

Introduction

The present report represents an initial step of a broader study aimed at testing the therapeutic strategy of transplanting autologous adult neural progenitor cells in parkinsonian (MPTP) macaque monkeys. To extract and put in culture autologous progenitor cells to be subsequently transplanted in the striatum, a unilateral biopsy was first performed in the dorsolateral prefrontal cortex (dlPFC) in four adult monkeys (Figure 1). MRI was used to establish the location and size of the cortical biopsies (Figure 4). This study demonstrates the behavioral effects of the dlPFC biopsy in fine motor tasks.

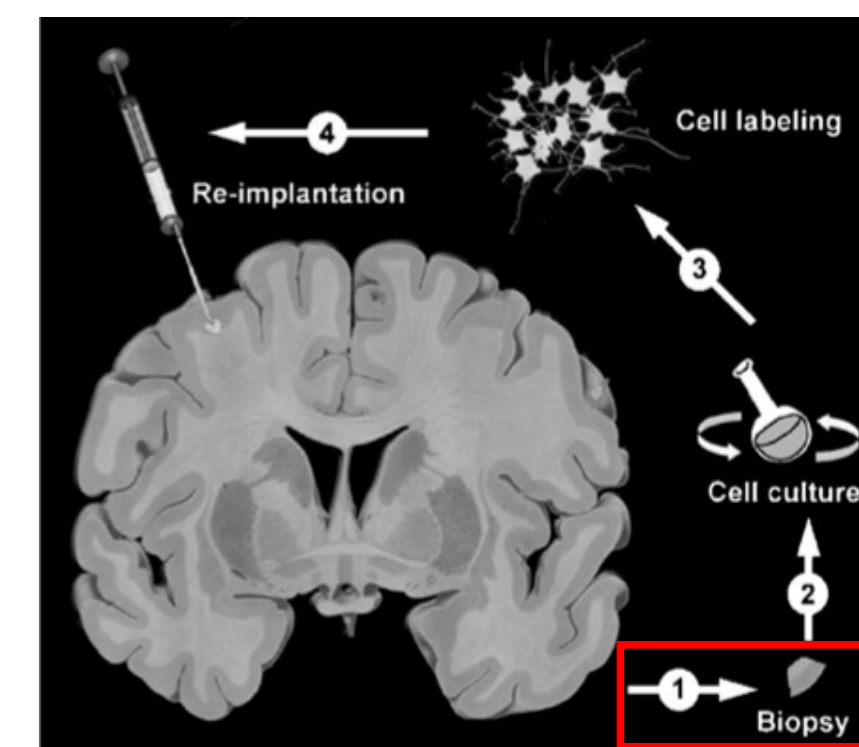


Figure 1: Illustration of the therapeutic strategy of autologous adult neural progenitor cells. The first step consists in performing a small cortical biopsy in the dorsolateral prefrontal cortex (dlPFC) in each monkey. Cells are then put in culture, labeled before being transplanted bilaterally into the striatum of the same subject (Brunet et al. 2005).

Methods

Before cortical biopsy in dlPFC, the four animals were daily trained to perform, with one or the other hand, two unimanual motor tasks: (1) the “Modified-Brinkman board task” in which monkeys have to retrieve food pellets from 25 vertical and 25 horizontal wells (Figure 2); and (2) “the reach and grasp drawer task” in which monkeys have to pull open a drawer against increasing resistances. The force required opening the drawer (load force) and the force applied on the knob (grip force) were recorded (Figure 3). One of the animals was excluded from the reach and grasp drawer task analysis as the task was not executed adequately.

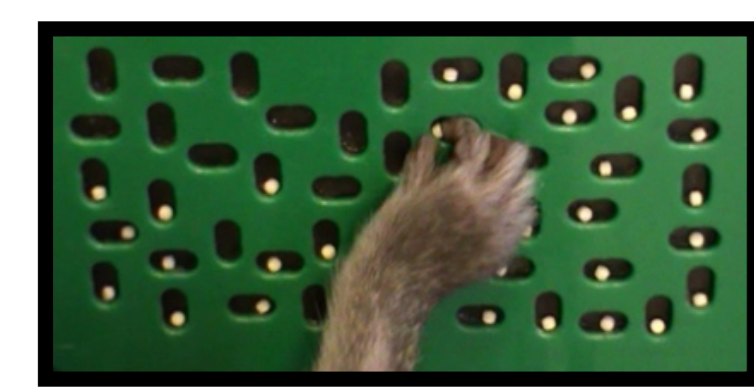


Figure 2: The «Modified-Brinkman board task», in which the monkey has to retrieve banana food pellets, from 25 horizontal and 25 vertical slots. Dimension of slots: 15 mm long, 8 mm wide and 6 mm deep.

