Anti-Nogo-A antibody treatment enhanced recovery after unilateral lesion of the primary motor cortex (M1) in monkeys

A. Wyss[1], A. Belhaj-Saif[1], T. Wannier[1,2], J. Bloch[3], A. Mir[4], M.E. Schwab[2] and E.M. Rouiller[1]

1. Dept. Med., Univ. Fribourg, 1700 Fribourg, Switzerland 2. Dept. Neuromorphol., Univ. Zurich, 8057 Zurich, Switzerland
3. Dept. Neurosurg., Univ. Lausanne, 1011 Lausanne, Switzerland 4. Inst. Biomed. Res., Novartis, 4002 Basel, Switzerland

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INTRODUCTION

Recent studies in rats subjected to motor cortex lesion and treated with anti-NOGO-A antibody showed a significant behavioral recovery (Emerick et al., 2004; Papadopoulos et al., 2002; Wenk et al., 1999). In a recent study from our laboratory in non-human primates, anti-Nogo-A antibody treatment enhanced the recovery of hand dexterity after hemi section of spinal cervical cord (Freund et al. 2006).
The goal of this study is to assess the recovery of the hand dexterity in non-human primates, using sophisticated behavioral tests, following a lesion of the hand representation in motor cortex and treatment with anti-Nogo-A antibody.

METHODS

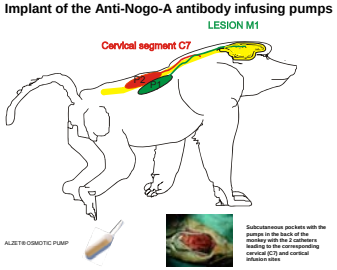
Experimental Protocol

Experiments were conducted on three adult monkeys (*macaca fascicularis)*

1. Behavioral training for various manual dexterity tasks
2. Mapping of M1 in left hemisphere using ICMS (intracortical microstimulation)
3. Lesion of hand representation (fingers) in left hemisphere by infusion of ibotenic acid (13.5µl (C,T) 16µl (V) [10µg ibotenic acid / 1µl saline])
4. 2 (T) or 4 (V) weeks of anti-NOGO-A treatment (11C7 [3.7mg /ml]) in 2 of the 3 monkeys
5. Behavioral assessment during several months post - lesion
6. Remapping of M1 in left hemisphere using ICMS

Behavioural evaluation of manual dexterity

Implant of the Anti-Nogo-A antibody infusing pumps

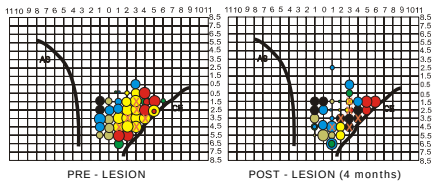


RESULTS

MAPPING DATA (ICMS)

UNTREATED monkey C

ICMS left hemisphere



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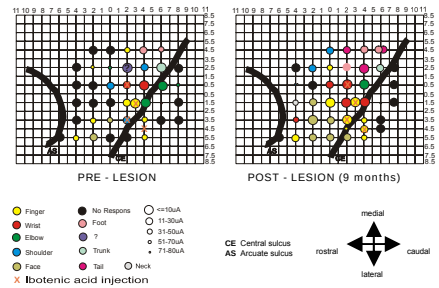
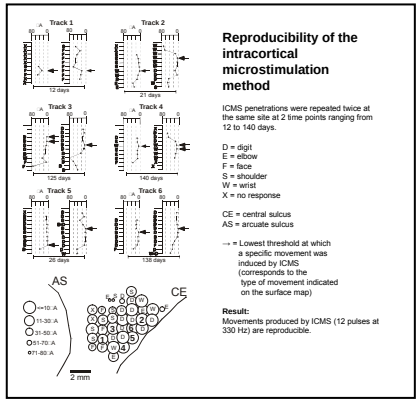
ICMS left hemisphere





Reproducibility of the intracortical microstimulation method

ICMS penetrations were repeated twice at the same site at 2 time points ranging from 12 to 140 days.

D = digit
E = elbow
F = face
S = shoulder
W = wrist
X = no response

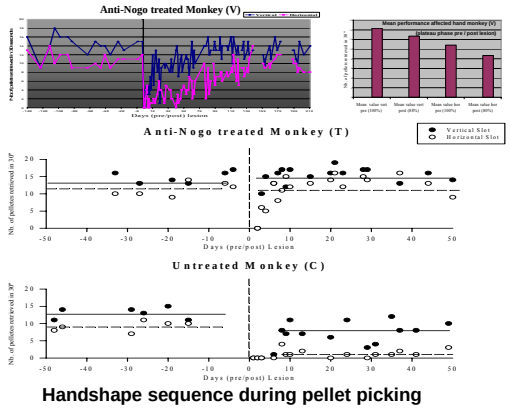
CE = central sulcus
AS = arcuate sulcus

→ = Lowest threshold at which a specific movement was induced by ICMS (corresponds to the type of movement indicated on the surface map)

Result:
Movements produced by ICMS (12 pulses at 330 Hz) are reproducible.

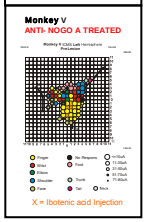
BEHAVIOURAL AND HISTOLOGICAL DATA

Modified Brinkman board scores of the right hand



Lesion reconstruction on two representative sections for the **UNTREATED** monkey

FUTURE DIRECTIONS, PRELIMINARY DATA



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The ibotenic acid injection disturbed the cytoarchitecture of the hand area in M1, but less than in the untreated monkey (is it related to the treatment ?)

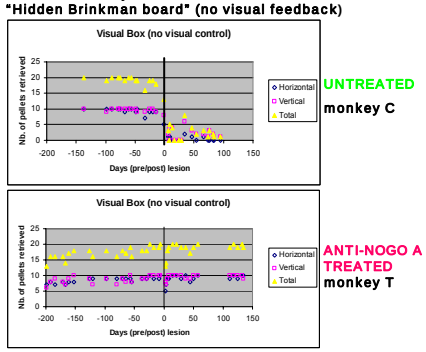
Handshape sequence during pellet picking

POST - LESION (118 days) UNTREATED monkey C

POST - LESION (8 days) ANTI-NOGO A TREATED monkey T

POST - LESION (30 days) ANTI-NOGO A TREATED monkey V

Manual dexterity assessed with the "Hidden Brinkman board" (no visual feedback)



CONCLUSIONS

These preliminary data using anti-nogo-A-antibody treatment after cortical lesion of the hand representation in M1 show that:

1. Behavioural recovery in the treated monkeys reached about 80 - 100% of the pre-lesion scores versus 30% for the untreated monkey.
2. ICMS effects were persistent in lesion sites in the treated monkeys and were absent in the untreated monkey.

In conclusion it is important to emphasize that the present observations were based on comparing data from two treated monkeys with that from one untreated monkey. Nevertheless, we believe that these data are important in revealing a remarkable degree of recovery in the treated monkeys, an observation which needs to be confirmed on a larger number of monkeys.

ACKNOWLEDGMENT

Supported by: SNF grants (31-61857.00,310000-110005 and 3100-110005); The National Center of competence in Research (NCCR): "Neuronal plasticity and repair"; Novartis Pharma