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Variability of manual dexterity performance in non-human primates (*Macaca fascicularis*)

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The goal of this study was to quantify the inter-individual and intra-individual variability of manual (digits) skill in adult macaque monkeys, over a motor learning phase and, later on, when motor skills were consolidated. The hypothesis is that several attributes of the stable manual dexterity performance can be predicted from learning characteristics. The behavioral data were collected from 20 adult *Macaca fascicularis*, derived from their dominant hand, defined as the hand exhibiting a better performance than the other. Two manual dexterity tasks were tested: (i) the "modified Brinkman board" task, consisting in the retrieval of food pellets placed in 50 slots in a board, using the precision grip (opposition of the thumb and index finger); (ii) the "reach and grasp drawer" task, in which the grip force and the load force were continuously monitored while the monkey opened a drawer against a resistance, before grasping a pellet inside the drawer. The hypothesis was verified for the performance of manual dexterity after consolidation, correlated with the initial score before learning. Motor habit, reflected by the temporal order of sequential movements executed in the modified Brinkman board task, was established very early during the learning phase. As mostly expected, motor learning led to an optimization of manual dexterity parameters, such as score, contact time, as well as a decrease in intra-individual variability. Overall, the data demonstrate the substantial inter-individual variability of manual dexterity in non-human primates, to be considered for further pre-clinical applications based on this animal model.

In the common language, some people are described as clumsy whereas others have recognized talents to practice challenging motor tasks with great manual (digits) dexterity, such as musicians, top sports performers, as well as in some professional activities requiring high degree of precision in motor control (e.g., handmade watchmakers). Such inter-individual variability of motor skill is accompanied by some degree of intra-individual variability as the manual dexterity of a human being is subjected to variations from one day to the next, as well as to improvement resulting from motor practice. Manual dexterity corresponds to the skill to control independently and precisely each finger. From an evolutionary point of view, exquisite manual dexterity is largely considered as a prerogative of primates, as other mammalian orders do not exhibit such a high degree of manual dexterity, in spite of some recent findings providing evidence in favor of some manual skill in rodents for instance (see e.g., Sacrey, Alaverdashvili, & Whishaw, 2009; Whishaw, Whishaw, & Gorny, 2008; Whishaw, Travis, Koppe, Sacrey, Gholamrezaei, & Gorny, 2010; but see also Klein, Sacrey, Whishaw, & Dunnett, 2012). The specialty of primates for manual dexterity is based on the specific anatomical organization of the primate motor system, comprising the direct cortico-spinal projection called the cortico-motoneuronal (CM) system (see Lawrence & Hopkins, 1976; Lawrence, Porter, & Redman, 1985;

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Lemon, 2008). The progressive evolution of the CM system across mammalian species is correlated with an increasing manual skill (see e.g., Courtine et al., 2007). Consequently, the non-human primates represent a unique animal model to study mechanisms involved in manual dexterity, which are also applicable to human subjects. For instance, monkeys have been used extensively to investigate experimentally the consequences on manual dexterity of various types of lesions affecting the motor system (e.g., Bashir et al., 2012; Beaud et al., 2008; Beaud et al., 2012; Bihel et al., 2010; Brinkman, 1984; Brinkman & Kuypers, 1973; Dancause & Nudo, 2011; Dancause et al., 2005; Dancause et al., 2006; Darling et al., 2009; Darling et al., 2010; Darling et al., 2011; Darling et al., 2013; Eisner-Janowicz et al., 2008; Friel & Nudo, 1998; Friel, Heddings & Nudo, 2000; Frost, Barbay, Friel, Plautz & Nudo, 2003; Galea & Darian-Smith 1997; Glees & Cole, 1950; Hoogewoud et al., 2013; Kaeser et al., 2010; Kaeser et al., 2013; Liu & Rouiller 1999; Marshall et al., 2003; McNeal et al., 2010; Murata et al., 2008; Nishimura et al., 2007; Nudo & Milliken, 1996; Nudo, Wise, SiFuentes, & Milliken, 1996; Ogden & Franz, 1917; Passingham, Perry, & Wilkinson, 1983; Pizzimenti et al., 2007; Roitberg et al., 2003; Rouiller et al., 1998; Sasaki & Gemba, 1984; Schmidlin, Wannier, Bloch, & Rouiller, 2004; Schmidlin et al., 2005; Schmidlin et al., 2011; Travis, 1955; Wannier, Schmidlin, Bloch, & Rouiller, 2005) and, in some cases, also to test the potential of various treatments after such lesions (e.g., Freund et al., 2006; Freund et al., 2007; Freund et al., 2009; Hamadjida et al., 2012; Kaeser et al., 2011; Plautz et al., 2003; Sugiyama et al., 2013; Wyss et al., 2013).

Numerous studies shed light on the anatomical, physiological and developmental aspects underlying manual dexterity in monkeys (e.g., Alstermark et al., 2011, Alstermark & Isa, 2002, 2012; Armand, Edgley, Lemon, & Olivier, 1994; Armand, Olivier, Edgley, & Lemon, 1997; Borra, Belmalih, Gerbella, Rozzi, & Luppino, 2010; Bortoff & Strick, 1993; Darian-Smith, Galea, & Darian-Smith, 1996; Darian-Smith et al., 1996; Darian-Smith, Burman, & Darian-Smith, 1999; Flament, Hall, & Lemon, 1992; Galea & Darian-Smith, 1994, 1995; Iwaniuk, Pellis, & Whishaw, 1999; Kinoshita et al., 2012; Lacroix et al., 2004; Lemon, Johansson, & Westling, 1996; Lemon, 1999; Maier et al., 2002; Manoel & Connolly, 1995; Ogihara & Oishi, 2012; Olivier, Edgley, Armand, & Lemon, 1997; Padberg et al., 2007; Rathelot & Strick, 2009; Rouiller, Moret, Tanné, & Boussaoud, 1996; Sasaki et al., 2004). Furthermore, various aspects linked with manual dexterity were studied, such as manual coordination and strategies, handedness and tool use, as well as phylogenetic characteristics (e.g., Chalmeau, Visalberghi, & Gallo, 1997; Chatagny et al., 2013; Christel & Billard, 2002; Costello & Fragaszy, 1988; Falk, Pyne, Helmkamp, & DeRousseau, 1988; Fragaszy & Adams-Curtis, 1997; Gash et al., 1999; Fragaszy, 1998; Iwaniuk & Whishaw, 1999, 2000; King, 1986; King & Landau, 1993; Lacreuse & Fragaszy, 1999; Leca, Gunst, & Huffman, 2011; Lemon & Griffiths, 2005; Lindshield & Rodrigues, 2009; Nahallage & Huffman, 2007; Pouydebat, Laurin, Gorce, & Bels, 2008; Pouydebat, Gorce, Coppens, & Bels, 2009; Pouydebat, Reghem, Borel, & Gorce, 2011; Van Schaik, Deaner, & Merrill, 1999; Spinozzi, Castorina, & Truppa, 1998; Spinozzi, Truppa, & Lagana, 2004; Spinozzi, Lagana, & Truppa, 2007; Wiesendanger, 1999; Zhao, Hopkins, & Li, 2012).

In the present study, our goal was to use two complementary manual dexterity tasks, namely the *modified Brinkman board* task and the *reach and grasp drawer* task, to quantify the inter-individual variability of manual skill in adult macaque monkeys, as well as the intra-individual variations along a motor learning phase and, later on, during motor skills consolidation. More specifically, our main hypothesis is that manual dexterity performance and variability in the modified Brinkman board task, when acquired, can be predicted from the duration of the learning phase, and/or from the learning slope and/or from the initial score before any training took place. For the two tasks, it is also expected that the learning phase contributes: (i) to significantly reduce the intra-individual variability of manual skills, when a plateau of performance is reached; (ii) to optimize several attributes of manual dexterity, underlying the better motor performance reached at plateau. Nevertheless, in line with the principle of motor equivalence (see Lashley, 1930), the same motor goals with comparable levels of performance can be achieved using highly different motor strategies, as reflected by a wide inter-individual variability in manual skill parameters exhibited by adult macaque monkeys.

Method

Subjects

The behavioral experiments were conducted on 20 adult macaque monkeys (see Table 1 for individual parameters related to sex, weight, age, etc). Detailed information about the detention conditions of the monkeys, the veterinary authorizations, reward procedures and inclusion of the monkeys in previous studies can be found in the supplementary Methods and Results. As illustrated previously in the form of a video sequence (Schmidlin et al., 2011), the first experimental step (lasting 1-3 months) was to habituate the monkeys to be transferred into a primate chair, without direct manipulation of the animals by the experimenters, a procedure reducing the stress on the animals and the risks for the experimenters. Placed in the primate chair, the monkeys were weighed, and then transferred to the behavioral set-up in the laboratory.

Procedure

On each behavioral session (3-5 days a week), the monkeys systematically performed the modified Brinkman board task (derived from the initial task of Brinkman & Kuypers, 1973; Brinkman, 1984), representing the basic manual dexterity task on which the present data are based. In addition, shifting from one session to the next, the monkeys performed additional tasks (rotating Brinkman board task; Brinkman box task; reach and grasp drawer task; as illustrated in Schmidlin et al., 2011). In the present report, only the reach and grasp drawer task is considered as an additional behavioral test to the modified Brinkman board task and in a subgroup of the monkeys only as this quantitative test was introduced fairly recently.

Taking advantage of two separate windows in front of the primate chair, each hand was tested separately and the first hand tested was alternated at each session. Typically, a daily behavioral session lasted about one hour, to test separately each hand. All behavioral tests were videotaped for off-line analysis. The present report is however restricted to data derived from the **dominant hand**, defined as the hand exhibiting the highest score in the modified Brinkman board task at plateau, to be distinguished from the preferred hand defined as the hand preferably chosen to perform a task when the monkey had the choice to use one or the other hand, irrespective of the performance (see Chatagny et al., 2013).

Materials and Measures

The modified Brinkman board task requires the precision grip (opposition of thumb and index finger) to grasp food pellets from 50 slots dug in a perspex board (see Schmidlin et al., 2011), placed in front of the monkey (see also Figure 5D). The 50 slots are divided into 25 vertically oriented slots and 25 horizontally oriented slots, randomly distributed on the board. Banana flavor 45 mg pellets were used (*Bio-Serv, US and Canada: www.bio-serv.com)*.

As previously reported (Schmidlin et al., 2011), the following 4 parameters were analyzed in the modified Brinkman board task: i) the **score** (number of food pellets retrieved during the first 30 seconds); ii) the **contact time** (CT = duration in seconds of contact between the fingers and the food pellets in the slot), determined for the first 5 vertical slots and the first 5 horizontal slots; iii) the **temporal sequence** followed by the monkey's hand to visit the 50 slots of the board; iv) the **types of movements** and **strategies** used to retrieve the pellets from the slots, as well as the quantification of errors of grasping.

The reach and grasp drawer task also measures the ability to unimanually catch a food pellet in a well, but this action is preceded by the opening of a drawer, requiring to counteract a variable resistance opposing the pulling. The test thus allows quantifying via sensors the force applied to hold the knob of the drawer in between the thumb and the index finger (grip force), as well as the load force (applied to pull the drawer). Moreover, several other sensors allow quantifying distinct consecutive phases of the task (Figure 6A; Schmidlin et al., 2011). In the reach and grasp drawer task, emphasis was put on aspects not covered by the modified Brinkman board task, namely the ability of the monkey to generate different levels of force to counteract the resistances opposing the opening of the drawer (load force), while precisely controlling the grip force between the thumb and index finger to prevent the loss of contact with the drawer knob (see Schmidlin et al., 2011). The following parameters were specifically analyzed in the reach and grasp drawer task: i) the **maximal grip force**; ii) the **maximal load force**; iii) the **duration of the grip force** application; iv) the **duration of the load force** application. The load force is believed to be initiated only when the grip force has reached a sufficient level to prevent sliding of the fingers on the knob due to the resistance opposing the opening of the drawer. Further details about the behavioral set-ups were described earlier (Schmidlin et al., 2011).