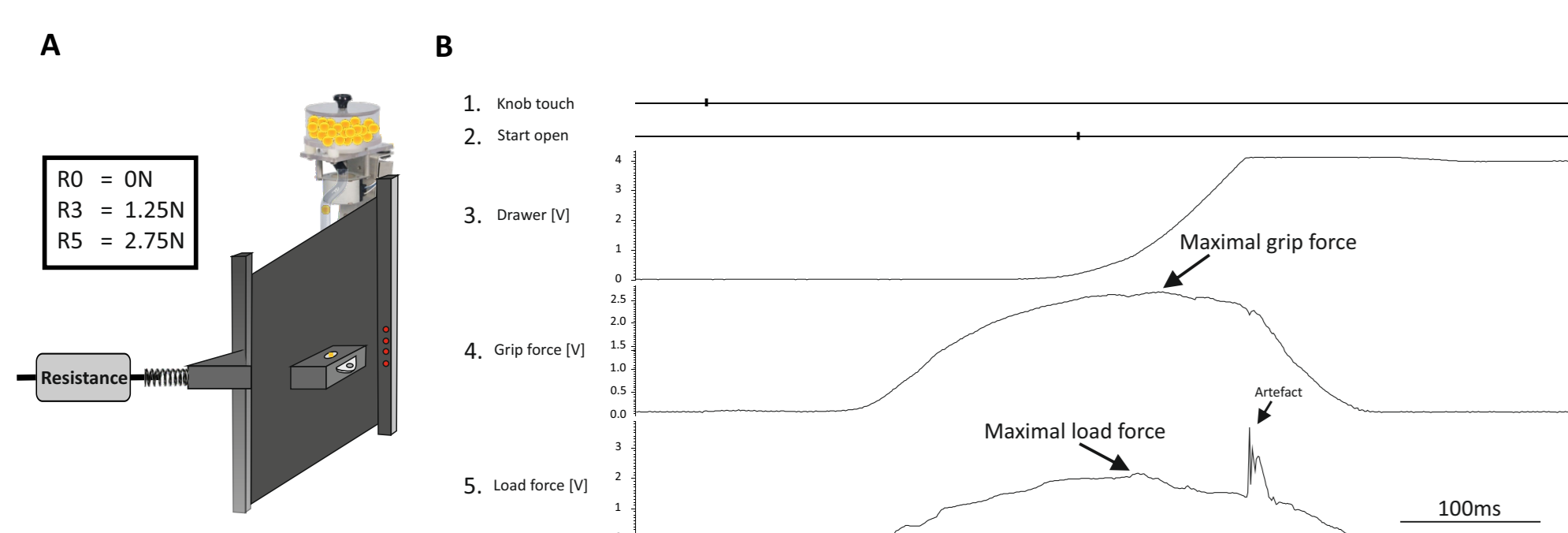


Figure 3: (A) Representation of the «reach and grasp drawer task» setup with the adjustable resistances in Newtons. (B) Raw data curves are shown: 1. The “tic” represents the time point when the monkey touches the knob of the drawer. 2. The “tic” represents the time point when the drawer starts opening. 3. The displacement of the drawer. 4. The grip force (the force applied on the knob) and 5. The load force (the force applied to open the drawer).

Biopsies (MRI)

