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Research report

Sub-processes of motor learning revealed by a robotic manipulandum for rodents

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HIGHLIGHTS

- We examine motor learning (easy vs. complex task) using a robotic device for rats.
- Both tasks differ in performance level and the temporal evolution of kinematic parameters.
- Different sub-processes of motor learning can be revealed in the complex task.

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ABSTRACT

Rodent models are widely used to investigate neural changes in response to motor learning. Usually, the behavioral readout of motor learning tasks used for this purpose is restricted to a binary measure of performance (i.e. "successful" movement vs. "failure"). Thus, the assignability of research in rodents to concepts gained in human research – implying diverse internal models that constitute motor learning – is still limited. To solve this problem, we recently introduced a three-degree-of-freedom robotic platform designed for rats (the ETH-Pattus) that combines an accurate behavioral readout (in the form of kinematics) with the possibility to invasively assess learning related changes within the brain (e.g. by performing immunohistochemistry or electrophysiology in acute slice preparations).

Here, we validate this platform as a tool to study motor learning by establishing two forelimb-reaching paradigms that differ in degree of skill. Both conditions can be precisely differentiated in terms of their temporal pattern and performance levels. Based on behavioral data, we hypothesize the presence of several sub-processes contributing to motor learning. These share close similarities with concepts gained in humans or primates.

1. Introduction

Motor learning as a form of procedural learning [1] is generally defined as the gradual improvement of motor performance with practice [2]. Studies in primates and humans revealed several different sub-processes that contribute to this improvement in a specific sequence: an initial phase of defining basic movement strategies [3] is followed by a period of refining movement precision, whereas movement speed increases in a final phase [4,5].

Animal models of motor skill learning involve tasks that are not familiar to the animal, e.g. skilled forelimb reaching [6]. However, skilled reaching is restricted to a binary performance-measure (i.e. "did the movements meet the requirements defined by the experimenter or not?") [7]. Only by observation or video tracking, limited information about movement strategies and kinematics can be obtained. It is therefore not possible to identify sub-processes of motor learning as it was done in human experiments [8,9].

Recently we introduced the ETH Pattus [10,11], a robotic platform designed for interaction with forelimb movements in rats that allows for automatized training and accurate behavioral readout in the form of interaction kinematics. Here, we investigate two different reaching paradigms that differ in complexity, i.e. a 10 mm free-pulling task (FP) and a 10 mm straight-pulling task (SP) where an additional precision constraint is added for the movement to be considered successful. Based on kinematic data acquired with

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the robot, we report on the evolution of sub-processes constituting motor learning under both training paradigms.

2. Materials and methods

2.1. Animals and experiments

Naïve adult 10–12 weeks old male Long-Evan rats ($n = 19$; 220–270 g; Center d'Elevage R. Janvier, Le Genest—St. Isle, France) were used for this study. Animals were housed in cages in groups of three individuals in a 12/12-h light/dark cycle (light on: 8 pm, off: 8 am). Animals were food-deprived for 24 h prior to the first training session. Daily food supplements (ca. 50 g/kg of standard diet) were given after training to maintain constant body weight. Access to water was ad libitum. All experiments were conducted in accordance with Swiss regulations and were approved by the Committee for Animal Experimentation of the Canton of Zürich.

2.2. Experimental setup

The ETH Pattus (Fig. 1A and B, for more detailed information [10,11]) was used to provide kinematic analysis of movements during acquisition of different motor tasks. The ETH Pattus is a three-degree-of-freedom robotic manipulandum that allows planar movement in x–y-direction and pro/supination—although the tasks designed for this study required merely movements within the x–y-plane. It was designed to particularly meet the kinematic requirements of rat forelimb movements (e.g. planar reaching, grasping and pulling). Rats interact with the robot via a spherical handle (end-effector, 6 mm diameter) that can be manipulated in order to perform a specific motor task, which is automatically rewarded when accomplished correctly. During movements, the handle position and velocity are continuously recorded with a sampling frequency of 1 kHz. The ETH Pattus is placed in front of a custom-made Plexiglas chamber (width: 400 mm, depth: 150 mm, height: 450 mm) with a vertical opening (width: 10 mm, height: 50 mm). The handle is located 55 mm above the ground. In the back of the chamber, a tray is mounted to hold pellets (45 mg, Bioserve Inc., Frenchtown, NJ, USA) which are delivered by a pellet dispenser (Model 80208, Lafayette Instrument Comp., IN, USA) in case of a successful trial.

