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Direct comparison of two techniques of transient inactivation of the primary motor cortex in macaque monkeys affecting motor control and precision grip

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Introduction

In human patients, to assess possible roles played by cortical motor areas in the limited spontaneous recovery of voluntary movements observed after unilateral stroke, a non-invasive transient inactivation technique such as repetitive transcranial magnetic stimulation (rTMS) would be valuable if reliable to functionally block cortical control.
The non-human primate model is adequate to directly compare the efficiency on motor behavior of a transient inactivation of the motor cortex by a non-invasive technique such as rTMS, and by an invasive pharmacological method such as micro-infusion of a GABA-ergic agonist, muscimol, allowing the distinction between a network inactivation (rTMS) and a focal cellular inactivation (muscimol).

A «reach and grasp drawer» task requiring opposition of thumb and index finger (precision grip) was used to assess monkey´s manual dexterity.
Thus, a direct comparison of the motor consequences resulting from different cortical inactivation methods observed in the same subject and for the same behavioral task could give valuable information on the role played by the primary motor cortex (M1) and/or the motor network involved in functional recovery.

I Inactivation of M1

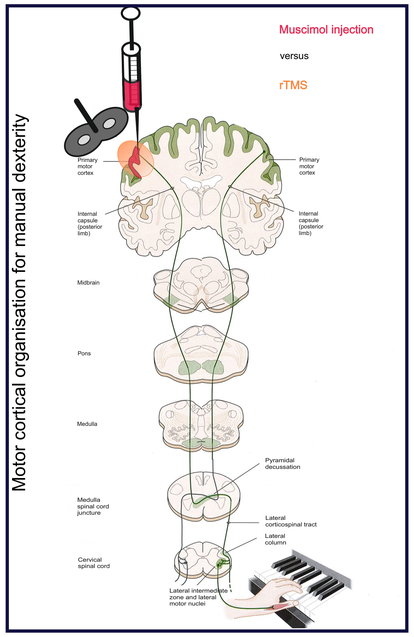


Fig. I: Schematic representation of the experimental paradigm, showing muscimol inactivation of the hand representation in the primairy motor cortex (red) and application of rTMS using a «figure of eight» coil over M1 (orange).

II Unimanual «reach and grasp drawer» task

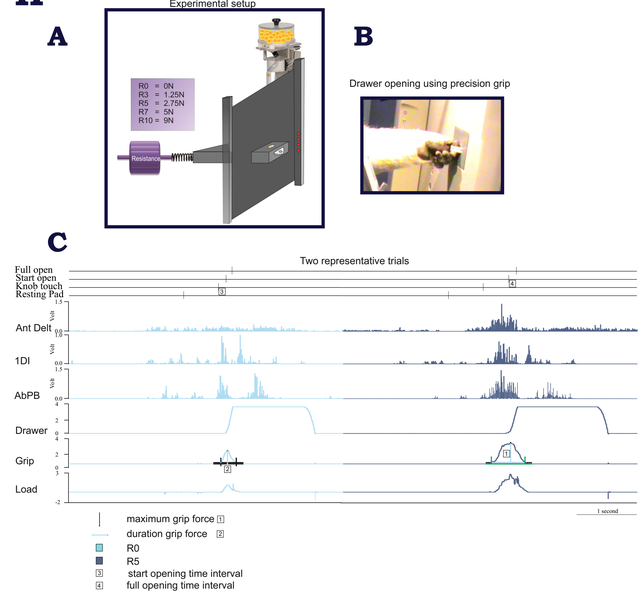


Fig. II Panel A: Schematic representation of the «reach and grasp drawer» task. Panel B: Picture showing the precision grip used by a behaving non-human primate to grasp the knob and pull the drawer. Panel C: Recordings of motor parameters and rectified EMG activity of intrinsic hand muscles (1DI and AbPb) and proximal muscle (Ant Delt) showing changes between low resistance to the opening (light blue) and high resistance (dark blue).