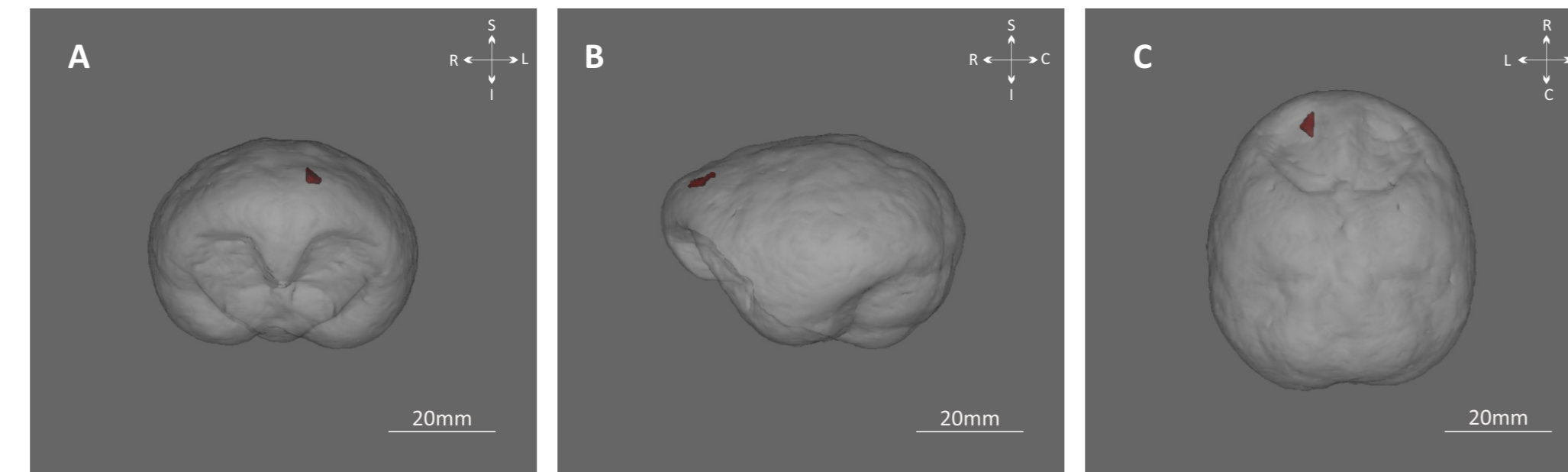
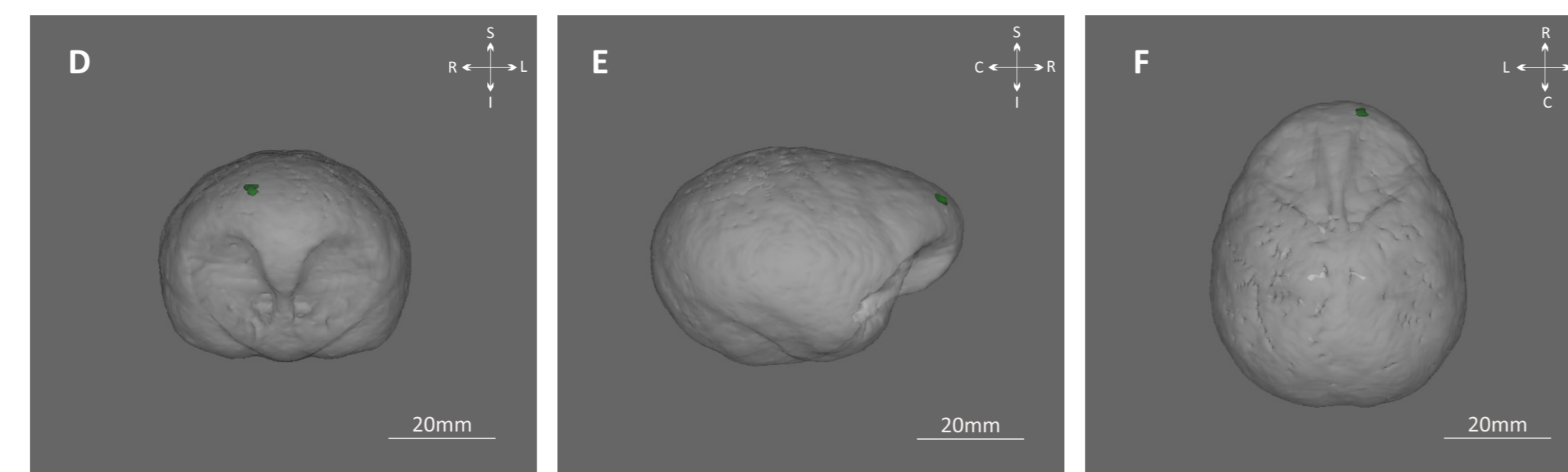
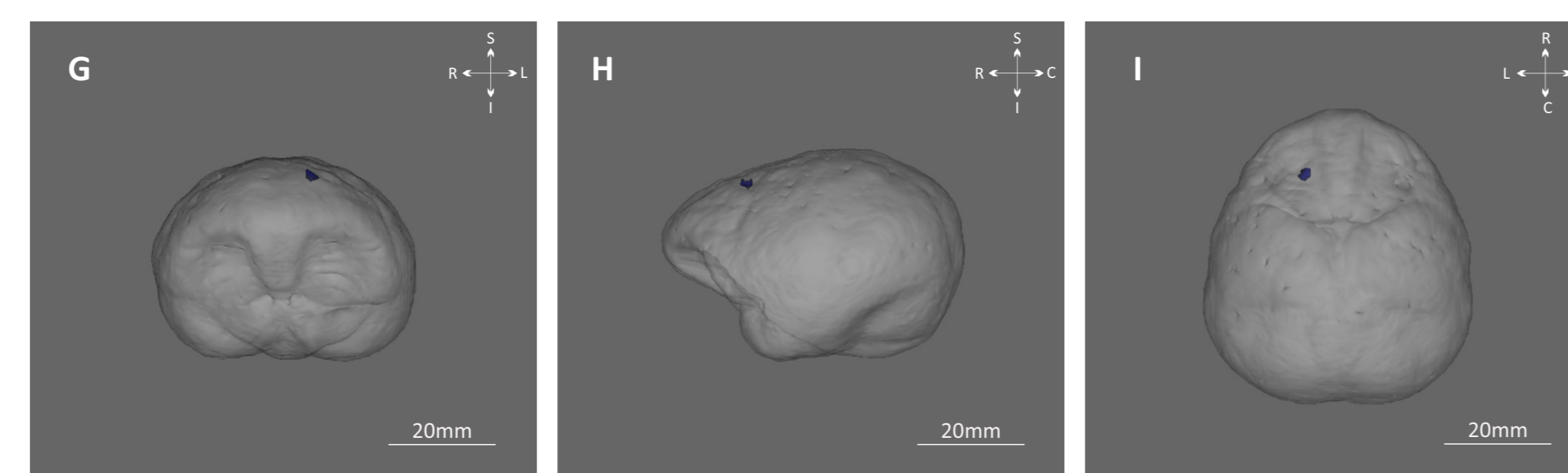
Mk-LY - Volume of dlPFC biopsy = 14 mm³Mk-MY - Volume of dlPFC biopsy = 7 mm³Mk-LL - Volume of dlPFC = 7 mm³