2.3. Behavioral conditions

The behavioral protocol consisted of three different phases: (1) to familiarize the animals with the new environmental conditions (without the robot), rats were placed in the Plexiglas chamber for 1 h/day whereas a quantity of 20–30 pellets was freely administered. In the majority of cases animals consumed all pellets after 1–2 days and were subsequently assigned to the second phase of training the next day. (2) To familiarize the animals to the robot and especially to the end-effector, the second phase consisted of positioning the robot handle in close distance (4 mm) to the chamber window. When animals touched the handle and displaced it by a minimum of 0.2 mm in the x- or y-direction, an auditory cue (beep sound, 1 s) was presented and rats were rewarded with a food pellet delivered into the tray at the rear wall of the training chamber. When task performance reached 200 successful trials in 60 min, animals started motor skill training. Repeated measurement ANOVA showed no statistically significant difference in performance level (i.e. number of trials completed per minute) between groups ($F = 1.29$; $p = 0.28$) emphasizing a comparable baseline performance prior to the start of phase 3. (3) To allow 10 mm pulling movements and to avoid the end-effector from entering the chamber window at the end of the movement, training was initiated by increasing the distance between the handle and the chamber window from 4 mm to 18 mm. Animals were then split into two groups and trained on either of two motor-learning tasks. For both tasks, animals had to perform 200 trials a day (successful or not). Thus, this number was constant over all animals, groups and over time.

Free-pulling group (FP; $n = 6$; Fig. 1C): Animals had to reach out for the handle and pull it over a distance of at least 10 mm in y-direction within an area of ±12 mm distance from the x-axis corresponding to the workspace limits of the robot. When animals fulfilled this criterion, a trial was rated as "success" and an auditory cue (beep sound, 1 s) was presented, while a pellet was automatically released into the tray. At the end of each trial the handle was automatically retracted outside of the reachable workspace of the rat, before moving back in front of the chamber window to initiate the next trial.

Straight-pulling group (SP; $n = 13$; Fig. 1C): To increase the degree of difficulty, a precision constraint was added, requiring the rat to pull the handle within a corridor around the straight line (i.e. y-axis) of 2 mm in width to either side (x-direction).

Motor training sessions (phase 3) consisted of 200 trials. If the animals did not perform 200 trials, a session was terminated after 60 min. Overall, training sessions were conducted over 25 consecutive days, with one session per day. Particular attention was paid with respect to the handedness of a rat. Once an animal developed a preference for a paw, it maintained this preference throughout the experiment. We therefore refrained from reinforcing a certain forelimb.

2.4. Data processing

During all trials of phase 3, the position (x, y) of the handle was recorded by the ETH Pattus at a sampling frequency of 1 kHz and stored on a desktop computer. Offline data processing and analysis was performed using Matlab (Matworks Inc., Natick MA, USA; Supplementary Fig. 1). Velocity signals were low-pass filtered using a 2nd order Butterworth filter with a cutoff frequency of 50 Hz. For each trial, the initiation of the rat's pulling movement was then determined using an empirically chosen velocity threshold along the pulling direction. This threshold ($v_y > 30$ mm/s) was defined rather high to differentiate the pulling movement from unspecific displacement that occurs when rats initially grab the handle. A trial was automatically rated as "fail" when the handle was released before the pulling-distance of 10 mm was completed, when the pulling movement was interrupted for more than 2 s or when the handle was not touched for >180 s. For the analysis of kinematics and parameter extraction, all "valid" (i.e. no fail) trials were taken into account for both, SP and FP group regardless if they were rated as successful or not. Position- and velocity- (norm of the velocity vector) traces were further resampled using b-spline interpolation to obtain a constant number of samples per trial and allow for calculation of mean trajectories and mean velocity profiles over an entire session.

For comparison with a well-established measure of skill learning [7,12] *percentages of successful trials* per session (success rate; inter-session learning; **SR**), as well as per blocks of "quintiles" (=40 trials) within each session (intra-session learning) were calculated. As a measure of motivation and handling of the operant conditioning paradigm incorporated into the task, the *grasping latencies* (**L**) between the automatic positioning of the robot in front of the chamber window and the grasp of the end-effector by the animal were calculated. Four additional parameters were extracted from the kinematic data collected by the ETH Pattus: (1) *mean variability in trajectories* (**VAR**) within a session was evaluated by calculating the area of the 95% confidence interval of the mean of all successful pulling movements. This parameter is thought to display the formation of a strategy for successful movements [13]. (2) As