Strategies to enhance functional recovery from motor cortex lesion in non-human primates.

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OBJECTIVE

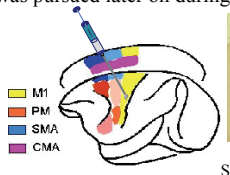
The goal of this study was to test two strategies to promote functional recovery from unilateral lesion of the primary motor cortex (M1) in non-human primates (Macaca fascicularis):

- **Cell therapy** (by autologous transplantation of adult cortical progenitor cells)
- **Anti-Nogo-A antibody**.

METHODS

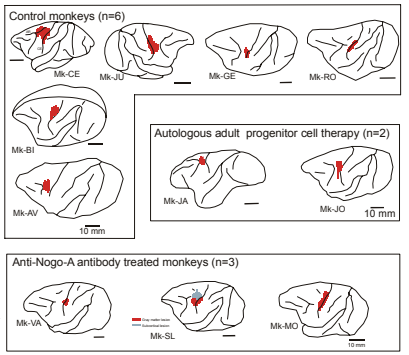
Experiments were conducted on **11** adult macaque monkeys trained to perform various manual dexterity tasks, including the "modified Brinkman board", requiring precision grip. The monkeys were then subjected to an unilateral permanent lesion of the hand representation in M1. Monkeys' behavioral performance was measured for each hand, before and after the lesion, until the recovery (complete or incomplete) of the contralesional hand reached a plateau and was pursued later on during several weeks.

Subjects
6 control monkeys (Mks)
3 anti-Nogo-A antibody treated Mks
2 Mks subjected to cell therapy



M1 lesion as seen in SMI-32 material for Mk-VA

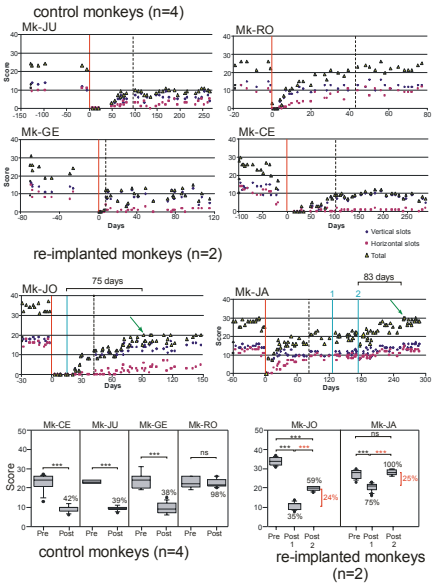
Initially, after the monkeys had reached a behavioral plateau, a lesion of the hand representation's area (fingers) was performed unilaterally in M1 by infusion of ibotenic acid. Six monkeys did not receive any treatment (control monkeys) while 2 monkeys were subjected to a cell therapy and 3 monkeys were treated with an anti-Nogo-A antibody.



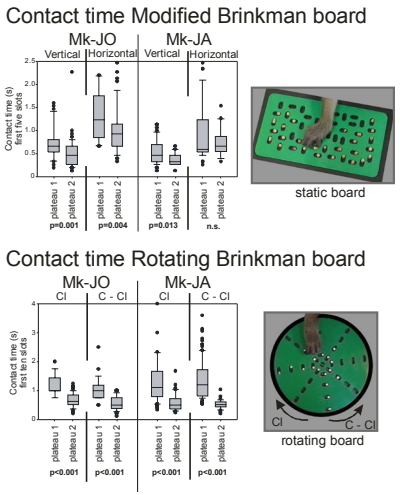
Lateral views of the M1 lesion in the eleven monkeys included in the present study

RESULTS

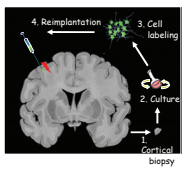
A Cell therapy



The manual dexterity was assessed by the score (nb. of pellets retrieved in 30 seconds from the slots in the modified Brinkman board task). Note, as expected, the deficit immediately after the lesion for the contralesional hand. In the control monkeys (no treatment), there was a "spontaneous" functional recovery reaching a final plateau. In contrast, in the two monkeys subjected to cell therapy, the first "spontaneous" plateau was followed by a rebound of recovery (corresponding to a second plateau), established about 80 days after cell implantation. The bottom graphs display the percentage of functional recovery for the control monkeys (left) and the treated monkeys (right).

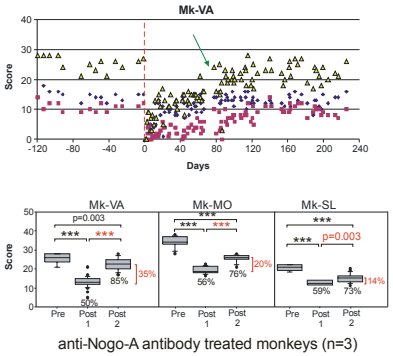


In addition to the score (see on the left), the manual dexterity was assessed more specifically by the "contact time" defined as the time of contact between the fingers and the successful grasping (in sec). The shorter the contact time the more dexterous is the monkey. The contact time data in the two treated monkeys demonstrate that the dexterity at the second plateau is (in most cases) significantly better than at the first plateau, as assessed in the modified Brinkman board (static pellets) or in the rotating Brinkman board (moving pellets).



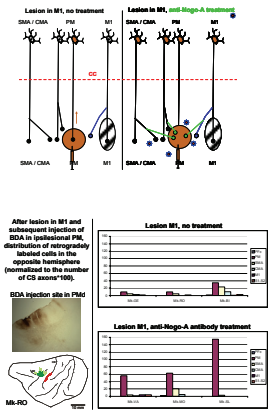
Principle of autologous adult cortical cell implantation

B Anti-Nogo-A antibody treatment



As observed for the monkeys subjected to cell therapy (panel A), the anti-Nogo-A antibody treated monkeys also show a rebound in their functional recovery curve (second plateau: see green arrow in Mk-VA), occurring about 80 days after onset of the treatment. No such second plateau was observed in the control monkeys (see panel A). The bottom graphs show the percentages of functional recovery in the 3 anti-Nogo-A antibody treated monkeys, to be compared with the control monkeys (in pannel A). The data are behavioral scores in the modified Brinkman board.

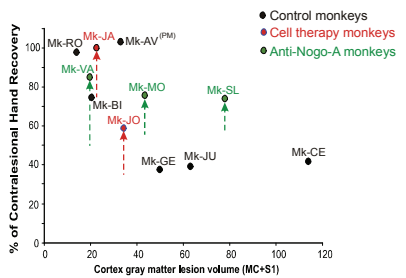
Tracing data



As PM plays a role in the functional recovery (Liu and Rouiller, 1999), we tested the hypothesis that the anti-Nogo-A antibody treatment promoted sprouting of the connections of PM (callosal connections in the present case). After BDA injection in PM, the number of callosal labeled cells in the intact hemisphere was higher in the anti-Nogo-A antibody treated monkeys than in the control monkeys.

CONCLUSION

Both treatments (cell therapy and anti-Nogo-A antibody) promote a better functional recovery from unilateral lesion of the motor cortex in macaque monkeys. In the anti-Nogo-A antibody treated monkeys, the recovery was accompanied by an enhanced sprouting of the callosal connections of the ipsilesional premotor cortex (PM).



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