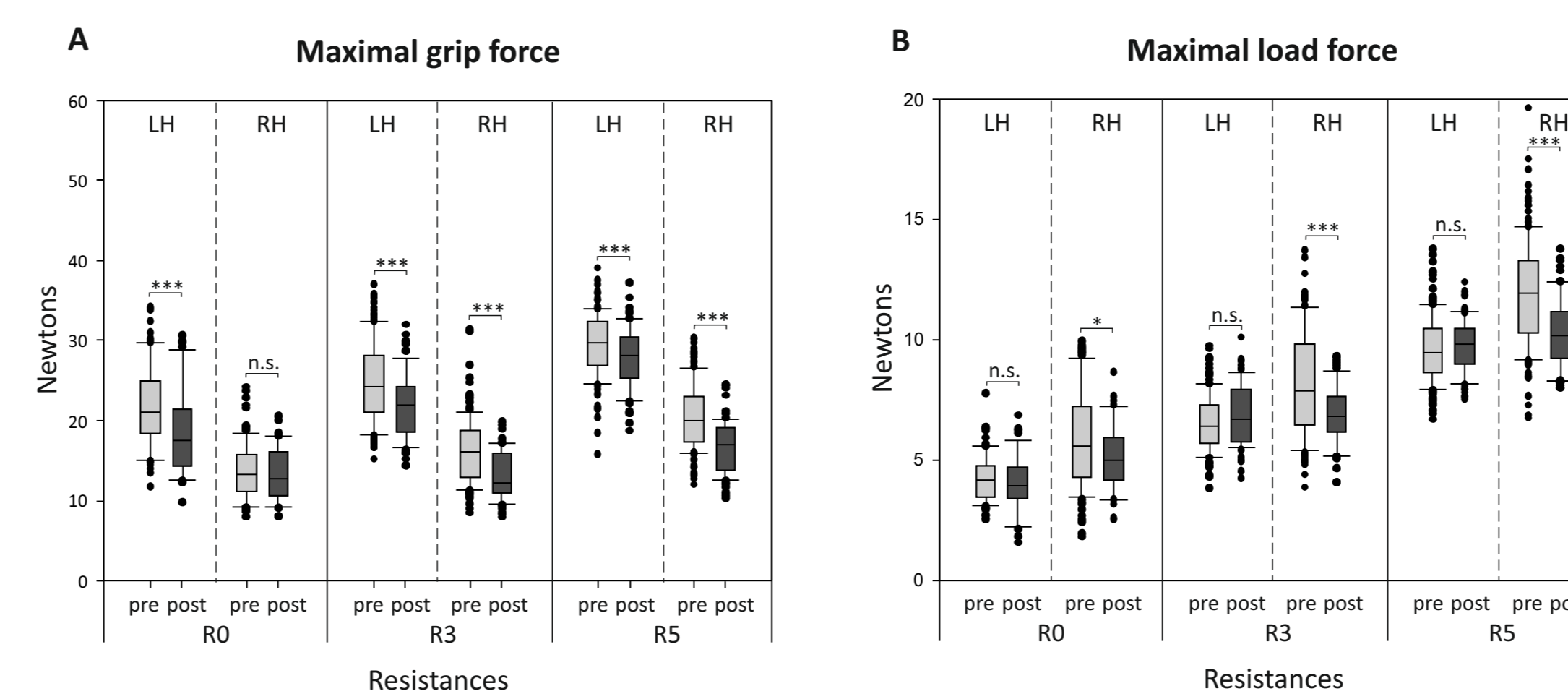
Figure 4: Illustration of the dlPFC biopsy in a 3D view of the brain. Each biopsy was estimated in a T1-weighted MRI scan using software FSLView v3.2.0. (A,B,C) Cortical biopsy of Mk-LY (in red). Volume of the biopsy is 14mm³. (D,E,F) Cortical biopsy of Mk-MY (in green). Volume of the biopsy is 7mm³. (G,H,I) Cortical biopsy of Mk-LL (in blue). Volume of the biopsy is 7mm³. Legends: (A,D,G) Frontal view of the brain. S=superior, I=inferior, R=right, L=left. (B,E,H) Lateral view of the brain. S=superior, I=inferior, R=rostral, C=caudal. (C,F,I) Top view of the brain. R=rostral, C=caudal, L=left, R=right.