The behavioral data were represented graphically and analyzed statistically using the Sigmaplot 12.0 software package (*www.sigmaplot.com*). Accordingly, group comparisons were based on parametric tests (paired or unpaired t-tests) when the normality criteria were satisfied or, if not, on non-parametric tests (Wilcoxon rank-sum test or Mann-Whitney U test). Relationships between two behavioral parameters were assessed based on the Pearson correlation test.

Results

Modified Brinkman Board Task

The modified Brinkman board task is largely intuitive in the sense that an experimentaly-naïve monkey placed in front of the board rapidly starts to grasp flavored food pellets, thus representing a fairly *natural* motor task. However, as a result of practice, the performance measured by the number of pellets retrieved in 30 seconds (score) increased from one session to the next, during the learning phase (Figure 1 and Supplementary Figure 1). The use of the precision grip to perform the task is also naturally adopted by all monkeys, although there may be subtle variations in the prehension pattern itself (see below). Furthermore, as there is no time constraint imposed to visit the 50 slots, the monkeys perform the task at their own pace depending on their motivation, a task thus assimilated to a voluntary behavior. In absence of strong constraints imposing a learning schedule and a level of performance on the monkeys, there is the possibility to assess the inter-individual variability related to manual skill, both during the learning phase and the plateau phase. The data will be first, and mainly, described based on the total score.

Learning phase: Total score. The learning phase of the modified Brinkman board task appeared quite variable from one animal to the next. A unique case is Mk-RO (Figure 1), exhibiting more a substantial decrease in variability along the 146 days of practice than a true increase in performance (modest regression line slope; see also Table 1). Another particular case is Mk-MO (Figure 1), with an impressive score from beginning, maintained during more than 100 days, before a moderate enhancement of score taking place at day 110, considered as the end of the learning phase. The regression line with a slightly negative slope is meaningless (Table 1), reflecting the absence of progressive improvement of score during the first 110 days.

All other monkeys exhibited a progressive increase in score, although the slope and the duration of the corresponding learning period were highly variable across animals (see Figure 1 and Supplementary Figure 1; Table 1). Four monkeys were characterized by a very steep learning slope (Figure 2 panel A; Table 1): Mk-AT (see also Figure 1), Mk-DI (see also Supplementary Figure 1), Mk-WI and Mk-CE. In the rest of the monkeys, the learning slope ranged from low to medium values (Figure 2 panel A), as illustrated for instance by Mk-JO (Figure 1; Table 1).

Another parameter of interest in relation to the learning phase is the intercept of the learning regression line with the y-axis (score), yielding an estimate of the initial performance at the onset of the training. As shown in Figure 2 (panel B: filled circles), the intercept values are quite variable from one monkey to the next, without however forming separate clusters. In Figure 1, three monkeys illustrate a low initial value (Mk-AN), a medium initial score (Mk-JA) and a high initial value (Mk-MO), respectively.

Highly variable also was the duration of the learning phase (Figure 2 panel C). With the exception of Mk-RO (as discussed above), the end of the learning phase was defined using the following criterion (as already used in a recent study on hand dominance/preference: Chatagny et al., 2013): when the progressive increase in score approached a plateau perceived by visual inspection, as observed in most monkeys, the first score value considered as the onset of the plateau is the score which is not exceeded by another value among the five next score values. Consequently, the end of the learning phase, indicated by the vertical dashed line in

Table 1

List of monkeys and relevant parameters for the modified Brinkman board task

	Sex+	**Weight***	**Age***	**Learning phase (days)$^{\&}$**	**Plateau (days)$^{\&}$**	**First score value$^{\&\,ç}$**	**Median plateau value$^{\&}$**	**Mean plateau value$^{\&}$**	***SD* plateau value$^{\&}$**	**Slope learning phase$^{\&}$**	**Score plateau$^{\#}$ Comparison H vs V slots**	**Median contact time at plateau V slots**	**Median contact time at plateau H slots**	**Mean errors (learning; plateau)**
Mk-AN	f ^{1,b}	3.2	6	151	44	8.894	22	21.889	1.987	0.0795	H>V	0.32	0.48	5; 0 (c)
Mk-AT	f ^{1,b}	3.4	7	32	129	18.266	30	29.507	3.521	0.418	**V>H (W)**	0.16	0.26	4.5; 1.2 (c)
Mk-CA	f ^{1,b}	3.7	7	210	30	12.177	28	26.875	4.303	0.0598	**V>H (t)**	0.2	0.36	3.8; 2.1 (e)
Mk-LO	f ^{1,b}	3	7	97	92	12.302	22	21.528	2.408	0.0827	**V>H (t)**	0.32	0.8	2.3; 0.4 (c)
Mk-MA	f ^{1,b}	3.2	7	89	133	17.416	33	33.179	2.984	0.176	**V>H (t)**	0.24	0.2	16; 0.7 (c)
Mk-MI	f ^{1,b}	3.1	7	86	85	19.846	26	25.465	3.397	0.0611	**V>H (t)**	0.2	0.36	9.8; 1.4 (c)
Mk-TH	f ^{1,b}	3.9	6	101	26	16.77	31.5	30.938	4.389	0.15	**V>H (t)**	0.2	0.32	7; 0.5 (c)
Mk-DI	f ^{1,b}	3.4	7	41	109	20.516	31	31.154	3.294	0.410	**H>V (W)**	0.2	0.2	4.8; 1 (c)
Mk-EN	m ^{3,a}	4.2	5	213	216	27.816	33	32.78	2.339	0.0095	**V>H (W)**	0.2	0.32	2; 0.4 (c)
Mk-AV	m ^{2,b}	3.2	3	31	120	20.132	31	30.35	2.854	0.198	H>V	0.24	0.44	0; 0 (d)
Mk-JO	m ^{2,b}	3.2	3	63	34	24.52	34.5	34.25	2.817	0.121	**V>H (W)**	0.16	0.28	1; 0.7 (d)
Mk-JA	m ^{2,b}	2.5	3	163	60	22.75	28	28.2	2.783	0.0199	**V>H (t)**	0.333	0.867	0; 0.7 (d)
Mk-WI	m ^{2,b}	2.7	3.5	16	234	30.116	35	34.95	3.306	0.409	**V>H (W)**	0.24	0.32	3.8; 0.2 (c)
Mk-VA	m ^{2,a}	3.4	3.5	64	404	24.12	26.5	26.875	4.463	0.0937	**V>H (W)**	0.333	0.6	2.3; 0 (c)
Mk-BI	m ^{2,a}	3.7	4.5	163	142	29.567	34.5	33.817	3.362	0.0336	**V>H (W)**	0.18	0.32	0.7; 0.3 (d)
Mk-MO	m ^{2,a}	4	4.5	110	114	33.318	35	34.424	2.681	-0.00370	**V>H (t)**	0.133	0.267	1; 0.5 (c)
Mk-GE	f ^{2,a}	3.5	5	70	447	17.751	21	20.955	4.817	0.0516	**V>H (t)**	0.34	0.56	1.9; 0.1 (c)
Mk-RO	m ^{2,a}	3.7	3	146	181	23.651	28	27.667	2.087	0.0288	**V>H (W)**	0.44	0.52	6.1; 0.9 (c)
Mk-CE	m ^{2,a}	3.5	4	21	77	21.75	25.5	23.5	4.468	0.274	**V>H (t)**	0.667	0.8	0.8; 0.9 (d)
Mk-DG	m ^{3,a}	5.2	4	107	64	20.58	31	31.68	4.13	0.119	**V>H (t)**	0.23	0.32	2.3; 1.8 (e)

Notes. + f = female; m = male. The following number (^{1}, ^{2} or ^{3}) indicates the housing conditions: 1 = 45 m^3 housing facility; 2 = 15 m^3 facility; 3 = transfer from 15 m^3 to 45 m^3 (data acquired however after transfer). The following letter (^{a}, ^{b}) indicates whether the animal has been subjected to preliminary habituation to the behavioral set-up (a) or not (b), before data collection.

* at beginning of training (age rounded 0.5).

& established for total score in the modified Brinkman board task (all monkeys).

ç intercept of regression line with y-axis in score plot.

Bold characters are for statistically significant differences between H (horizontal slots) and V (vertical slots): paired t-test (**t**) or Wilcoxon (**W**) test; see also text for learning phase.

In the rightmost column, c, d and e correspond to three different error profiles (see text).

Figure 1 and Supplementary Figure 1, precedes the first score value defined as the onset of the plateau. Mk-AV is representative of a very quick learning (Supplementary Figure 1), with a plateau reached after only 31 days. At the other extremity, Mk-EN exhibited a very long learning phase, with a weak slope, completed after 213 days (Supplementary Figure 1). An average duration of learning phase is illustrated by Mk-MA (Supplementary Figure 1), with a plateau reached after about 3 months.

The difference between the average score at plateau and the initial score before training yields an estimate of the score enhancement obtained during the learning phase. This value is represented for the total score by crosses in Figure 2 (panel B). As one might have expected, there is a trend towards a larger improvement of score during the learning phase in the monkeys with a low initial score as compared to those with a higher initial score characterized by a limited score progression. The two (interdependent to some extent) parameters of initial score and score improvement during learning appear to present a difference with respect to sex. As shown in Figure 2 panel B, the nine females (identified by "f" the x-axis) exhibit lower initial values than most males. The average initial score was 15.99 pellets in 30 seconds in females (*SD* = 3.95) whereas, in males, it was 25.3 pellets in 30 seconds (*SD* = 4.3). This difference between females and males is statistically significant ($p < 0.001$; unpaired t-test). Consequently, females exhibited a larger margin of score progression during learning (average 10.84 pellets in 30 seconds; *SD* = 4.23) than males (average 5.47 pellets in 30 seconds; *SD* = 3.42); this difference related to sex is also statistically significant ($p = 0.006$; unpaired t-test). The other two parameters related to learning (learning slope and duration of training) did not differ between the sex groups (Figure 2 panels A and C).

Plateau phase: Total score. As illustrated in Figure 1 and Supplementary Figure 1, the plateau phase starts after the vertical dashed line. The average and median score values reached at plateau were also variable among monkeys, ranging from 21 to 35 pellets (Figure 2 panels E and F; Table 1). A relevant parameter at plateau is the intra-individual variability from one daily session to the next, estimated by the standard deviation (*SD*) of the score values during the entire plateau phase (Table 1). The *SD* was highly variable across monkeys (Figure 2 panel D), ranging from 1.99 to 4.82. A "typical" monkey is represented by Mk-AN (Figure 1), whereas a monkey exhibiting an atypical performance at plateau is illustrated by Mk-MI (Supplementary Figure 1).

