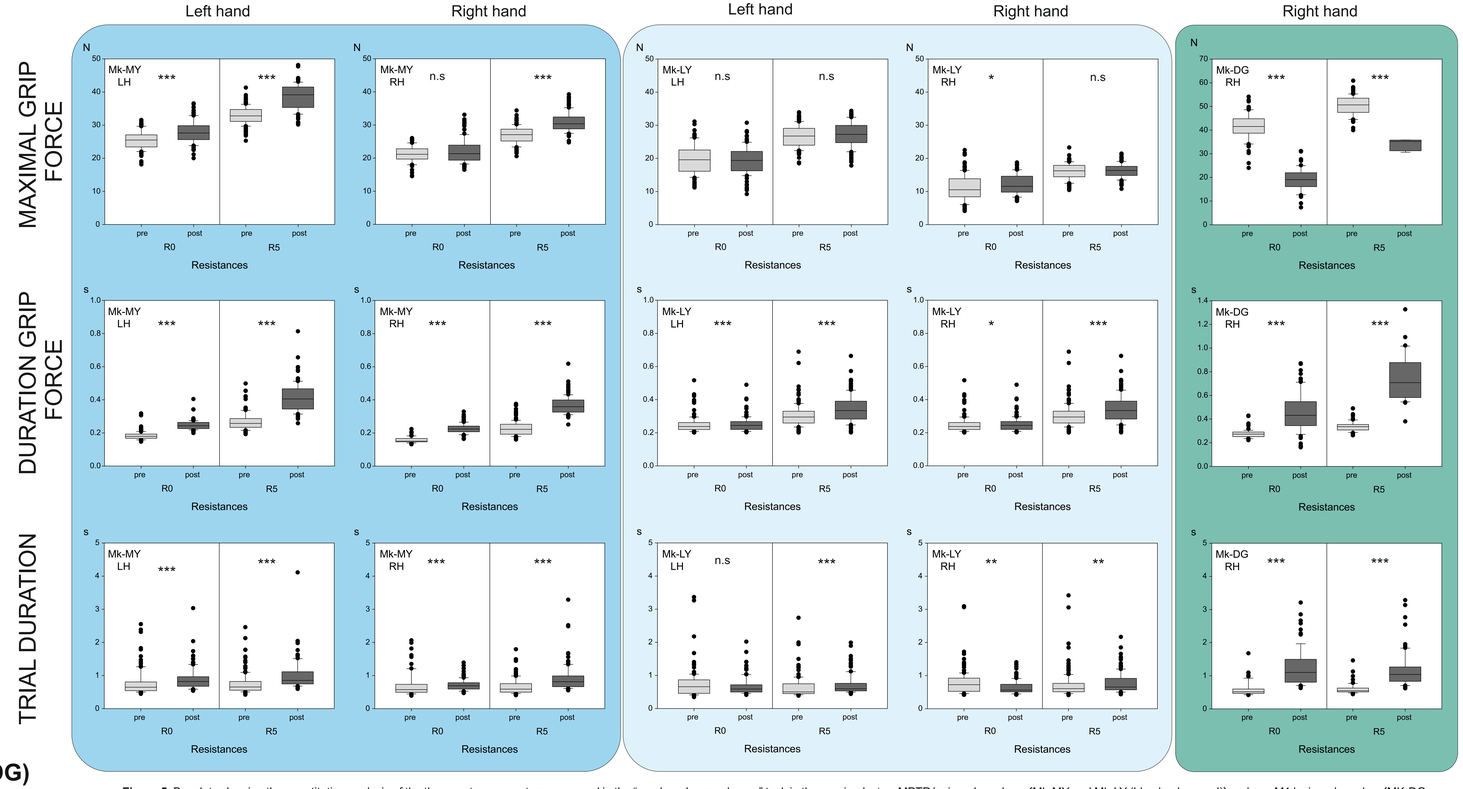

Figure 5: Boxplots showing the quantitative analysis of the three motor parameters measured in the “reach and grasp drawer” task in three animals: two MPTP lesioned monkeys {Mk-MY and Mk-LY (blue background)} and one M1 lesioned monkey {MK-DG (green background)}. For Mk-MY **(A)** and Mk-LY **(B)** both hands (left hand (LH) and the right hand (RH)) are represented whereas for Mk-DG **(C)** only the right (contralesional) hand is shown. Maximal grip force (N= Newtons) top row, duration of grip force in middle row and trial duration bottom row. Box plots are composed of all trials before (pre) and after (post) the lesion. Statistical analyses (t-test/Mann-Whitney test) compare the maximal grip force, the grip force duration and the trial duration before and after the lesion for resistances 0 and 5. Statistically significant differences are indicated with : * is for p≤0.05, ** for p≤0.01, *** for p≤0.001. «n.s.» meaning statistically non-significant.