Results

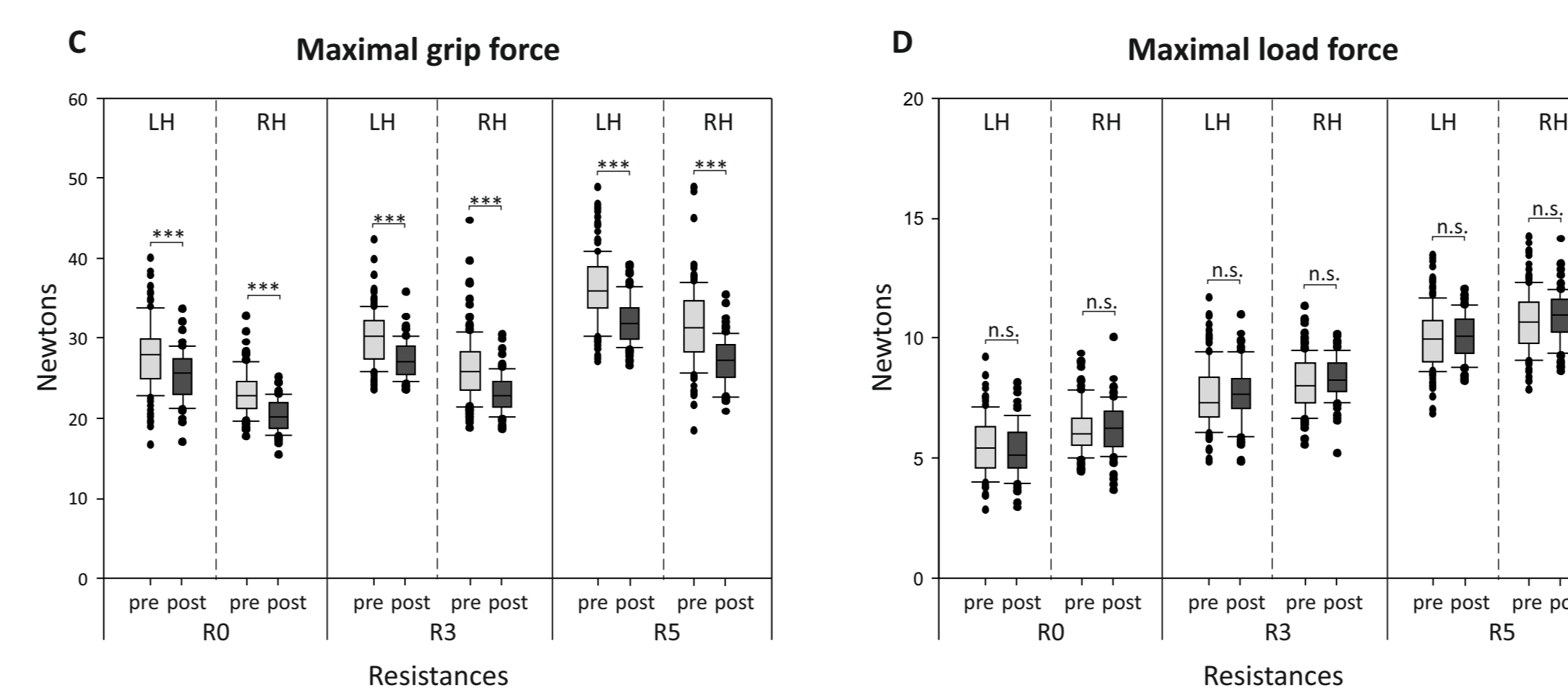
As expected for a small biopsy volume in dlPFC, there was no significant change both in motor performance (number of pellets retrieved) and in motor strategy (temporal sequence of visiting the wells) for the “Modified-Brinkman board task” (Figure 6). In contrast, in the “reach and grasp drawer task”, a significant decrease of the maximum grip force was observed post-biopsy sessions for each resistance and for each hand. In Mk-MY, the maximal grip force decrease was present for both hands and at all resistances (Figure 5C) whereas, in Mk-LL, the effect on grip force was restricted to the ipsilesional hand (Figure 5E); in addition, a decrease of the load force was largely observed in the ipsilesional hand (Figure 5F); in addition, the load force was affected in the contralesional hand (Figure 5A); in addition, the load force was affected in the contralesional hand.