To assess whether the performance reached at plateau (score and variability) depends on learning properties, such as the duration of the learning phase, the slope of the learning regression line or the initial score before training, the average score at plateau and its *SD* were plotted for the 20 monkeys as a function of the corresponding learning parameters (Supplementary Figure 2). There was correlation neither between the learning duration (in days) and the average score at plateau, nor between the learning duration and the *SD* of the score at plateau (top two panels in Supplementary Figure 2). The same absence of correlations was found during the first five learning sessions. Similarly, the speed of learning, estimated by the slope of the learning regression line, was not correlated with the manual performance at plateau (score or *SD*; bottom two panels in Supplementary Figure 2). In contrast, the initial score before training was to some extent a predictor of the score at plateau, as there was a statistically significant correlation between these two parameters (top right panel in Figure 3; Pearson correlation test). On the other hand, there was no correlation between the initial score before training and the variability (*SD*) of the score at plateau (middle right panel in Supplementary Figure 2).

Both the inter-individual and intra-individual variations of the total score can be better visualized when displayed in the form of box and whisker plots (Figure 3 top left panel). Some animals exhibited a fairly small variability of their total score at plateau, from one daily session to the next (Mk-AN, Mk-CA, Mk-LO, Mk-JO and Mk-RO). In these monkeys, the distance between the 25 and 75 percentiles was equal to or smaller than

3.6 pellets. At the other extreme, some monkeys were characterized by a large variability across daily sessions (Mk-GE and Mk-WI), with a distance between the 25 and 75 percentiles equal to or larger than 10 pellets.

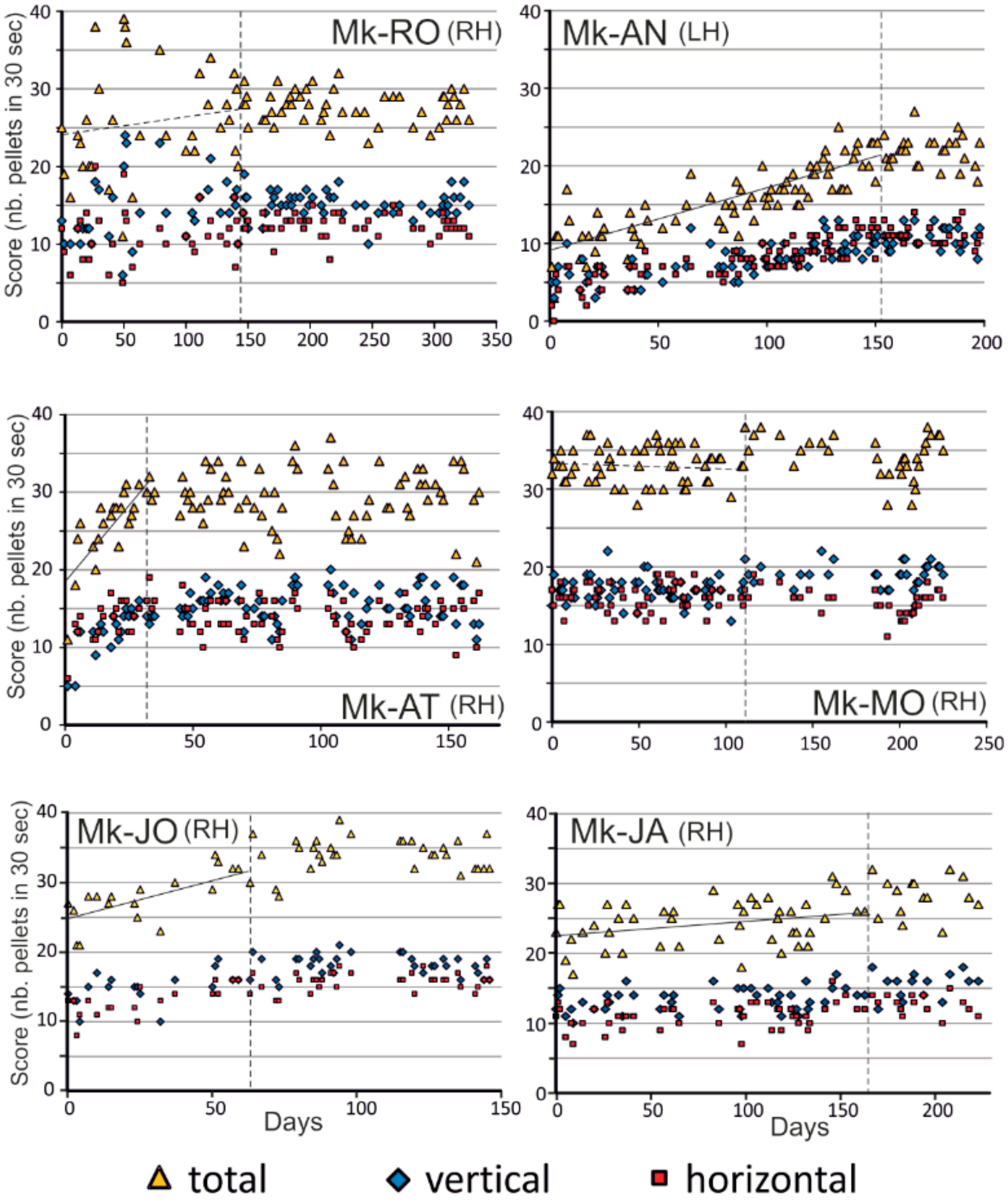

Figure 1. Plots showing the score obtained by 6 monkeys (Mk-RO, Mk-AT, Mk-JO, Mk-AN, Mk-MO, MK-JA) in the modified Brinkman board task for the dominant hand (RH=right hand; LH=left hand). Yellow triangles represent the total score, whereas the separate scores in vertical and horizontal slots are displayed by blue diamonds and purple squares, respectively. The time in days from the first day of testing is represented on the x-axis. For instance, in absence of test during the weekend, there is a delta of 3 days between tests conducted on Friday and then on next Monday. The vertical dashed lines represent the end of the learning phase and consequently the onset of the plateau phase (see text). A learning regression line on the total score is displayed for each animal (see text). The regression lines for Mk-RO and Mk-MO are represented with dashed lines as they are special cases (see text).

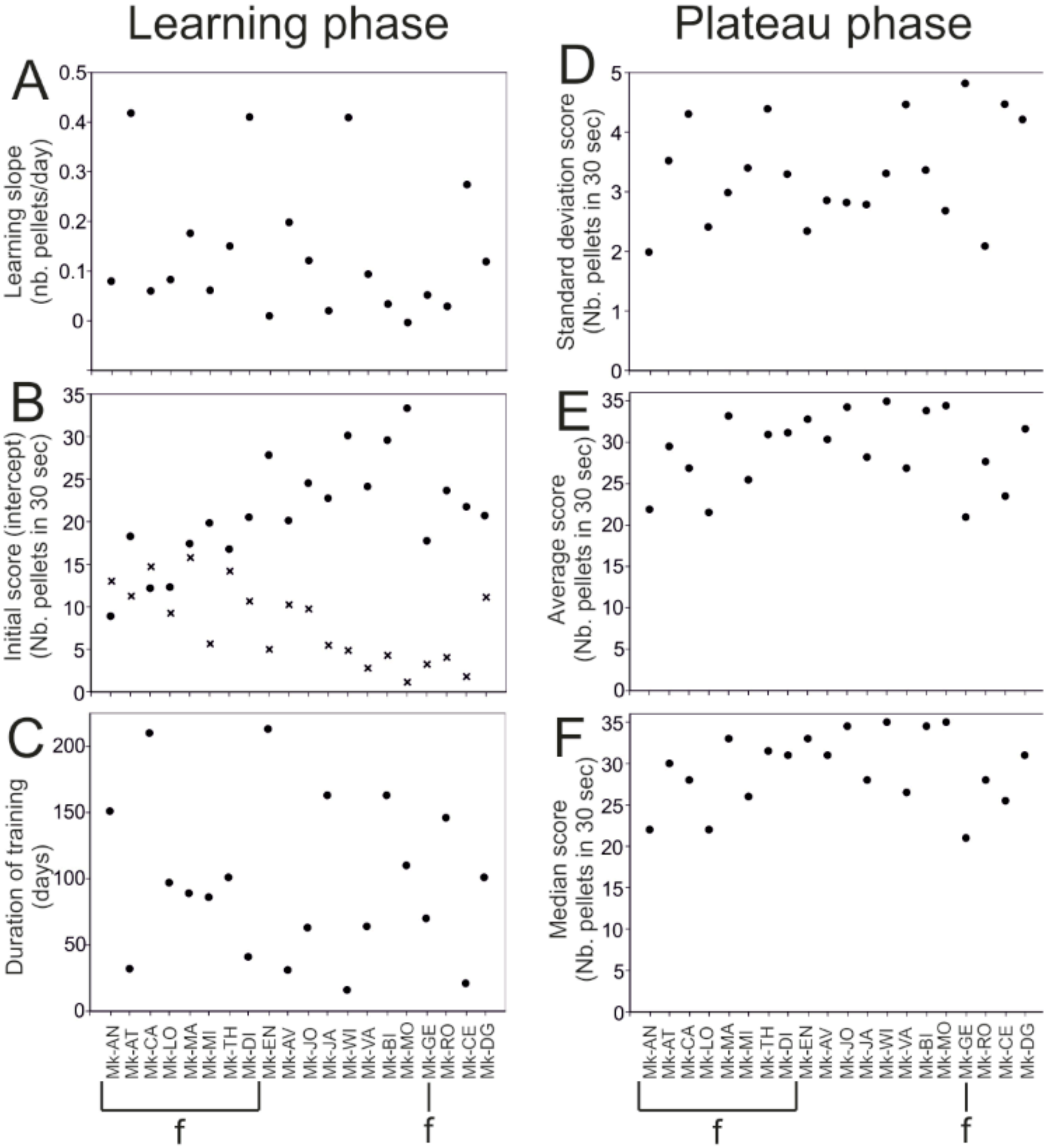

Figure 2. Plots showing relevant parameters for motor performance by all monkeys during the learning phase and the plateau phase of the modified Brinkman board task. The data concern the total score. The ID name of the monkeys appears below each bottom graphs. The 9 females monkeys are identified by "f" below the ID names. The other 11 monkeys are males. In panel B, crosses represent the progress of score obtained during the learning phase: it is the average score at plateau minus the initial score (also expressed as a number of pellets in 30 seconds; see text).

Score in vertical and horizontal slots. Pellet retrieval from the horizontal slots is more challenging than from the vertical ones (see Chatagny et al., 2013; Freund et al., 2009; Hoogewoud et al., 2013; Schmidlin et al., 2011), as the precision grip is usually accompanied by a deviation of the wrist/arm, not necessary for the vertical slots, corresponding either to an ulnar deviation or a radial deviation (see below, Variable Patterns of

Food Pellet Grasping). Below, the data are presented first at plateau, where they are more stable, and then, for comparison, during the learning phase.

At plateau, the scores were in most cases lower in the horizontal slots than in the vertical slots (Figure 1 and Supplementary Figure 1; Table 1): this difference was statistically significant in 17 monkeys ($p < 0.001$ in 15 monkeys; $p = 0.016$ in Mk-CE and $p = 0.011$ in Mk-TH; see Table 1). In contrast, in three monkeys, the horizontal scores were higher than the vertical scores, but the difference was not statistically significant ($p > 0.05$) in two monkeys (Mk-AN, see Figure 1; Mk-AV, see Supplementary Figure 1). In the third monkey (Mk-DI), the horizontal score was significantly higher than the vertical score ($p < 0.001$; see Supplementary Figure 1 and Table 1). At the plateau phase, there was no statistically significant difference between females and males in the median score for the vertical and horizontal slots taken separately, as well as for the variability of both of them (Figure 3).