III Temporal unfolding of the experimental procedure

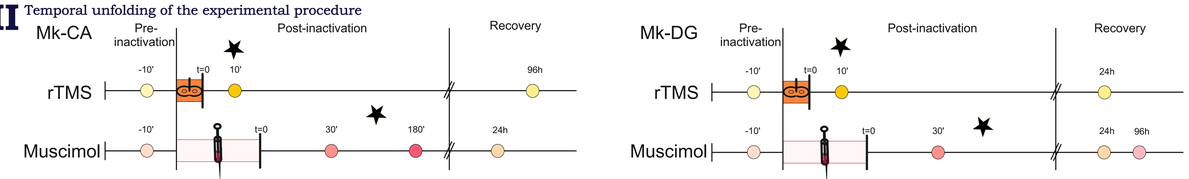
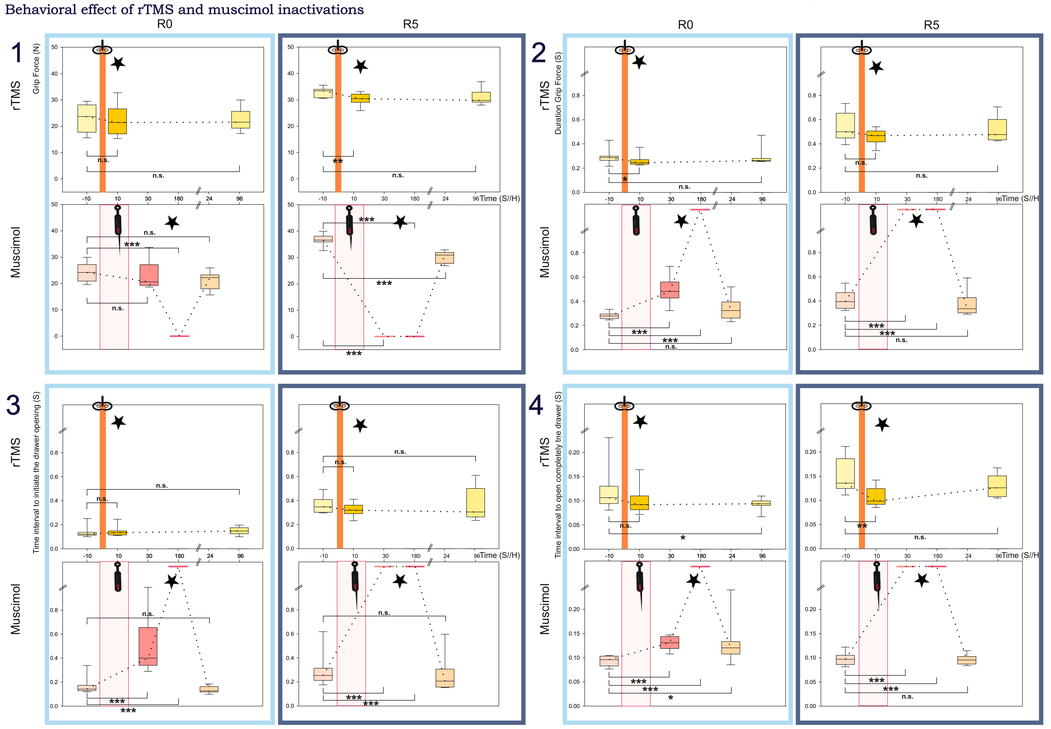


Fig.III:Temporal unfolding of the experimental procedure of the 2 different types of inactivation and of the «reach and grasp drawer» task session, in both animals (Mk-CA and Mk-DG). The star corresponds, according to litterature, to the moment where the more dramatic effect of the inactivation is expected.

IV Behavioral effect of rTMS and muscimol inactivations



	Mk-CA				Mk-DG			
	R0		R5		R0		R5	
Pre versus post effect (%)								
rTMS	*		*		*		*	
Maximal grip force	-3	-3	-8	-6	-11	+10	+2	+13
Grip force duration	-6	-1	-12	-4	-3	+1	-4	-14
Timing start drawer opening	+12	+9	-7	-1	-10	-8	-3	+17
Timing full drawer opening	-24	-8	-23	-14	-2	-5	+6	+6
Muscimol	*		*		*		*	
Maximal grip force	-6	-2	nil	-44	-9	nil *	nil	nil *
Grip force duration	+76	+20	∞	-10	+280	∞ *	∞	∞ *
Timing start drawer opening	+195	+80	∞	-12	+220	∞ *	∞	∞ *
Timing full drawer opening	+40	+40	∞	-2	+179	∞ *	∞	∞ *

Fig. IV: Box plots showing the direct comparison of the effect of the reversible inactivations, rTMS, versus muscimol, on maximal grip force, force duration and time needed to perform the «reach and grasp drawer» task, at resistances 0 (0N) and 5 (2.75N) in one monkey (Mk-CA). Statistical significance: n.s.: none, *: p<0.05, **: p<0.01, ***: p<0.001.