Reach and grasp drawer task results

Mk-LY



Mk-MY



Mk-LL

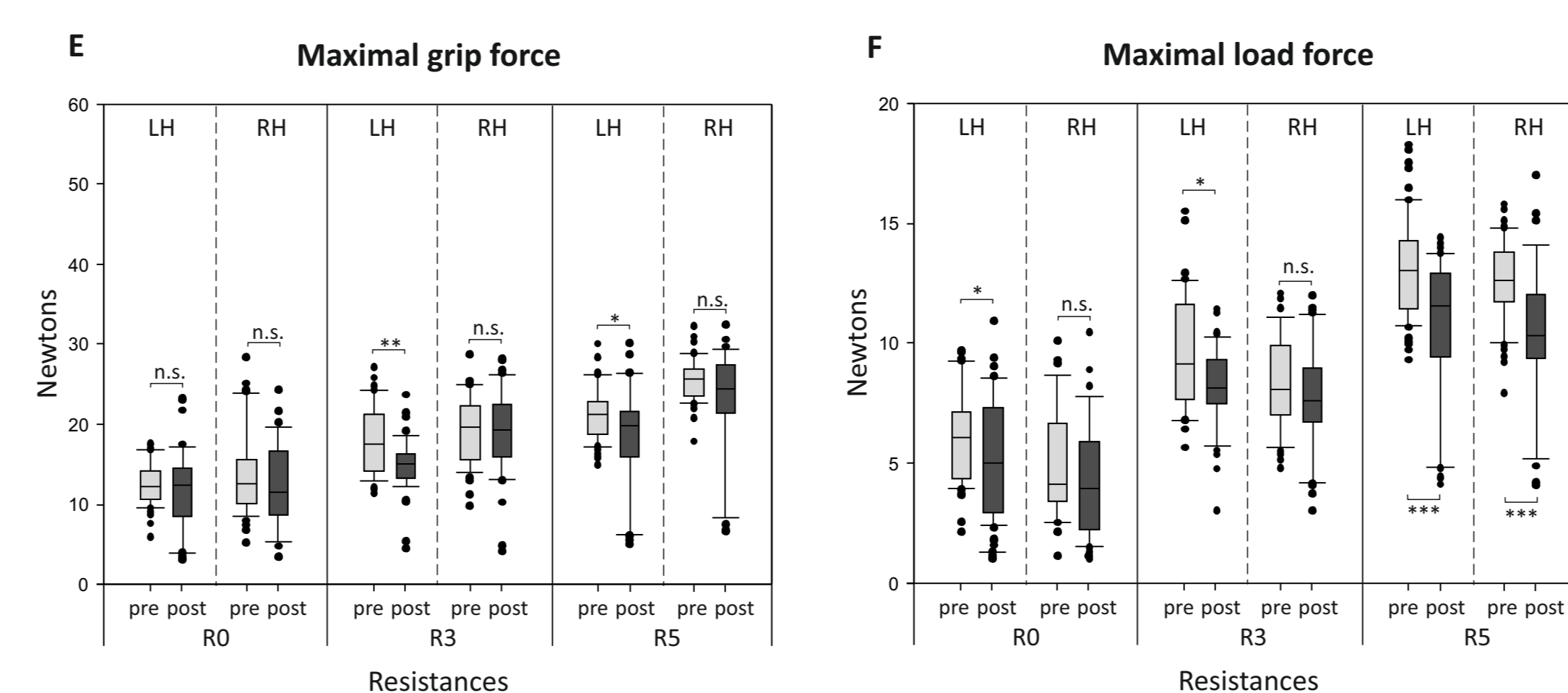
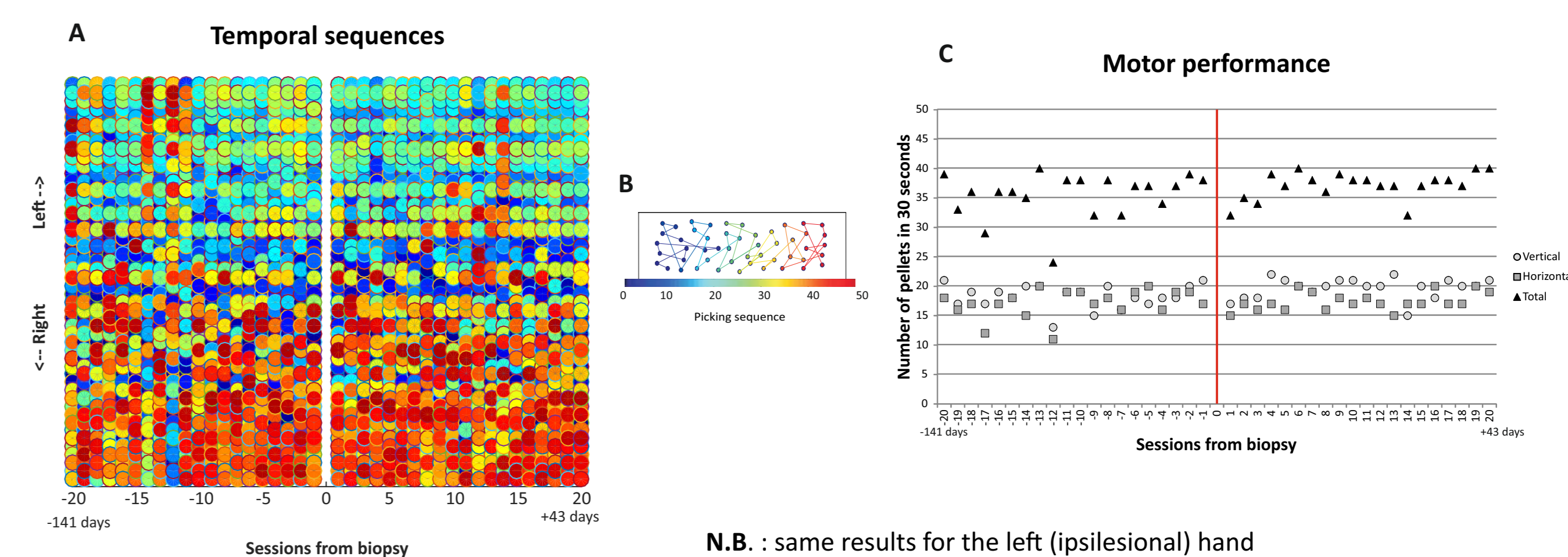


Figure 5: The graphs show the quantitative assessment in the “reach and grasp drawer task”, separately for the 3 resistances R0, R3 and R5. For each resistance, the left hand (LH) and the right hand (RH) are presented. Box plots are composed of all trials before (pre) and after (post) the cortical biopsy. Statistical analyses (t-test/Mann-Whitney test) compare maximal grip and load forces between pre-biopsy and post-biopsy sessions for each resistance and for each hand. Statistical differences are indicated with: * is for $p < 0.05$, ** for $p < 0.01$, *** for $p < 0.001$. n.s. = meaning statistically non-significant. (A,B) The graphs show the maximal grip force and maximal load force for Mk-LY where right hand is the contralesional hand. (C,D) The graphs show the maximal grip force and maximal load force for Mk-MY where the right hand is the ipsilesional hand. (E,F) The graphs show the maximal grip force and maximal load force for Mk-LL where the right hand is the contralesional hand.

To sum up, in Mk-LL, the ipsilesional hand was more affected (in load force and grip force) than the contralesional hand (only the load force at R5); the biopsy was located more caudally than in the two other monkeys. In addition, the load force amplitude in Mk-LY was only affected in the contralesional hand and the grip force decrease in both hands (except for one resistance); the biopsy was located more rostrally than in Mk-LL. Mk-MY, in which the biopsy was located more rostrally than in the two other monkeys, showed a decrease only for the grip force at all resistances and for both hands.