The variability of the scores at plateau taken separately for the horizontal and the vertical slots can be visualized when the scores are displayed in the form of box and whisker plots (Figure 3 bottom two panels). In this way, the 20 monkeys can be distributed in three subgroups. First, in eight monkeys the variability of scores at plateau was comparable for both slot orientations. Second, the variability of scores at plateau was lower in the vertical slots in six monkeys. Third, it was the other way around in six monkeys with a lower variability in the horizontal slots.

In the learning phase, there was a positive correlation between vertical and horizontal mean scores ($r = 0.79$), indicating that the learning performance for one slot orientation is consistent with that for the other orientation. Nevertheless, no significant correlation appeared neither between vertical and horizontal *SD*s, nor between mean and *SD* for both slots orientations. However, differences between the scores observed in the vertical slots and in the horizontal slots at plateau were already visible during the learning phase (see all monkeys illustrated in Figure 1 and Supplementary Figure 1, except Mk-AT). In the three monkeys (Mk-AN, Mk-AV and Mk-DI) with a higher score in the horizontal slots at plateau, this difference was already present during the learning phase. However, it was only a trend as the differences were not statistically significant ($p > 0.05$, paired t-test or Wilcoxon rank-sum test). In the 17 monkeys exhibiting higher scores in the vertical slots at plateau, this difference was already present and statistically significant in 13 of them during the learning phase ($p < 0.05$, paired t-test or Wilcoxon rank-sum test test); it was only a trend in two monkeys (Mk-CE and Mk-EN; $p > 0.05$, paired t-test or Wilcoxon rank-sum test); there was a statistically non-significant trend towards a better score in the horizontal slots during learning in Mk-GE ($p > 0.05$, paired t-test); surprisingly, in Mk-AT, there were statistically better scores in the horizontal slots during the learning phase ($p = 0.023$, Wilcoxon rank-sum test), whereas this was the opposite at plateau (Figure 1).

Contact time (CT). The score data of the modified Brinkman board task described above involve motor components that are not purely part of the precision grip itself, such as the time of transport of the arm first towards and then away from the board. The contact time (CT) represents the time interval used by the monkey's hand to retrieve the pellets from the slots (see Method). As the precision grip movement is different with respect to slot orientation, the CT was measured separately in the horizontal and in the vertical slots in all 20 monkeys during the plateau phase (Figure 4; same plateau phase as defined for the score data). As expected, in the vast majority of monkeys ($n = 18$), the median CT at plateau was shorter in the vertical slots than in the horizontal slots (Table 1). The median CT was equal in both slot orientations in Mk-DI (0.2 second), and it was shorter in the horizontal slots in Mk-MA (Table 1). At plateau, the median CTs ranged from 0.13 sec to 0.67 sec across the 20 monkeys in the vertical slots and from 0.20 sec to 0.87 sec in the horizontal slots (see Table 1 and left panels of Figures 4A and B). The variability of the CTs at plateau (Figure 4) was greater for the horizontal slots in all monkeys. Three monkeys (Mk-CE, Mk-JA and Mk-RO) exhibited consistent highly variable CTs at plateau in both horizontal and vertical slots (Figure 4).

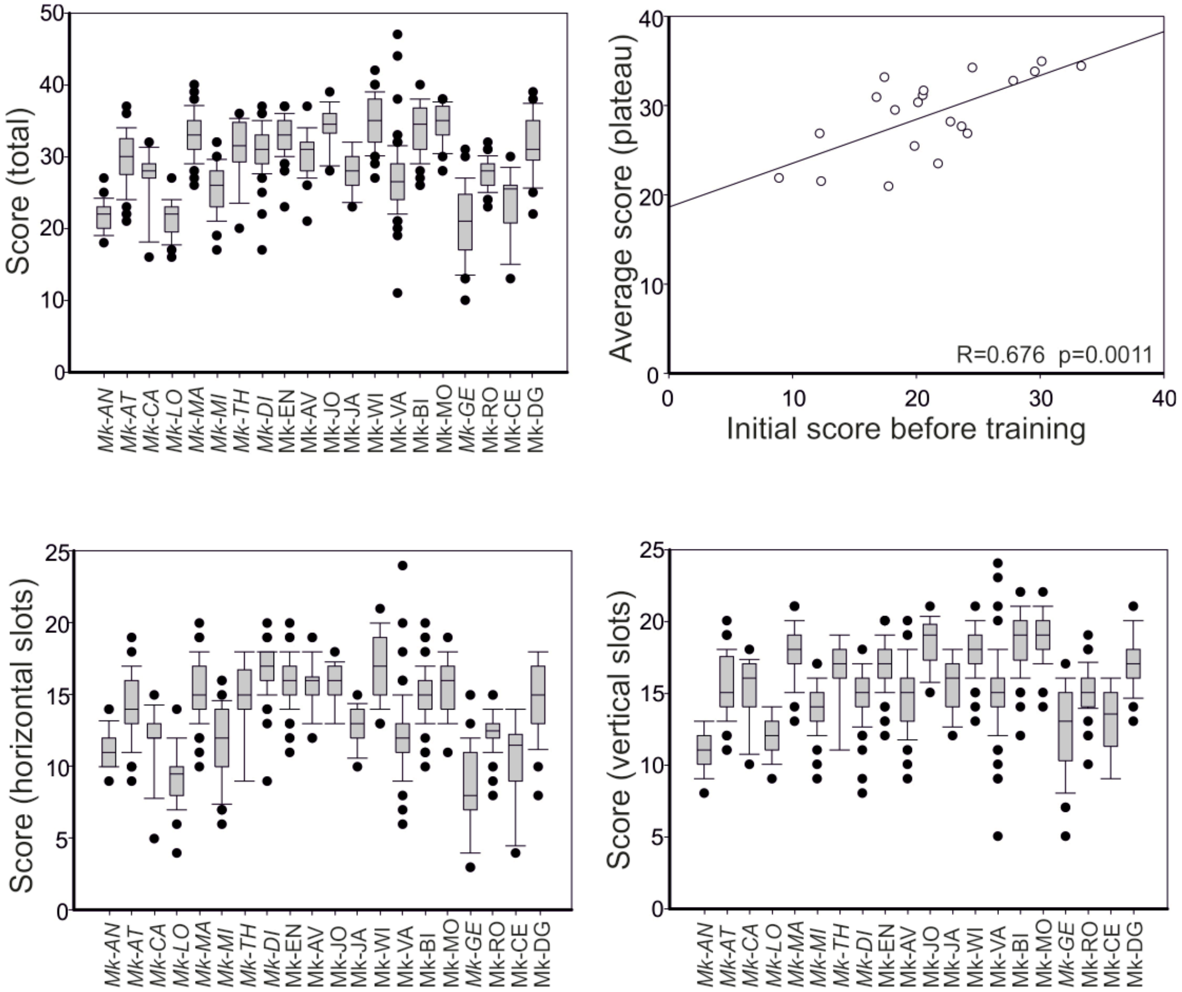

Figure 3. Scores obtained by all monkeys at **plateau phase** in the modified Brinkman board task, represented in the form of box and whisker plots. The horizontal line in the boxes represents the median value. The top and bottom of the boxes are for the 75 and 25 percentiles, respectively. The top and bottom of the whiskers represent the 90 and 10 percentiles, respectively. Black dots are for individual values above and below the 90 and 10 percentiles. The top left graph displays the total score, whereas the scores in the horizontal and vertical slots are shown in the bottom left and bottom right graphs, respectively. The ID names of females are shown in italics. The plot on the top right shows the statistically significant correlation between the average total score at plateau and the initial score before training, with the regression line. The corresponding coefficient of correlation (R) is given at the bottom right of the plot, followed by the p value (Pearson correlation test).

The CTs established at plateau were compared with those at the onset of the learning phase. The CT was assessed during the first four daily behavioral sessions (right panel in Figures 4A and B, for the horizontal and vertical slots, respectively), based on previous evidence that individual differences and intra-individual variations are greatest during the first four practice trials during motor learning (e.g., Carron & Leavitt, 1968; Marteniuk, 1974). The median CT values at onset of learning are clearly longer than those measured at plateau (Figure 4), reflecting a decrease in CT during the learning phase, corresponding to an enhancement of precision grip performance. An in-depth comparison of CTs at plateau with those at onset of learning is presented in the supplementary Methods and Results, together with supplementary Figure 3. Moreover, how the CTs progressively decrease during the first four days of learning is also reported in the supplementary Methods and Results.

Temporal sequence of grasping (motor habit). As the modified Brinkman board task is a voluntary motor task, there was no constraint on the monkey on how to perform the task, for instance in which temporal order to visit the 50 slots. However, as previously reported (Kaeser et al., 2013; Schmidlin et al., 2011), most monkeys did not visit the 50 slots randomly at plateau, but they generally adopted a preferential temporal sequence, for instance starting to empty the slots at one extremity of the board (right side for instance) and then scanning the board progressively and systematically towards the opposite extremity (left side in this example), as illustrated by the bottom inset in Figure 5A.

Such preferential temporal sequence, generally maintained at plateau from one daily session to the next, was considered as a **motor habit** and was found to be affected by a unilateral lesion of the dorsolateral prefrontal cortex (Kaeser et al., 2013; as assessed in five monkeys). In the present study, these data were extended by investigating variability of motor habit across 20 monkeys and by assessing whether the motor habit was already introduced at the beginning of the learning phase.

Overall, the comparison of the temporal sequence at the beginning of the learning phase with that at plateau yielded a distribution of the monkeys into four profiles (Figure 5 panels A and B). Profile 1, illustrated by Mk-AV, is characterized by variable temporal sequences to visit the 50 slots across daily sessions, without significant difference between the learning phase and the plateau phase. Several monkeys (n = 10 including Mk-AV) exhibited a similar sequence pattern (Mk-AT, Mk-BI, Mk-EN, Mk-GE, Mk-LO, Mk-MA, Mk-MI, Mk-RO, Mk-TH). Profile 2, illustrated by Mk-MO, is shared by three monkeys (Mk-AN, Mk-CE, Mk-MO) also exhibiting variable daily temporal sequences to visit the 50 slots but, in addition to a daily variability, the general pattern during the learning phase appears different from the one adopted during the plateau phase. Profile 3 includes four monkeys (Mk-JA, Mk-JO, Mk-VA, Mk-WI), and is characterized by a systematic temporal sequence to visit the 50 slots, present already during the learning phase and maintained during the plateau phase (illustrated by Mk-JA in Figure 5A). Finally, Profile 4 comprises three monkeys (Mk-CA, Mk-DG, Mk-DI), in which there was also a systematic daily temporal sequence to visit the 50 slots, but the sequence was significantly different during the learning phase from the one during the plateau phase (illustrated by Mk-DG in Figure 5A). The four profiles of motor habit are illustrated quantitatively in Figure 5B, where the positions of the 50 slots were given increasing numbers going from the left extremity of the Brinkman board to the right. Then, these numbers were subtracted from the temporal order (first slot visited, second, third, etc), cumulating their absolute values yielded a low cumulative value for a systematic scan from left to right; on the contrary, a systematic scan from right to left yielded a high cumulative value.

In the above four profiles of temporal sequences to visit the 50 slots, Profiles 1 and 3 exhibited comparable patterns at both learning phase and plateau phase, corresponding quantitatively to an absence of statistically significant difference between the two phases (*ns* in Figure 5B for Mk-AV and Mk-VA for instance). In contrast, the other two profiles (2 and 4) exhibited statistically significant differences in patterns of temporal sequences between the learning phase and the plateau phase (Figure 5B, *stars*, Mk-MO and Mk-DG for instance; see legend for a description of the statistical tests used).