Table: Summary of the effects of the rTMS versus muscimol inactivations in the two monkeys (Mk-CA and Mk-DG). The data are expressed in % of lack (red) or gain (green) of maximal grip force, duration of the grip force, timing of drawer initiation of the opening, and timing of drawer fully opening to perform the «reach and grasp drawer» task, at resistances 0 (0N) and 5 (2.75N) (light to dark colored according to the lack or gain: 1-9%/10-19%/20-99%/ and >100%. The comparison is done between the pre session versus the session post-inactivation with most awaited effect (star) and versus the session post awaited recovery.
*Mk-DG received a higher concentration of muscimol than Mk-CA, but completely recovered from the inactivation after 23 days.

Methods

Subjects:
2 adult macaca fascicularis, 1 male (Mk-DG) and 1 female (Mk-CA). Presentation of the detailed results for Mk-CA, plus summary of results for both (Mk-DG and Mk-CA).

Cortical inactivation (Fig.I):

- Invasive transient* inactivation: microinfusion of GABA-A agonist Muscimol in several tracks in M1where ICMS elicited single joint finger movements (ICMS=intracortical microstimulation: train of 6-9 pulses 0.2 ms width at 333 Hz).

*Transient inactivation refers to the behavior.

- Non-invasive repetitive transcranial magnetic stimulation (rTMS): rTMS at 80% of active motor threshold over hand area M1, identified by functional mapping, using a pediatric coil (Magventure©, theta burst stimulation: 600 pulses within 30 seconds at trains of 3 pulses).

Behavioral assessement of manual dexterity (Fig.II):
We applied a similar temporal unfolding in both experiments between transient inacivation and acquisition of behavioral data. The «reach and grasp drawer» task consists for the animal to pull a drawer against different levels of resistance to the opening and to retrieve a food pellet located inside the drawer. Several parameters are continously measured, such as maximal grip force, duration of the grip force and time needed to perform the task: time to initiate the opening of the drawer and time to fully open the drawer (Fig.IV.1,2,3,4, repectively). Load forces data are not presented here.

Results

A more challenging task obtained by increased resistance to the opening of the drawer did not affect motor performance in the cortical non-invasive inactivation (rTMS), whereas after cortical invasive inactivation (muscimol), at similar time points after the inactivation, the manual dexterity was affected in grip force duration and time needed to perform the task, as the animals were not able to perform the task at all.
Muscimol inactivation significantly decreased the grip force, which became insufficient to open the drawer at the highest resistance. rTMS inactivation produced almost no decrease of grip force, which remained however sufficient to sucessfully open the drawer at all resistances (Fig.IV.1).
Consistently, the time needed to perform the task drastically increased consequently to muscimol inactivation whereas it tended to stay stable at the rTMS inactivation (Fig.IV.2,3,4).

Conclusions and perspectives

According to our results, when both techniques of inactivation were similarly applied in two macaque monkeys, the same pattern of effects were observed in the two animals, such as some changes in the expression of the motor behavior. Nevertheless, these effects were very small in network inactivation (rTMS) as compared to focal inactivation (muscimol), although sometimes significant.
We did not measure the motor evoked potentials (MEPs) of finger muscles before and after rTMS, which is a sign of the effectiveness of the rTMS, but we confirmed the position of the coil after the rTMS by stimulating the cortex and observed the same movement as before the rTMS. Therefore, theta-burst rTMS (applied according to Goldsworthy et al. (2012)) could be insufficient to obtain a behavioral effect even in a complex motor task, which is however adequate to assess fine manual dexterity. These results should be confirmed with more subjects.