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An autonomous, automated and mobile device to concurrently assess several cognitive functions in group-living non-human primates

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ABSTRACT

Research methods in cognitive neuroscience using non-human primates have undergone notable changes over the last decades. Recently, several research groups have described freely accessible devices equipped with a touchscreen interface. Two characteristics of such systems are of particular interest: some apparatuses include automated identification of subjects, while others are mobile. Here, we designed, tested and validated an experimental system that, for the first time, combine automatization and mobility. Moreover, our system allows autonomous learning and testing of cognitive performance in group-living subjects, including follow-up assessments. The mobile apparatus is designed to be available 24 h a day, 7 days a week, in a typical confined primate breeding and housing facility. Here we present as proof of concept, the results of two pilot studies. We report that rhesus macaques (*Macaca mulatta*) learned the tasks rapidly and achieved high-level of stable performance. Approaches of this kind should be developed for future pharmacological and biomedical studies in non-human primates.

1. Introduction

In cognitive neuroscience research, nonhuman primates (NHPs) represent an interesting model of study. Due to their strong phylogenetic proximity, monkeys share many anatomical, physiological and functional characteristics with humans. In addition, the strong equivalence between the respective sensorimotor functions allows the use of very similar cognitive tests and experimental devices in both species, potentially improving the translational power of studies. However, although the relevance of the model has been demonstrated in many domains, its use raises many ethical questions. So, the maximization of animal welfare and the reduction in the number of subjects used in a study are a central concern. In this sense, any kind of evolution making possible the improvement of experimental conditions for monkeys represents a notable progress. Many aspects can be concerned, such as to maintain animals in social groups, to reduce physical constraints on all or part of the testing processes, or even to optimize the number of subjects used and reused during and between successive studies.

Over the past 30 years, cognitive neuroscience research methods using captive NHPs have evolved simultaneously with progress in new technologies. Semi-automated devices incorporating computerized systems (e.g., operating levers, sensors, touch-sensitive screens) have (i) reduced the necessity for interactions between the experimenter and the monkey, (ii) increased the number of cognitive tests that can be administered, (iii) better standardized experimental designs, and (iv) improved measurement accuracy (Hopkins, Washburn, Berke, & Williams, 1992; Vauclair & Fagot, 1993; Wilde, Vauclair, & Fagot, 1994, 1989; Washburn, Hopkins, Washburn, & Rumbaugh, 1989). In such approaches, it is typical that subjects are repeatedly removed from their group and isolated in an experimental area equipped with the testing device. Depending on the research issues and experimental needs, subjects may be restrained for a given time in a primate chair or in a cage specifically adapted to the cognitive evaluation (e.g. Weed & Gold, 1998). It may take several weeks or months of daily training before performance is stabilized (Gould, Garg, Garg, & Nader, 2013; Schneider, Williams, Ault, & Guilarte, 2015; Taffe & Taffe, 2011; Weed et al., 1999), allowing testing to take place, as in e.g.,

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pharmacological studies, or brain activity recording. It is interesting to note that similar approaches were used in a wide range of animal models, each presenting valuable specificities. For example, semi-automated devices have been developed for big carnivores (e.g. bears (Perdue, 2016), dogs (Müller, Schmitt, Barber, & Huber, 2015)), rodents (e.g. Bussey et al., 2012), birds (e.g. Aust & Huber, 2006), and even fishes (Parker, Brock, Sudwarts, & Brennan, 2014).

In NHPs, most studies using devices equipped with a tactile interface were based on such semi-automated approaches (e.g. Schneider et al., 2015; Taffe & Taffe, 2011; Taffe, Weed, & Gold, 1999). In 2008, Evans and colleagues developed a procedure for capuchin monkeys that provided free access to the testing area in which they were isolated (Evans, Beran, Chan, Klein, & Menzel, 2008). This method had the advantage of limiting captures, hence capture-related stress. According to several authors, voluntary engagement with the device could lead to greater motivation and better learning (Andrews & Rosenblum, 1994; Calapai et al., 2016; Evans et al., 2008; Gazes, Brown, Basile, & Hampton, 2013). However, this method still required human intervention to manage the subjects. Fagot and Paleressompoulle (2009) described a new experimental device allowing automatic identification of subjects via a radio frequency identification (RFID) system. The subjects (baboons), implanted with electronic chips in their forearms, were maintained in social groups and could freely and voluntarily access the experimental devices. When a subject was identified, the device automatically suggested a sequence of previously presented trials. The sequence was potentially specific to each subject. In addition, the device allowed each subject to take up the sequence of trials where it had stopped in the previous working session. According to the authors, this new experimental procedure presents four main advantages: (i) it allows testing subjects in their social group, (ii) it makes the presence of the experimenter unnecessary, (iii) it allows large volumes of data to be recorded (Fagot & Bonte, 2010), and (iv) it allows the study of both nonsocial (e.g. Bonte, Flemming, & Fagot, 2011) and social cognitive skills (e.g. Fagot, Marzouki, Huguet, Gullstrand, & Claidiere, 2015). Interestingly, Fagot, Gullstrand, Kemp, Defilles, and Mekaouche (2014) have demonstrated positive effects of this approach on behavior and stress levels of NHPs in semi-free ranging conditions.