Variable patterns of food pellet grasping. Although the monkeys generally used the standard precision grip (opposition of thumb and index finger) to grasp the food pellets in the modified Brinkman board task, there was some subtle variability in the precise pattern of grasping. For instance, already at the beginning

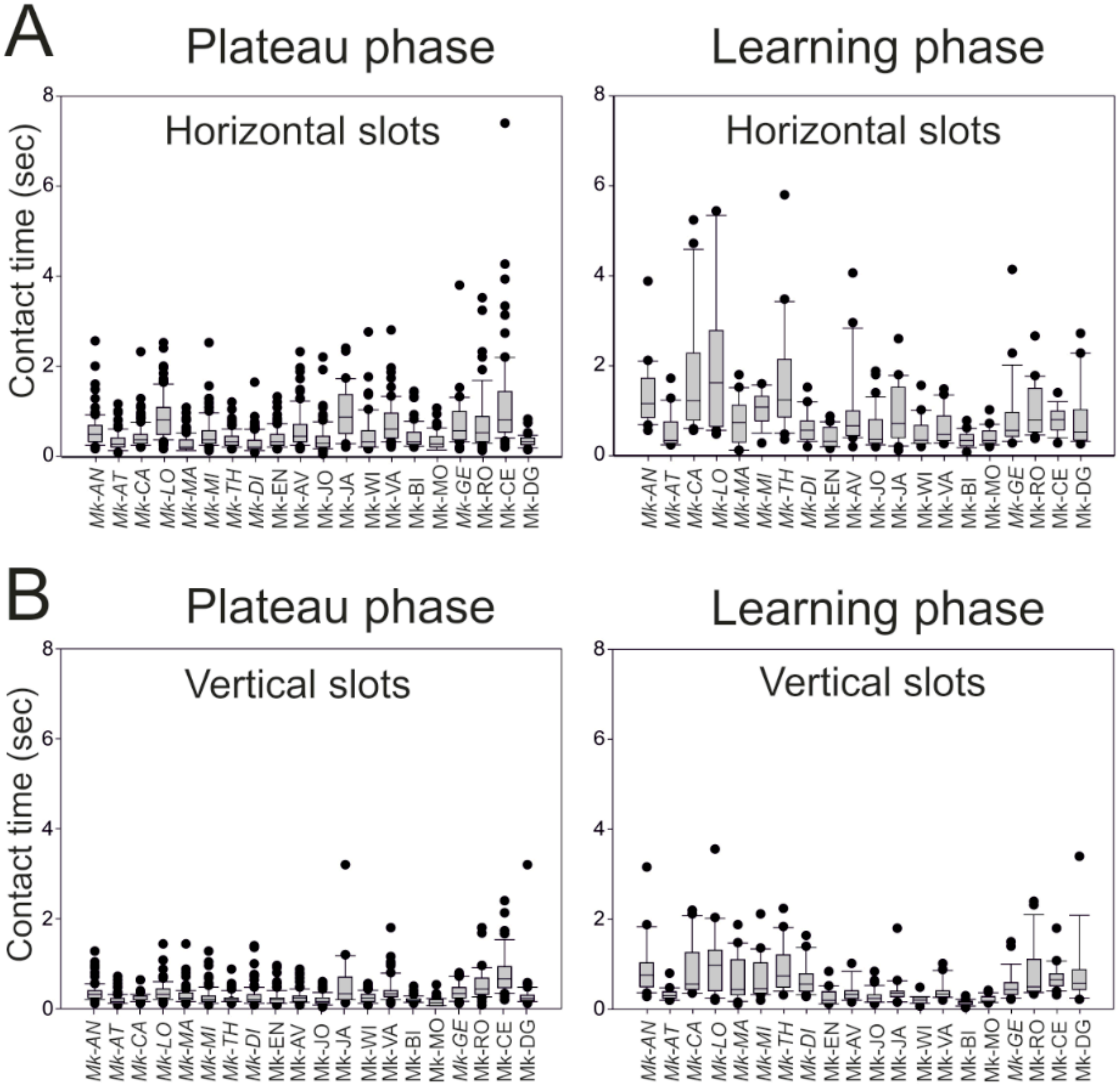

Figure 4. Contact times measured at **plateau phase** and at the **onset of the learning phase** for all monkeys in the modified Brinkman board task, in the horizontal (panel A) and vertical (panel B) slots, represented in the form of box and whiskers plots. The ID names of females are shown in italics. Same conventions as in Figure 3.

of practice, Mk-EN did not grasp a single food pellet with the left hand at a time to bring it to the mouth, as seen in the other monkeys, but grasped a first pellet, stored it in the palm of the hand, and then grasped a second pellet, before transporting both of them together to the mouth (see video sequence at http://www.unifr.ch/neuro/rouiller/ijcp/fr0.html). Conversely, single pellets were transported to the mouth with the right hand at the beginning of the learning phase. After about 10 months of practice, Mk-EN adopted frequently the strategy to collect two pellets at the same time with the left hand (Figure 5C). At the same time point, this strategy was also present for the right hand, but less systematically than for the left hand. Later, after two years of practice, Mk-EN systematically exhibited the prehension of two pellets at the same time with the left hand, extending it even to the grasping of three pellets together on a few trials (http://www.unifr.ch/neuro/rouiller/ijcp/fr0.html). This strategy to collect two pellets at the same time was also observed in few other monkeys, but more occasionally, for instance in Mk-JO and Mk-WI (Figure 5C) during the plateau phase only, and in Mk-AV and Mk-JA, both during the learning phase and the plateau phase.

The standard grasping from the vertical slots (one single pellet after the other) was highly stereotyped among the monkeys with the use of the standard precision grip (opposition of thumb and index finger). The temporal sequence of movement was such that the monkeys first established contact between the index finger and the pellet, moved the pellet toward the bottom extremity of the vertical slot and finally put the thumb in contact with the pellet to perform the retrieval itself from the slot.

The pattern of grasping was more variable for the horizontal slots. The first contact might be performed with the index finger first (as for the vertical slots) but also sometimes with the thumb first (see a few examples in Mk-EN at http://www.unifr.ch/neuro/rouiller/ijcp/fr0.html). Seven monkeys used the strategy to contact the pellet only with index finger first (Mk-BI, Mk-CA, Mk-GE, Mk-JO, Mk-LO, Mk-MO, Mk-VA). Episodic first contacts with the thumb were observed in six monkeys (Mk-AV, Mk-CE, Mk-EN, Mk-JA, Mk-MI, Mk-WI). Finally, first contacts with the thumb were frequent in seven monkeys, amounting to about 30% of trials in Mk-DG, Mk-RO and Mk-TH; in the other four monkeys, first contact established with the thumb were as frequent (Mk-AN) or even more frequent (Mk-AT, Mk-DI, Mk-MA) than with the index finger. In two of these seven monkeys with frequent first contacts with the thumb, this behavior appeared only at the plateau phase (Mk-MA, Mk-TH), whereas for the other five monkeys it was present already during the learning phase, with increasing frequency of occurrence over time.

To retrieve pellets from the horizontal slots, in part depending on their position on the Brinkman board, the monkeys performed the precision grip with the wrist/arm either in a radial deviation posture or in an ulnar deviation posture (Figure 5D; nomenclature derived from Hoffman and Strick, 1986). In 11 monkeys, the ulnar deviation was highly predominant (Mk-AN, Mk-AT, Mk-BI, Mk-GE, Mk-LO, Mk-MA, Mk-MI, Mk-MO, Mk-RO, Mk-TH, Mk-WI; see Figure 5E for Mk-LO). In one of them, the wrist/arm in radial deviation posture occurred only during the learning phase (Mk-MA), whereas in Mk-MI and Mk-RO the radial deviation posture was observed only at the plateau phase. In the other nine monkeys, ulnar and radial deviation postures of the wrist/arm were mixed with usually fewer radial deviations (ranging mostly from 20 to 40%) than ulnar deviations in eight of them (Mk-AV, Mk-CA, Mk-DG, Mk-DI, Mk-EN, Mk-JA, Mk-JO, Mk-VA; Figure 5E for Mk-JA and Mk-DG), whereas radial deviations were as frequent as ulnar deviations in Mk-CE. Overall, in the nine monkeys using a mix of radial and ulnar deviation postures, this behavior was in most cases already present during the learning phase (Figure 5E).

Errors of food pellet grasping. In the modified Brinkman board task, the monkeys made episodic errors in the form of unsuccessful trials, for instance when the pellet was ejected from the slot instead of being grasped, or when the pellet was dropped before transport to the mouth. Three profiles were identified among the 20 monkeys. The first profile (in 13 monkeys; see (c) in the rightmost column of Table 1) is defined by a progressive decrease in the number of errors from one day to the next during the few days at onset of learning followed by a further decrease at plateau, as expected. The second profile was observed in five monkeys (see (d) in Table 1), with a surprising constant and low number of errors both at onset of the learning phase and at plateau. The third profile included two monkeys (see (e) in Table 1), in which the errors occurred randomly (low to moderate number of errors), irrespective of the phase (onset of learning or plateau). As shown in Table 1, the mean number of errors at the onset of the learning phase ranged across monkeys from 0 to 16 and at plateau from 0 to 2. There was no correlation between the mean number of errors at onset of learning and the mean number of errors at plateau.

