Effect of Anti Nogo-A antibody treatment on cortical lesion of the motor cortex of macaque monkeys assessed on Magnetic Resonance Imagery (MRI).

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Introduction

1. Central Nervous system lesions in adult human patients are intractable and often results in permanent deficits.
2. Anti Nogo-A antibody treatment enhances the reorganization of rodents sensorimotor cortex after cortical lesion in parallel to functinal recovery.
3. Transfer of the obtained results from rodents to non-human primate models required before eventual clinical trials.
4. Aim: MRI assessment of cortical lesion delimited to primary motor cortex (M1) (rostral to central sulcus) at regular time points before and after the lesion.

Methods

Three young adults macaque monkeys (age: 3-8 years, weight: 4-8 kg) one treated with an anti Nogo-A antibody (MK-AM), one treated with a control antibody (Mk-CB) and one untreated (Mk-CJ).

MRI session: duration about 45 minutes
Light dose of Ketalar for transport purposes
Complete anesthesia during the MRI acquisition by intramuscular injection (IM) of Medetomidine/Ketalar
Reverse of the anesthesia at the end of the experiment using IM injection of Antisedan.

MRI protocol:
The location and orientation of the head were constant along the different sessions (Fig. 1). The MRI acquisition parameters of the main protocol were the following: Siemens© 1.5 Tesla, slice thickness: 2mm, 2 TSE (TR: 4500 ms and TE 129 ms), FOV 140 mm). Image analysis was performed using the OsiriX© software.
Fig 3B: 2mm, MPR (TR 1390 and TE 4.85)
Fig 4B: 2mm, TIR (TR 7500 and TE 78)

Hypersingnal quantification
Using the Osirix software, delimitation of the hypersignal and determination of the volume (surface multiplied by the section's thickness and arithmetic addition of the consecutive volumes) in Fig.11.
Position of a virtual line going through the hypersignal defined as starting from the cingulate sulcus horizontally to the cortical surface and histogram showing the pixels intensity distribution along this axis.

Note: Mk-CB received an additional injection of Ibotenic acid 7 Days after the first injection as he showed good behavioural recovery. Therefore the analysis of the data made immediately after the lesion is not relevant, whereas the data obtained several weeks after the injections can be analysed.

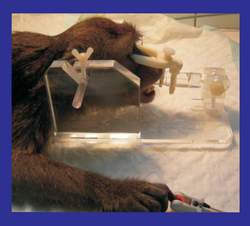

Fig 1: Picture showing the fixation of the head of the anaesthetised monkey in the head holder

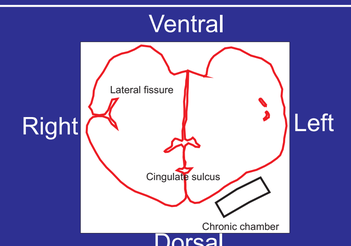

Fig. 2: Drawing of the coronal section of the brain at the level of the primary motor cortex

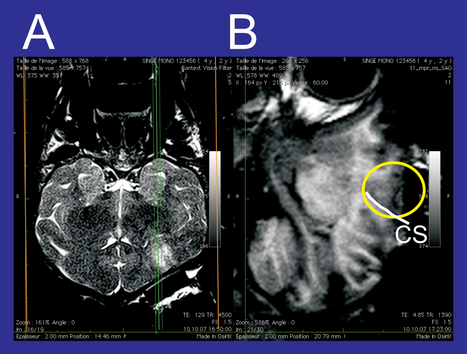

Fig.3 : MRI showing the localisation of the lesion in Mk-AM and its corresponding location on the parasagittal axis. B: Lesion: yellow circle. CS: central sulcus

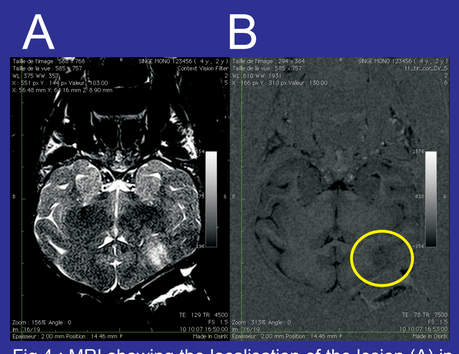

Fig.4 : MRI showing the localisation of the lesion (A) in Mk-AM in another acquisition protocol B, yellow circle)