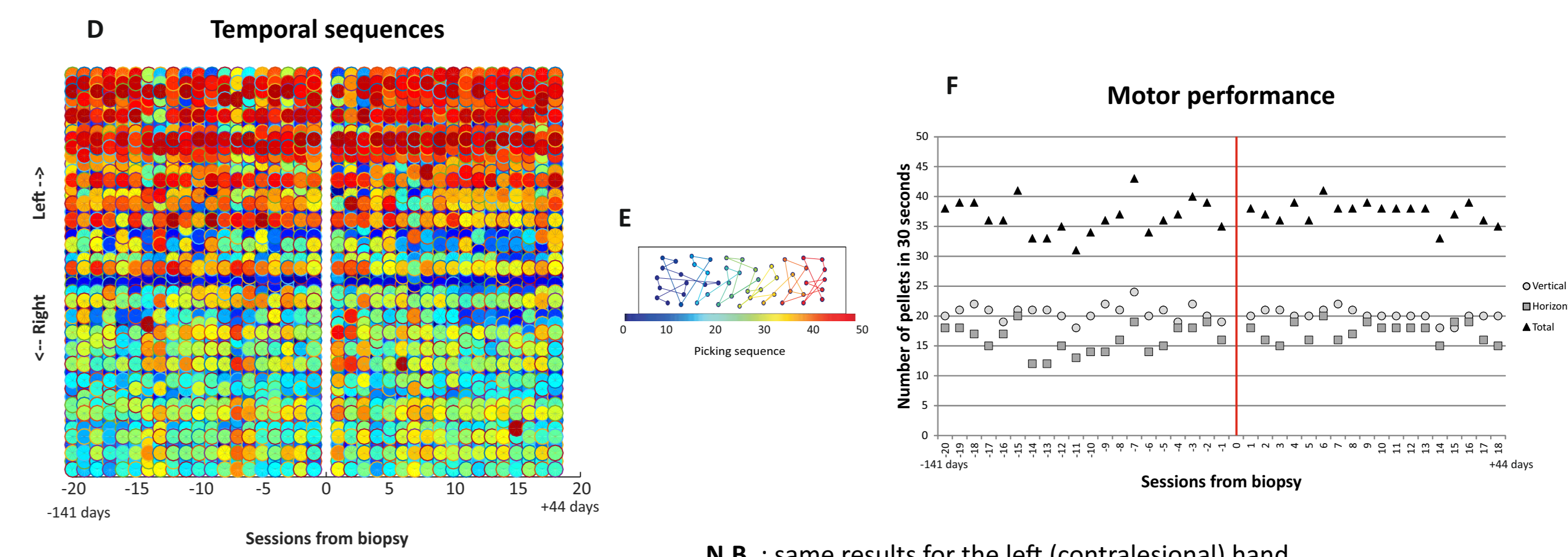
Modified-Brinkman board task results

Mk-LY - Right (contralesional) Hand



N.B. : same results for the left (ipsilesional) hand

Mk-MY - Right (ipsilesional) Hand



N.B. : same results for the left (contralesional) hand

Figure 6: The color coded graphs show the temporal sequences and the motor performance in the Modified-Brinkman board task, respectively. The x-axis displays the sessions from the biopsy (biopsy = session 0) and the x-y plots. (A,D) Graphs illustrate the right-left temporal sequences. The y-axis shows the right-left positions of the 50 slots. (B,E) An example of a right-left temporal sequence with the corresponding color code. The blue color represents the first slot visited by the monkey. The red color is the last slot visited by the monkey. (C,F) Graphs show the motor performance (number of pellets taken in 30 seconds = score).

Discussion

The results suggest a contribution of the dlPFC in the control of the grip force amplitude in monkeys, more precisely in the prediction of the grip force required. Indeed, at each resistance tested, the monkeys performed ten consecutive trials, allowing prediction based on working memory of the grip force to be produced. These data in non-human primates are consistent with a recent report in human subjects, arguing for a role of dlPFC in the prediction of grip force (Wasson et al., 2010). However, variations between the three monkeys may be due to different positions and sizes of the dlPFC biopsies. These various positions suggest a more pronounced contribution of the rostral dlPFC in the grip force prediction. Moreover, indirect interactions between dlPFC and primary motor cortex (M1) (contra- and ipsi-lateral) may vary according to either the rostro-caudal axis and the type of movement (precision grip, proximal movement,...).

References

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