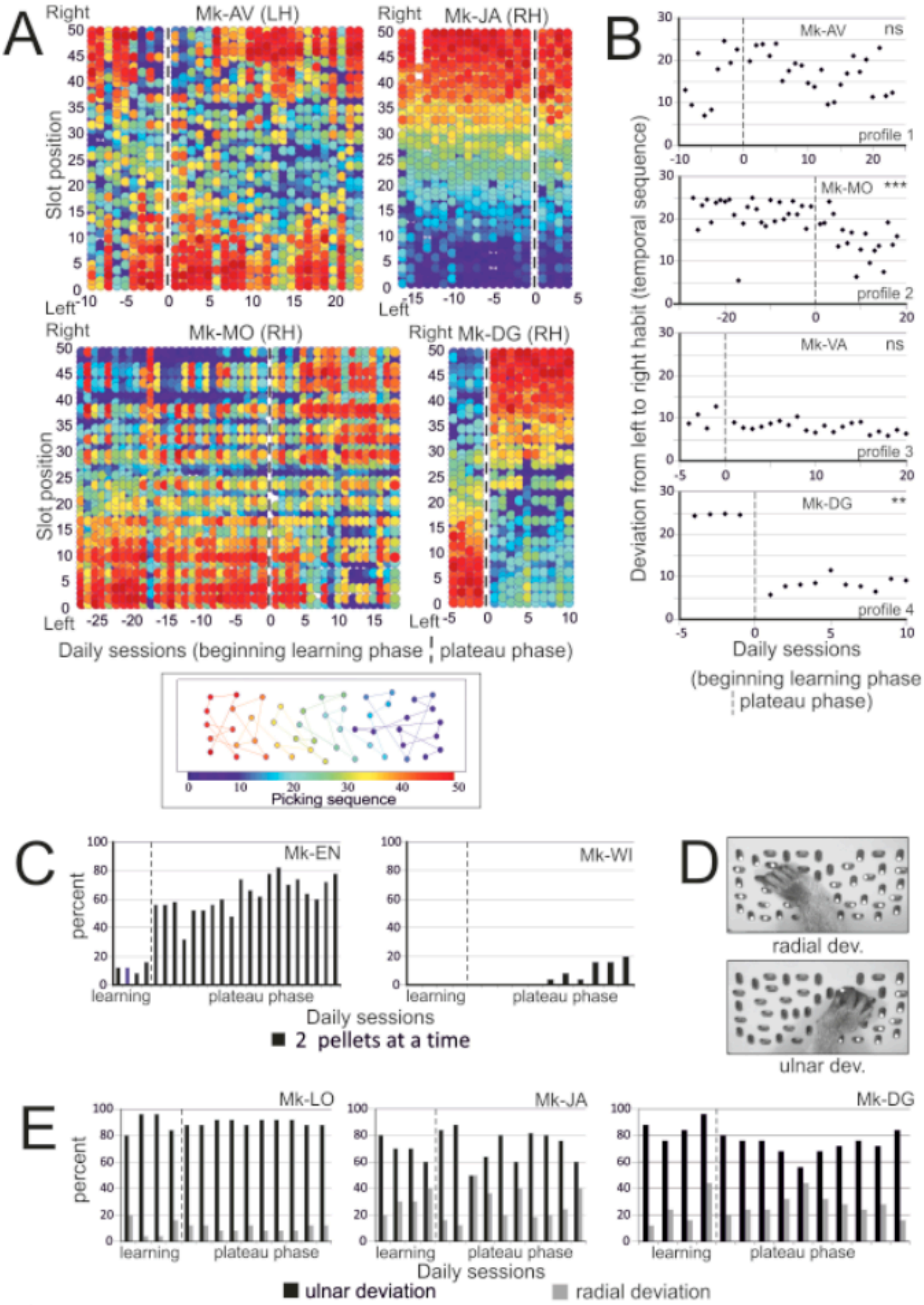

Figure 5. **Panel A:** Temporal sequence used by the monkeys to visit the 50 slots in the modified Brinkman board task. The picking sequence is shown by a color scale in the bottom inset, in which the first-visited slots are represented in blue, whereas the last visited

ones are represented in red (board scanning from right (blue slots) to left (red slots) in this example). In the top and middle displays, the temporal sequence was established for 4 monkeys, each representative of a behavioral profile (see text), both during the beginning of the learning phase (negative session numbers) and the plateau phase (positive session numbers). The x-axis displays the time in daily sessions, irrespective of the time interval (in days) between two consecutive sessions (different from the time scale in Figures 1 and Supplementary Figure 1). Each vertical column corresponds to a daily session of the modified Brinkman board task. Along each column, dots at the bottom are for slots located at the left extremity of the board, whereas dots at the top are for slots at the right extremity. RH=Right hand; LH=Left hand. **Panel B**: Quantitative assessment of the temporal sequence used to visit the 50 slots in the modified Brinkman board task for four monkeys, representative of the four profiles reported in the text. An index of systematic motor sequence (habit) was computed, indicating the extent of deviation from a systematic sequence starting from the left extremity of the board and terminating at its right extremity (corresponding to a low value for this precise sequence), and plotted in the y-axis as a function of behavioral daily sessions. The mirror sequence (systematic right to left scan) yields a high value. A small variability from one daily behavioral session to the next, indicating a reproducible motor sequence, reflects motor habit. The temporal sequence is shown qualitatively for the same monkeys Mk-AV, Mk-MO and Mk-DG in panel A. See text for detailed description of the results. The index of motor sequence was compared between the learning phase and the plateau phase with the non-parametric Mann-Whitney U test. The result of the statistical comparison is indicated at the top right of each graph: ns = statistically non-significant difference ($p > 0.05$); ** is for $p \leq 0.01$; *** is for $p \leq 0.001$. **Panel C**: Percentage of grasping patterns (at the beginning of learning and at plateau) in which two pellets were retrieved at the same time instead of a single one, in the modified Brinkman board task. In other words, the monkey grasped two pellets before transport to the mouth. In the other trials, the monkey retrieved a single pellet and brought it to the mouth. For this analysis, the vertical and horizontal slots were cumulated. **Panel D**: Usually, to retrieve pellets from the horizontal slots and depending on their position in the modified Brinkman board, the monkeys used a precision grip movement associated with a complementary wrist/arm movement. As illustrated for a right hand, on the left part of the Brinkman board, there was a trend to perform a radial deviation of the wrist/arm (top picture) whereas, on the right part of the Brinkman board, the trend was in favour of an ulnar deviation (bottom picture). **Panel E**: The distribution of wrist/arm radial deviation and ulnar deviation postures for pellet retrieval from the horizontal slots is illustrated for three monkeys over consecutive daily sessions, at the beginning of the learning phase and at plateau. For each daily session, the black bar and the gray one indicate the percentage of ulnar deviations and radial deviations, respectively. The sum of the radial and ulnar deviations is 100% in each daily session. Mk-LO is representative of 11 monkeys exhibiting a clear prevalence of ulnar deviations, during both the learning phase and the plateau phase. Mk-JA and Mk-DG also preferred ulnar deviations, but to a lesser extent.

Based on multiple correlation analyses (not shown), it turned out that the mean number of errors both at onset of the learning phase and at plateau was correlated with none of the following parameters: learning duration, slope of learning regression line, initial score value at onset of learning, median score value at plateau, *SD* of score at plateau, difference between the initial score at learning onset, or average score at plateau. Nevertheless, there was a positive correlation between the gain of score performance during practice and the mean number of errors at onset of learning ($p = 0.029$): monkeys with larger mean numbers of errors at onset of learning exhibited a larger gain of performance provided by the learning phase.

Reach and Grasp Drawer Task

Typical traces of grip force and load force recorded during a single trial of the reach and grasp drawer task are illustrated in Figure 6A, in parallel to the displacement of the drawer and discrete events, such as *touch knob*, *open onset*, *full open* and *picking*. Four monkeys were included in the analysis of the drawer task (Mk-LO, Mk-TH, Mk-DI and Mk-AT). Based on five daily sessions recorded both at the beginning of the learning phase and at plateau, the maximal grip force was measured for five correct trials at each resistance tested (R1 = 0 Newton, R2 = 1.25 N, R3 = 2.75 N, R4 = 5N) and plotted in the form of box and whisker plots (Figure 6C). Two of the monkeys (Mk-DI and Mk-TH) exhibited a systematic and statistically significant increase in the maximal grip force applied on the drawer knob when the task was performed at plateau as compared to the learning phase (Mann-Whitney U test). A comparable result was obtained in Mk-LO for the lowest two resistances, whereas there was no statistically significant difference between the learning and plateau phases at higher resistances (R3 and R4). A reverse behavior was found in Mk-AT, exhibiting in contrast a lower maximal grip force at plateau than during the learning phase at R1, R2 and R3, although the difference was statistically significant at R2 only (Figure 6C). At R4, Mk-AT used a statistically higher maximal grip force at plateau than during the learning phase, as Mk-TH.

The maximal load force was measured from the same trials, as shown in Figure 7A, and no difference between the learning and plateau phases appeared in Mk-AT and Mk-TH with the exception in the latter of the resistance R2, at which the maximal load force was significantly higher at plateau. Mk-DI used a lower maximal load force at plateau as compared to the learning phase (Figure 7A), but the difference was statistically significant only at the resistances R2 and R3. Mk-LO presented a more variable behavior, with a higher maximal load force at plateau at R1 and R2, but statistically significant at R1 only and a lower maximal load force at plateau as compared to the learning phase at R3 and R4, but statistically significant at R4 only. As illustrated for Mk-AT and for Mk-LO (Figure 7B), in the four monkeys enrolled in the reach and grasp drawer task the transition from the learning phase to the plateau phase was accompanied by a statistically significant decrease in both the grip force duration and the load force duration (Figure 7B), except at the highest level of resistance (R4). In Mk-TH, at resistance R4 as well, both durations were also statistically shorter at plateau than at the beginning of the learning phase.

The difference in grip force (solid lines in Figure 6B left column) and in load force (solid lines in Figure 6B right column) between the beginning of the learning phase and the end of the plateau phase is illustrated in Mk-DI, together with their variability (dashed lines representing plus and minus *SDs*). These data are representative of the observation (Figure 6C) that grip force was usually stronger at plateau phase than at the beginning of the learning phase, except in Mk-AT. However, variability was clearly larger at the onset of the learning phase than at the end of the plateau. Duration of grip application was shorter at plateau phase (as seen in Figure 7B). There was less difference between the two phases in the amplitude of the load force (Figure 6B right column), as compared to the grip force. However, load force duration was shorter and less variable at the end of the plateau than at onset of the learning phase, as shown in Figure 7B (right panel).

Discussion

Survey of the Main Results

Our main hypothesis that acquired manual (digits) dexterity performance and variability can be predicted from the duration of the learning phase, from the learning slope and from the initial score before any training was not verified for the most part, based on the modified Brinkman board data. Indeed, both performance and variability of manual dexterity, precision grip in the present case, were not related to the duration of training and to the slope of the learning regression line (Supplementary Figure 2). Only the performance of manual dexterity at plateau was correlated with the initial score before learning, the higher the initial score before training, the better the score at plateau (Figure 3, top right panel). On the other hand, the initial score of manual dexterity before learning was a poor predictor of intra-individual variability at plateau (Supplementary Figure 2).

As mostly expected, motor learning led to an optimization of manual dexterity parameters in the modified Brinkman board task, such as score, CT, as well as a substantial decrease in intra-individual variability, especially for the CT (Figures 1, 4 and Supplementary Figures 1, 3), in line with current theories (see e.g., Marteniuk 1974). The present study also demonstrates the considerable inter-individual variations in precision grip skills, reflected across monkeys both by wide ranges of motor parameters (score, CT, learning properties) and disparate qualitative characteristics of grasping patterns (e.g., grip type, hand posture, strategy, motor habit). Such large inter-individual variability is in line with the theory of motor equivalence claiming that a given motor goal can be achieved via multiple strategies. In relation to motor habit, reflected by the temporal order in which sequential movements were executed in the modified Brinkman board task, the data (Figure 5A and B) support the notion that motor habit is established very early during the learning phase in most animals. These data suggest that macaque monkeys, as most human subjects would do, adopt motor habits early, reflecting the capability to organize motor sequences following a strategy perceived as optimal, as opposed to a random scan of the board augmenting the probability of neglecting a slot and requiring more attention to detect yet unvisited slots. The early emergence of a preferential prehension sequence is present also in children (3-5 years old), as observed in the Pegboard with 12 pegs test (Kakebeeke, Caflisch, Chaouch, Rousson, Largo & Jenni, 2013; T. Kakebeeke, personal communication). In adult human subjects performing the modified Brinkman board task, a preferential prehension sequence is most often already present at first trial and then maintained over 10 repetitions of the test (data derived from Chatagny et al., 2013).

In the reach and grasp drawer task, the expectation that the monkeys would use exaggerated maximal grip and load forces to make sure to open the drawer during learning phase, then reduced at plateau to just exceed the minimal forces required, representing an energy conservation and behavioral optimization, was not verified, at least in three out of four monkeys tested (Figures 6 and 7: Mk-LO, Mk-TH and Mk-AT). This principle of optimization was observed only in one monkey (Mk-DI), for the load force but not for the grip force. On the other hand, the duration of application of both the grip force and load force was reduced at plateau as compared to the learning phase (Figure 7), as expected.