Ibotenic acid lesion

Mk-AM

Number of sites 7 20 µl total injected

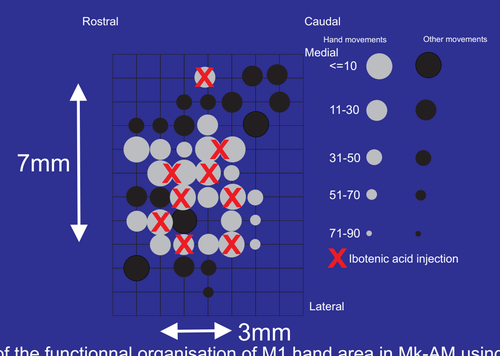

Fig. 5: Map of the functionnal organisation of M1 hand area in Mk-AM using Intracortical microstimulation (ICMS) and of ibotenic acid injections sites. Parameters of stimulation: stimulation train 13 pulses range 1-80 micramps.

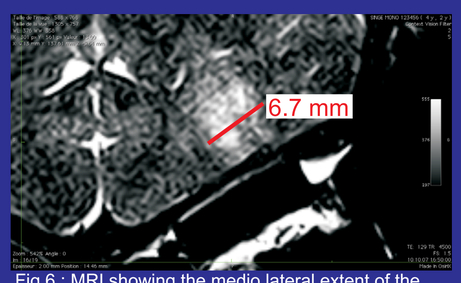

Fig.6 : MRI showing the medio lateral extent of the lesion in Mk-AM

Mk-CJ

Number of sites 6 18 µl total injected

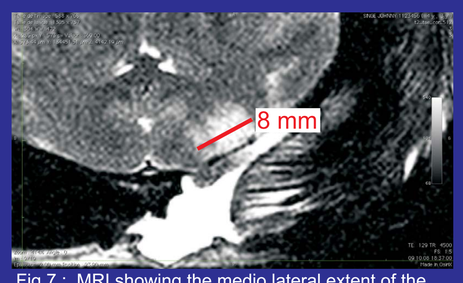

Fig.7 : MRI showing the medio lateral extent of the lesion in Mk-CJ

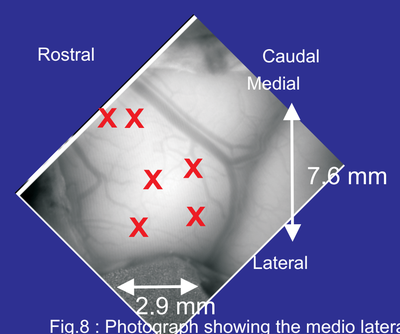

Fig.8 : Photograph showing the medio lateral extent of the lesion in Mk-AM

Results

1. 24 hours after the ibotenic acid infusion, lesion is detectable by the presence of hypersignal on several acquisition protocols (Figs. 3-4).
2. Hypersignal dimensions and locations correspond to the repartition of the ibotenic acid injections (Figs 5-8).
3. Hypersignal disappears already after 8 Days postlesion in the anti Nogo-A antibody treated animal (Mk-AM), whereas it remains at least a week longer in the control animals (Fig.9).
4. This is also observed in the quantification of results through histogram analysis of pixels and lesion volume measurement (Fig. 10).

Summary

Monkey	Before lesion	+ 1D	+ 8D	+ 15D	End
Mk-AM	-	++	+	-	-
Mk-CJ	-	++	++	++	-
Mk-CB	-	++	++	+	-

Table 1: Summary of the presence of hypersignal in the three monkeys involved in this study.