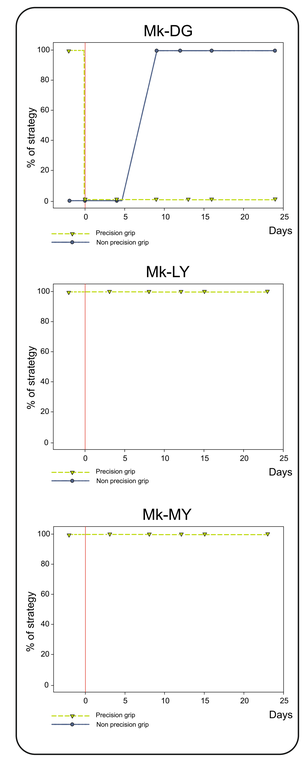

Figure 6: Graph of the dynamic changes of motor strategy used to perform the “reach and grasp drawer” task before and after the lesion. Green line represents the precision grip (opposition between the thumb and the index) whereas the blue line represents the strategy of substitution based on the use of a single finger on the drawer. The red line represents the time point of the lesion.

Row data from one trial in the «reach and grasp drawer» task

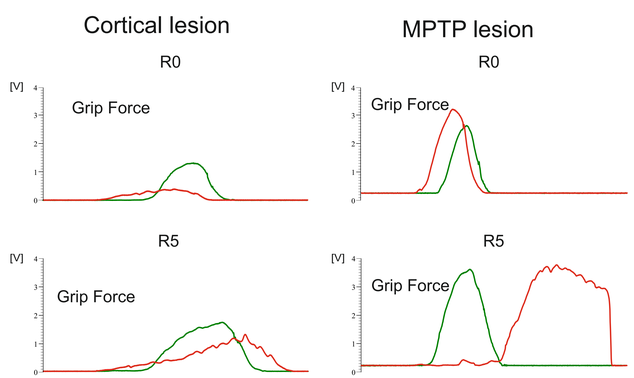

Figure 4: Examples of recordings of the grip force generated by the animal in a single trial at different levels of resistance to the opening (relative resistance 0 and 5, corresponding to 0 and 2.75 Newtons respectively), aligned on the time point when the animal touched the knob to open the drawer. Example of a trial pre-lesion is represented in green whereas the exemple of a trial post-lesion is shown in red.

RESULTS

According to a general evaluation (clinical scoring) of the symptoms mimicking Parkinson's disease, one animal was considered as moderately affected (Mk-LY) and the other one as severely affected (Mk-MY). In correlation to this observation, the behavioral results obtained in the “reach and grasp drawer” task showed more pronounced effects of the MPTP lesion on manual dexterity, and particularly the maximal grip force, in Mk-MY in comparison to Mk-LY. For both MPTP lesioned animals an increase of both the grip force duration and the trial duration was observed, with exception for the trial duration at R0 in Mk-LY (Figure 5 A and B).

In contrast, in the M1 lesioned animal a dramatic decrease of maximal grip force was observed at both levels of resistance. In addition an increase of both the grip force duration and the trial duration was observed (Figure 5 C).

No change of motor strategy was observed in the MPTP animals, whereas in the M1 lesioned monkey (Mk-DG) a strategy of substitution based on the use of a single finger on the drawer was observed during the recovery phase (Figure 6).

DISCUSSION

As expected, a unilateral permanent lesion of the hand representation in M1 resulted in marked behavioral changes affecting all measured motor parameters for the contralesional hand.
In MPTP lesioned animals, both hands were affected by the treatment. Interestingly, the maximal grip force in MPTP animals tended to increase in MK-MY after the lesion whereas in MK-LY it tended to remain constant. The increase of the maximal grip force may be explained by a loss of direct correlation between control of the force and sensitive feed-back. The increase of both the grip force duration and the trial duration may be related to the bradykinesia due to the MPTP treatment. MPTP animals tended to express a deficit in voluntary movements control , in opposition to the dramatic paresis observed in cortical lesioned monkeys.

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