Methodological Considerations and Limitations

In the present study, emphasis was put on an individual analysis of 20 adult macaques. This individual (*differential*) strategy was prompted by the notion that "averaging data over participants (the *experimental* approach) can mask the actual individual participant and trial functions of change, as well as it can also produce learning curves that are not representative of any single individual in the group" (Adi-Japha, Karni, Parnes, Loewenschuss & Vakil, 2008; Newell, Liu & Mayer-Kress, 2001; Schmidt & Lee, 2011: Chapter 9). These concerns emitted in relation to the learning curves apply also most likely to the motor performance at plateau. Indeed the data shown in all Figures of the present study emphasize the considerable inter-individual variability of manual dexterity performance across our population of 20 macaque monkeys, although they were housed for many years in groups in the same environment and performed the same motor tasks in well controlled and reproducible laboratory conditions.

Our study presents weaknesses in the data gathering due to variations in the experimental protocol, inherent to this type of non-human primate study and its related constraints. First, as expected for a study conducted over a long period of time (15 years), several conditions changed from one animal to the next. One example is the size of the housing facility and its degree of enrichment (Table 1), adapted over the years according to changes in the legislation dealing with the protection of animals involved in scientific research. A second confounding factor is the supervision of the monkeys by different experimenters: a given experimenter is devoted to the very same monkeys every day and therefore cannot supervise more than two monkeys daily.

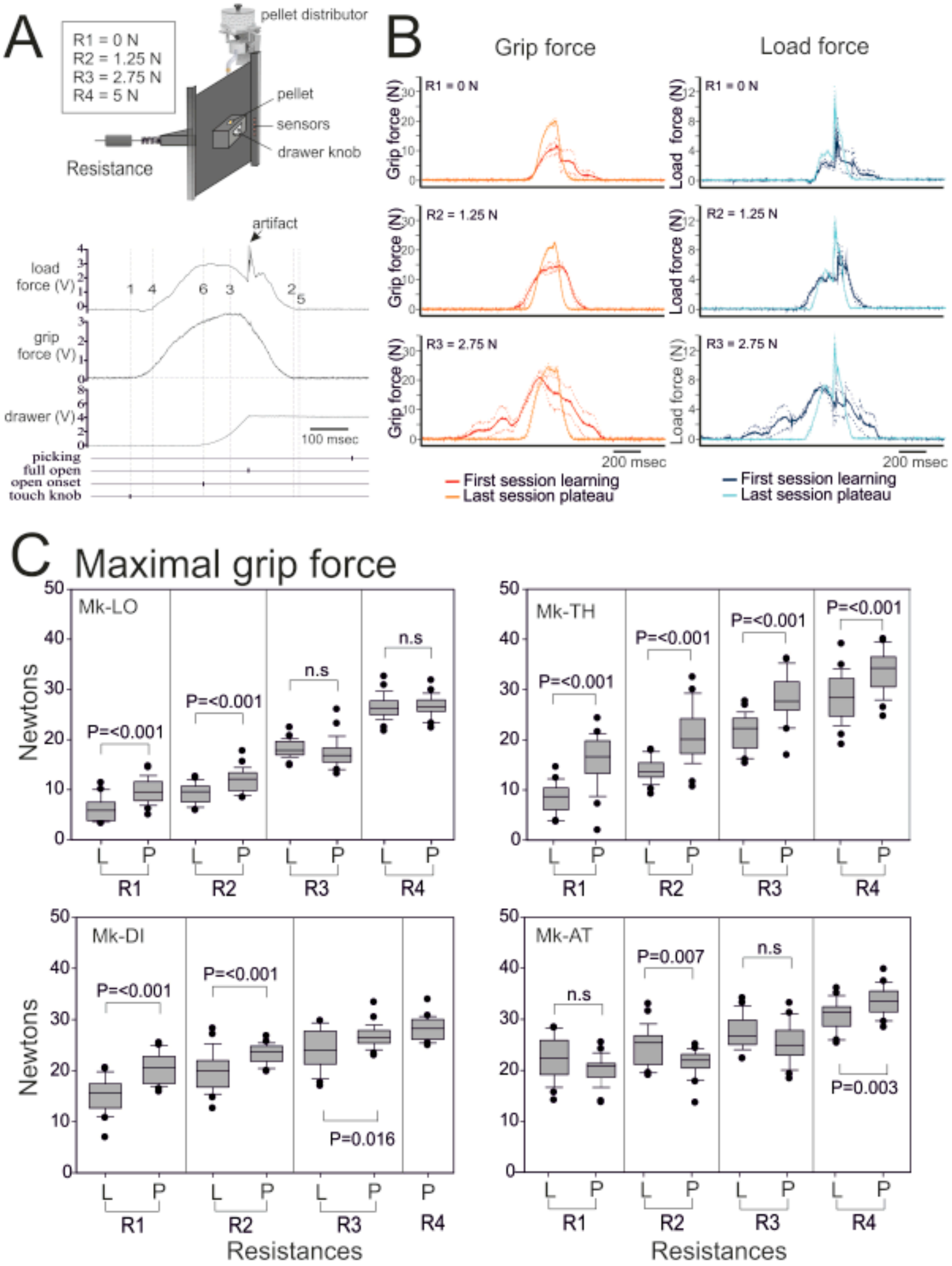

Figure 6. **Panel A**: Typical traces of the load force, grip force and drawer displacement as a function of time (from top to bottom) when a monkey executed a trial in the reach and grasp drawer task. The time occurrence of four discrete events is shown below (vertical tics). A schematic representation of the drawer set-up is shown on the top, with the four increasing resistances opposing the opening of the drawer (R1 to R4). The vertical dashed lines with numbers correspond to: *onset of grip force* (1), *offset of grip force* (2), *maximal grip*

force (3), *onset of load force* (4), *offset of load force* (5) and *maximal load force* (6). An artifact in the load force trace occurred when the drawer was blocked at its maximal opening. **Panel B**: Average traces (over 5 trials) and their variability (+/- 1 *SD*) in Newtons (N) for the grip force (left column) and load force (right column), recorded in Mk-DI. In each column, the two colors distinguish traces obtained at the beginning of the learning phase and at the end of the plateau phase. The traces are shown for three levels of resistances (R1, R2, R3; see panel A). For each curve, the variability is represented by the envelope in dashed lines. **Panel C**: Box and whisker plots (same conventions as in Fig. 3) of the maximal grip force recorded during the learning phase (L) and during the plateau phase (P), in the four monkeys involved in the reach and grasp drawer task, as a function of 4 increasing resistance levels opposing the opening of the drawer (R1, R2, R3, R4). The results of the statistical comparison between "L" and "P" are given with the corresponding p value or n.s when statistically non-significant ($p > 0.05$). Note that Mk-DI performed the task at resistance level R4 only during the plateau phase, after learning.

Moreover, the duration of the entire experiment on a given monkey may last up to two to three years and may consequently be conducted by several successive experimenters. Equally important, each experimenter develops his/her own approach to train each animal, depending also on the *personal* traits of the latter. In particular, some monkeys required a longer preliminary habituation phase than others before being actively involved in the experiment, before collecting the behavioral data for subsequent analysis (Table 1). Over the years, the monkeys originated from different sources, such as our own breeding colony (before 2010) or from different authorized suppliers (China, Mauritius Island, Vietnam), via various quarantine European centers. In spite of these multiple parameters influencing our monkey data, which cannot be strictly controlled over a 15 year period, it remains that they have most likely less impact than the even more numerous confounding factors associated with human studies, such as genetic variability, socio-cultural background, education, economical status, motivation, professional occupation, hobbies and so on.

The vast majority of lesion studies dealing with manual dexterity in non-human primates (see introduction) provide behavioral data restricted to two time points, namely before a lesion of the motor system (after reaching a plateau of performance) and after the lesion. In these studies, the data related to the learning phase of the motor tasks were rarely, if not at all, reported. The originality of the present study was to compare the manual dexterity properties of adult macaque monkeys at their plateau (before subsequent lesion) with those derived earlier from the acquisition of manual performance for two motor tasks, in the same animals. Furthermore, as the behavioral sessions took place three to five days a week, it was possible to precisely follow progressive changes in each monkey in order to assess intra-individual and inter-individual variability over a very long time frame. As the motor tests took place in the laboratory with the monkeys sitting in a primate chair, confounding factors such as the position of the monkeys with respect to the set-up and the separate use of each hand were well controlled.

Initial Score Before Training

The statistically significant correlation between the initial score before training and the score reached in the modified Brinkman board task at plateau (Figure 3, top right panel) suggests that there is a limited margin of progression during learning, meaning a ceiling effect. When the initial score was high (above 25 pellets; in four monkeys, see Table 1), the increase in score during the learning phase was modest (1-5 pellets at most; Figure 2B: crosses), corresponding to the ceiling effect, with a maximal score in the most dexterous monkeys ranging from about 30 to 35 pellets in 30 seconds. A few other monkeys ($n = 5$), in spite of a lower initial score before training (ranging from 18 to 24 pellets), also exhibited a limited gain of score during the learning phase (below 6 pellets; Figure 2B: crosses). Overall, 10 monkeys improved relatively modestly during the learning phase. In the other 10 monkeys, the margin of score progression during learning was more prominent (ranging from 9 to 16; Figure 2B: crosses). The latter monkeys were predominantly females (7 out of 10). In comparison with human subjects performing the modified Brinkman board task in 10 consecutive sessions on