MRI assessment of the evolution of the cortical lesion in time

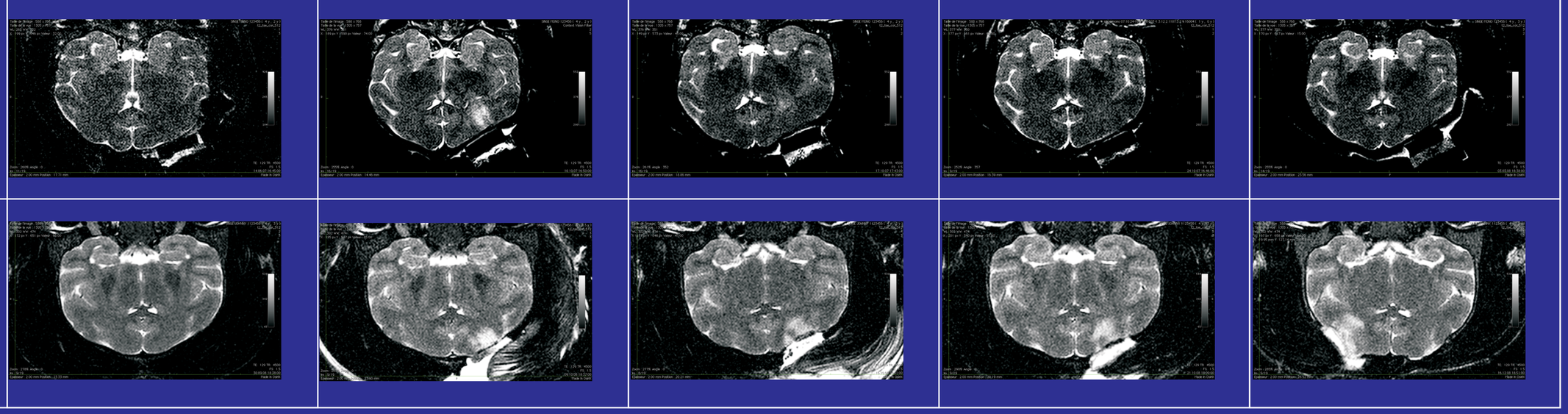

Fig.9 : MRI of coronal sections at the same location along the different sessions showing the evolution in time of the hypersignal in Mk-AM (upper row) and Mk-CJ (lower row) on the parasagittal axis

Quantification of the MRI data in time

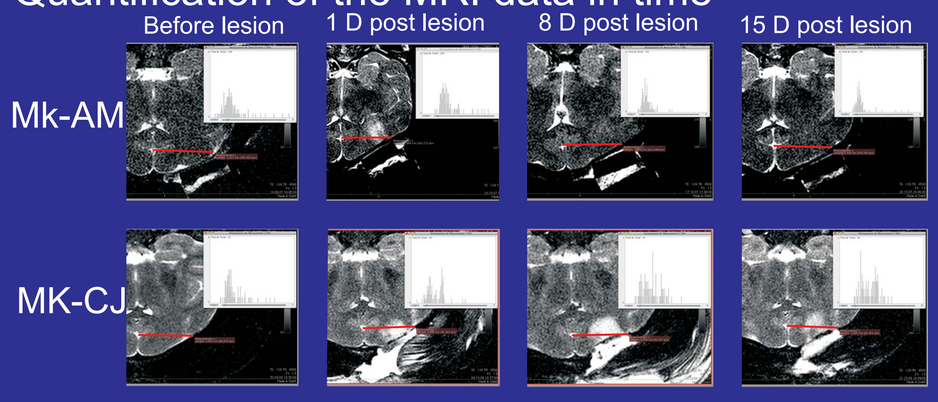

Fig.10 : Quantification of Cortical lesion made by analysis of the distribution of the pixels intensity along a virtual line crossing the lesion and similarly located in the different MRI sessions.

Lesion volume

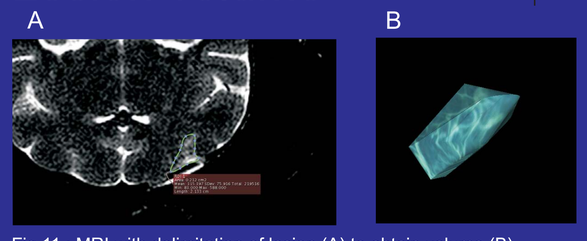

Fig.11 : MRI with delimitation of lesion (A) to obtain volume (B) performed in Mk-CB 22 D post lesions

Monkey	+ 1D	+ 22D
Mk-AM	202mm^3	0
Mk-CJ	230mm^3	52mm^3
Mk-CB	-	34mm^3

Table 2: Summary of the lesions volumes

Conclusion

In the anti-Nogo-A antibody treated monkey (Mk-AM), the hypersignal present immediately after the lesion disappeared more rapidely as compared to the control lesioned animals (Mk-CJ, Mk-CB).

Discussion

1. Correspondance between physiological extent of ibotenic acid infusions and hypersignal.
2. Clear difference of hypersignal dynamics between the two groups of animals (treated versus non treated): faster disappearance of the hypersignal in the treated animal compared to the control animals.
3. Note: MK-CJ: possible remaining lesion due to presence of strong oedema
4. Need further analysis including additional number of animals

Acknowledgments:
We would like to thank Véronique Moret, Christine Roulin and Françoise Tinguely (histology), Jocelyne Bloch (surgery), Joseph Corpataux and Laurent Bossy (animal keepers), Laurent Monney (informatics), Bernard Aebischer (electronics), André Gaillard (mechanics) and Jean-Marie Girard for MRI advises.