A current limitation of this automatic approach is that it cannot address all pertinent issues, e.g. when the experimental protocol requires a subject's immobility. However, it is clearly suitable for the early steps of training. For example, it can reduce stress linked to capture and physical restraint (Cacioppo, Cacioppo, Capitanio, & Cole, 2015; Calapai et al., 2016; Lutz, Well, & Novak, 2003), as well as human time and costs of studies. To optimize the use of this type of approach and make it more accessible, it appeared necessary to develop a system that was automated, mobile and easy to handle in multiple experimental situations. These three specifications – automaticity, mobility, and remote control – motivated the development of the experimental device that we describe here. Our apparatus is (i) easily adapted to conventional cages, (ii) resistant to typical environmental conditions and constraints of a primate housing facility (e.g. physical shocks, dirt, dust, water spray), (iii) remotely controllable, (iv) equipped with two video cameras (giving a frontal view of the subject and a view of the touch-screen), and (v) able to deliver two different solid food reward systems concurrently. Finally, the device is not only automated in terms of detection and testing processes, but also fully autonomous regarding management of each subject's progress on the various cognitive tasks. The experimental aim was to get naive subjects to autonomously learn one or more cognitive tasks until stable baseline performance is reached, without any human intervention except for maintenance of the devices. This innovation in training methods should allow savings in human time and an increased standardization across studies.

Here, we describe the apparatus and the autonomous processes allowing subjects to learn and perform several cognitive tasks concurrently. This new approach should allow the study of interactions between different cognitive functions on a very small scale of time. It should also allow testing the effect of a pharmaceutical compound concurrently on several cognitive functions. This would maximize the reliability of observations and reduce the number of subjects in relation to an approach by sequential studies on different subjects. Moreover, the use of an automated device allowing working on unconstrained animals, housed in social groups, allows among other things i) to improve the experimental conditions, ii) to obtain a large amount of data on fewer animals and iii) to reduce study costs by a substantial reduction of training time and human cost. We report data from two first pilot studies conducted on a small heterogeneous group of naïve rhesus monkeys (*Macaca mulatta*) housed under conventional captive conditions. The main aim of the first study was to test the experimental device *in situ*, in order to identify and fix problems arising during subjects' learning of different cognitive tasks. The main aim of the second study was to validate a training protocol for bringing a subject to learn several cognitive tasks autonomously and concurrently. Finally, we discuss technical and methodological problems encountered during these studies and their solutions.

2. Material and methods

This experiment involved behavioral observations, routine training and non-invasive contact with non-human primate subjects. The procedures were approved by the Animal Experiment Committee of the Primatology Centre of Strasbourg University and by the CREMEAS ethics committee (2015123015405349- APAFIS#3371), and adhered to the French legal requirements.

2.1. Subjects and housing

The studies were conducted on four rhesus monkeys living in a mixed social group at the Primatology Centre of the University of Strasbourg. For the first study, the group contained an adolescent 3-year-old male – subject 1, an elderly 25-year-old female – subject 2, and a younger, 12-year-old female – subject 3. For the second study, a second adolescent 3-year-old male – subject 4 –was integrated into the initial group. All four subjects were naive with regard to touchscreen interactions and more generally to cognitive testing at the start of their respective training.

The housing area comprised a 16 m^2 indoor quarters connected to a 14 m^2 outdoor enclosure (see Fig. 1). The indoor quarters contained structures for climbing, water dispensers and a pellet feeder. The experimental device was attached to the front mesh of the indoor enclosure. The outdoor enclosure contained various structures for climbing, along with apparatuses for physical and cognitive enrichment. Pellets (Special Diets Services; Standard: OWM (E) (Ch), Form: Expanded Chunks Banana, 808003) and water were available *ad libitum*, 24 h/24. Once a week, subjects were maintained for approximately one hour in the outdoor enclosure while the indoor area was cleaned.

2.2. Experimental design

The device was positioned along the wire mesh of the indoor enclosure, in the indoor "human" area (see Fig. 1). An open trapdoor (height = 50; width = 37cm) allowed the subjects to freely interact with the front part of the device. A horizontal stainless-steel structure (i.e. the seat: depth = 35 cm; width = 20 cm) was