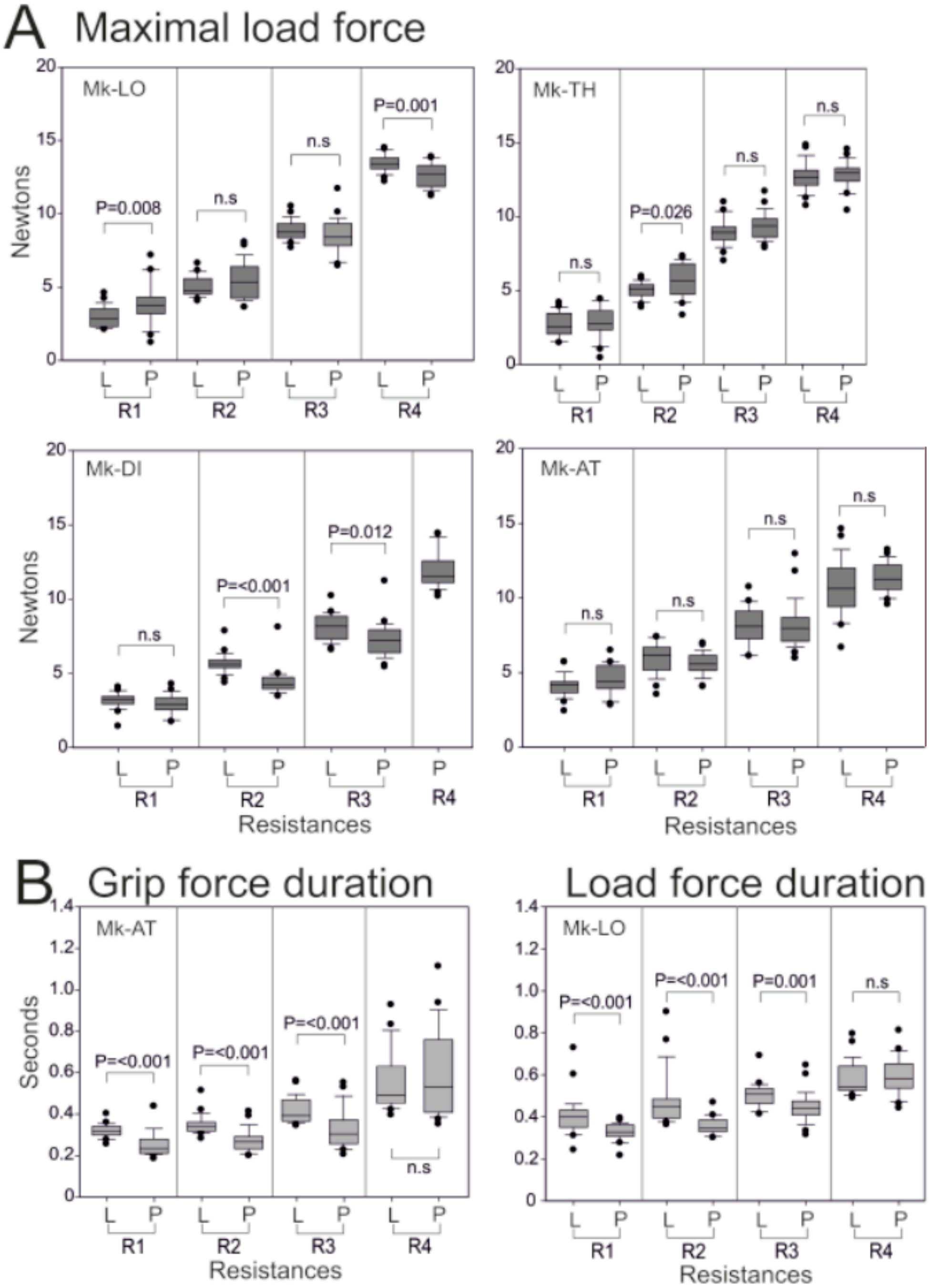

Figure 7. **Panel A**: Box and whisker plots (same conventions as in Fig. 3) of the maximal load force during the learning phase (L) and during the plateau phase (P), in the same four monkeys as in Figure 6. Same conventions as in Figure 6. **Panel B**: Grip force duration and load force duration measured in 2 animals during the learning phase (L) and the plateau phase (P), as a function of the resistance levels opposing the opening of the drawer (R1, R2, R3, R4). Same conventions as in Figure 6.

the same day, the training effect was less prominent than in monkeys (Chatagny et al., 2013), suggesting that humans started closer to the ceiling of performance.

The statistically significant lower scores in females than males (Figure 2B) is consistent with the lack of a few habituating sessions before collecting data in females, as opposed to the majority of males (Table 1). Moreover, other confounding factors might have played a role in this sex difference as well (e.g., size of housing facility, degree of enrichment; see Table 1). However, later on, when females were more familiar with the new environment and the tasks, their score increased more than in males so that the two groups exhibited largely overlapping mean or median scores at plateau (Figure 2, panels E and F). The absence of sex difference for the score at plateau in the macaque monkeys enrolled in the present study contrasts with the significantly better performance observed in women than in men in a human adapted version of the modified Brinkman board task (Chatagny et al., 2013).

Application to Lesion Studies

The large inter-individual variability of the average score at plateau (Table 1) may be considered as an inconvenience in comparing two groups of monkeys subjected to a lesion, one group receiving a treatment and the other not. Nevertheless, this drawback is actually attenuated because, in such studies and in contrast to clinical trials (see e.g., Kaeser et al., 2010), the most relevant comparison is made within the same monkey, between the pre-lesion score and the post-lesion score at plateau after functional recovery (usually incomplete; see e.g., Freund et al., 2009; Hamadjida et al., 2012). Thus, the comparison between two groups of animals is based on the percentage of functional recovery individually determined for each animal (see e.g., Freund et al., 2009; Hamadjida et al., 2012; Hoogewoud et al., 2013; Kaeser et al., 2010, 2011), which is less affected by inter-individual variability than group comparisons in clinical trials.

Learning Curves

As reviewed by Newell and collaborators (2001), the forms of the learning curves, defined as “plots of the outcome performance as a function of practice”, can be highly variable: “learning curves of almost every conceivable shape can and have been found”, corresponding to various mathematical functions, such as exponential, power law, S-shaped, hyperbolic, accelerating functions, etc. In the present case, one would have intuitively expected an exponential rise of performance (score) to a maximum (ceiling; see Schmidt & Lee, 2011: Chapter 10, their Figure 10.8). As illustrated in Figure 1 and Supplementary Figure 1 however, the majority of monkeys (*n* = 16 out of 20) exhibited a progression of performance during the learning phase that was rather better approximated by a regression line than by an exponential function. The exceptions are Mk-RO (Figure 1), Mk-DI, Mk-LO (Supplementary Figure 1) and Mk-TH (not shown). This linear learning progression observed here may be specific to the modified Brinkman board task, as well as to each monkey, in line with the proposition that the “learning rate is individual and task dependent” (Newell et al., 2001). In the same line, unlike recent studies in humans (e.g., Rosenblatt, Hurt, Latash, & Grabiner, 2014 in locomotor tasks; Wu et al., 2014 in arm movements tasks) demonstrating that a greater variability at the beginning of practice allows a faster learning rate, no such correlation was found in our monkeys performing unconditioned voluntary tasks requiring fine manual dexterity. Individual differences in motor skill learning are likely to be related to variations in the function and structure of specific brain regions, such as prefrontal, premotor and parietal cortices, as well as basal ganglia and cerebellum (Tomassini et al., 2011).

An important parameter here is the time scale when attempting to characterize the change in behavior resulting from motor learning (Newell et al., 2001). In most cases, especially in human subjects, the time range of observation of the learning phase was narrow (an hour to a single day most often; e.g., Chatagny et al., 2013). Longitudinal studies, though conducted in relation to infant motor development, are relatively rare and therefore the present study is original thanks to the long time period of observation during the learning phase (over weeks to months). Short daily sessions, during such a long time scale, may explain the very progressive and regular improvement of performance with practice observed in the majority of monkeys. In the present learning data on macaque monkeys, the learning phase may appear rather long for a relatively natural motor task, such as the precision grip performed in the modified Brinkman board task, at least in some individuals (Table 1). This underlies the fact that precision grip is an exquisite motor function subjected to very fine and progressive adjustments with practice. For instance, it was reported that the even more sophisticated skill in rolling cigars may still improve after many years (up to seven) of practice (Crossman, 1959).

Comparison with Previous Studies

Comparing the present behavioral data with the literature is limited to some extent, as the manual dexterity performance and variability strongly depends on the animal/primate species, on practice schedule (Stelmach, 1968), on expertise level (Schorer, Baker, Fath, & Jaitner, 2007), as well as on the type of task. Individual differences are indeed strongly task specific, corresponding to the theory of specificity (see e.g., Marteniuk, 1974). Even close species such as *Macaca fascicularis* and *Macaca mulatta* have different hand size (e.g., finger length), larger for the latter, corresponding consequently to different manual dexterity abilities (see e.g., Darling et al., 2013 for more details). A direct comparison of the present macaque data with rodent data (mainly rats) remains questionable, due to the strong difference between the pincer grasp (or precision grip) in primates and the arpeggio/power grasp in rodents (Klein et al., 2012). In the context of motor specificity, a strong influence is exerted by the size and shape of the object to be manipulated, as well as by the size of the well containing the object, when applicable. In a human study focused on precision grasps (Wong & Whishaw, 2004), it was shown that there was a high degree of variability of grasping pattern within and between subjects, like in our group of monkeys. Wong and Whishaw (2004) reported up to seven grasp types in human subjects, involving the thumb and various combinations of other digits, depending on the size of the bead being held. The proper precision grip (opposition of thumb and index finger only) was highly predominant when grasping the smallest beads, whereas the involvement of other fingers increased when progressively larger beads were grasped. In the present study on monkeys, only the proper precision grip was observed (opposition of thumb and index finger) because the food pellet was small compared to the finger size. Wong and Whishaw (2004) reported also in human subjects a large variability of first contact strategy with an object, depending on which and how the first finger contacted the object. This observation is in line with the large inter-individual variability observed here for the monkeys in the first digit used to contact the pellet in the horizontal slots (see results paragraph Variable Patterns of Food Pellet Grasping). The large inter- and intra-individual variability of grasping patterns observed in our monkeys and in humans (Wong & Whishaw, 2004) is consistent with the exquisitely complex somatotopic organization in mosaics of the primary motor cortex in primates (e.g., Schieber, 2001) as well as with complex movements synergies elicited in primates by microstimulation of the primary motor cortex (Graziano, Taylor, & Moore, 2002).

In two studies conducted on *Macaca fascicularis* (Brinkman, 1984) and *Macaca mulatta* (Brinkman & Kyupers, 1973), using a very comparable task (the original Brinkman board task), the data were mostly reported in a qualitative manner (movement pattern), preventing a direct comparison with the present quantitative data. The same limitation applies to other macaque studies using different manual tasks (e.g., Glees & Cole, 1950; Ogden & Franz, 1917; Passingham et al., 1983). In several studies on non-human primates (as listed in the introduction) involving a lesion of the motor system followed by functional recovery, the pre-lesion behavioral data were often limited to very few baseline data points, if not a single one, thus strongly limiting the comparison with the present progressive training phase over weeks, followed then by a long period of performance stabilization at plateau.

An exception is the study by Pizzimenti et al. (2007) conducted on *Macaca mulatta* and using a somewhat different behavioral apparatus, modified from the often used dexterity *Klüver* board. Although different from our modified Brinkman board, the wells A and B in the dexterity board used by Pizzimenti et al. (2007) had a size comparable to our slots. The manual dexterity was assessed quantitatively in three monkeys, using the so-called performance ratio, defined as the average score divided by the *SD* of the score, derived from five pre-lesion sessions (plateau). For the preferred hand, the performance ratios ranged from 2.5 to 3.0 in well A and from 3.5 to 8 in well B, the latter being the least difficult. Taking our data from the modified Brinkman board at plateau (Table 1) and computing similarly the performance ratio, values ranging from 4.4 to 14.0 (average = 9.3) among the 20 monkeys were obtained, thus corresponding to a generally better manual dexterity performance in our monkeys. However, such direct comparison may be biased due to important differences, such as species, manual task, duration of the considered plateau phase, scoring, as well as the time interval between the sessions (1-2 weeks in Pizzimenti et al., 2007 versus 1-3 days in our study). Furthermore, the monkeys of Pizzimenti et al. (2007) worked from their home cage (in a primate chair here).

As far as the reach and grasp drawer task is concerned, slightly different versions of the original set-up (Kazennikov et al., 1994) were used along the years (Kazennikov et al., 1998; Kazennikov et al., 1999; Kermadi, Liu, Tempini, & Rouiller, 1997; Kermadi, Liu, Tempini, Calciati, & Rouiller, 1998; Kermadi, Liu, & Rouiller, 2000), with special emphasis put on the issue of inter-limb coordination. In the current report, the reach and grasp drawer task was used in its unimanual version only, with focus on the assessment of the grip and load forces, a situation more closely related to studies on human subjects performing the reach and grasp drawer task (e.g., Grichting, Hediger, Kaluzny, & Wiesendanger, 2000; Serrien & Wiesendanger, 1999; Serrien, Kaluzny, Wicki & Wiesendanger, 1999). Interestingly, as compared to intact human subjects, cerebellar patients overestimated the proactive grip force requested to pull the drawer (Serrien & Wiesendanger, 1999). It can thus be expected that the reach and grasp drawer task will also be pertinent in macaque monkeys to evaluate deficits related to various motor dysfunctions (e.g., Parkinson disease, cortical lesion, spinal cord lesion) and to follow the time course and extent of functional recovery. In particular, it will be interesting to compare the properties of the initial learning phase of a motor task with those of the re-learning phase of the same task in the same animals following a lesion, in absence (spontaneous recovery) or presence of a specific treatment (induced recovery).

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Informative video material: http://www.unifr.ch/neuro/rouiller/ijcp/fr0.html.

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