Behavioural Brain Research 316 (2017) 54–58

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Short communication

MK-801 reduces sensitivity to Müller-Lyer's illusion in capuchin monkeys

M.E. Jacobsen[a], M. Barros[b], R.S. Maior[a,c,*]

[a] Primate Center and Laboratory of Neurosciences and Behavior, Department of Physiological Sciences, Institute of Biology, University of Brasília, CEP 70910-900, Brasilia, DF, Brazil
[b] Department of Pharmaceutical Sciences, School of Health Sciences, University of Brasilia, Brasilia, DF, Brazil
[c] Karolinska Institutet, Department of Clinical Neuroscience, Psychiatry Section, Karolinska Hospital, S-17176 Stockholm, Sweden

HIGHLIGHTS

- Arrowheads increased the point of subjective equality in capuchin monkeys.
- Repeated treatment with MK-801 reduced sensitivity to Müller-Lyer's illusion.
- MK-801-induced changes are similar to early stages of schizophrenia.

ARTICLE INFO

Article history:
Received 28 June 2016
Received in revised form 19 August 2016
Accepted 22 August 2016
Available online 26 August 2016

Keywords:
MK-801
Müller-Lyer illusion
Schizophrenia
Capuchin

ABSTRACT

The Müller-Lyer's illusion (MLI) is a visual illusion in which the presence of contextual cues (i.e., the orientation of arrowheads) changes the perception of the length of straight lines. An altered sensitivity to the MLI has been proposed as a marker for the progression of perceptual deficits in schizophrenia. Since dizocilpine (MK-801), a noncompetitive antagonist of the NMDA glutamate receptor, induces schizophrenic-like sensory impairments, it may have potential value for investigating the neurochemical basis of the perceptual changes in schizophrenia. Here we tested the effects of MK-801 on the perception of the MLI in a nonhuman primate. Five capuchin monkeys *Sapajus* spp. were trained on a MLI task using a touch screen monitor. After training, the Point of Subjective Equality (PSE; i.e., the minimum difference in length between two lines which the subject can distinguish) was determined for each subject. Then, during 12 consecutive days, we evaluated changes in PSE in response to vehicle, MK-801 (5.6 μg/kg, i.m.) and a no-treatment protocol (post- test). Each of these was given as a single daily treatment, on four consecutive days. Results showed that MK-801 increased the monkeys' performance in the MLI task, suggesting that NMDA receptor modulation reduces sensitivity to this illusion, similar to prodromal stage in schizophrenia patients. The MLI protocol may thus be used in nonhuman primates to screen potential antipsychotic drugs for early stages of this disease.

1. Introduction

The Müller-Lyer's Illusion (MLI) is a potential marker for the perceptual deficits in schizophrenia. Although previous studies in patients with schizophrenia have reported an altered sensitivity for this illusion [14], results are sometimes conflicting, owing to differences in protocol, cohort and medications being used at the time of the test. The stage of the disease, however, seems to be of particular importance. In prodromal patients sensitivity to the MLI was diminished, whereas longtime patients showed an increase in sensitivity [20].

Due to ethical limitations to experiments with patients, animal models are an important alternative to investigate the underpinnings of schizophrenia. Susceptibility to the MLI has been reported in pigeons [33], chicks [36], parrots [21], fish [25] and nonhuman primates [27,30]. Capuchin monkeys, in particular, are sensitive to the MLI and can be trained to perform this task on a touchscreen monitor [27]. As pointed out by Pessoa et al. [22], this protocol may thus be used to model schizophrenia-like sensory impairments of compounds such as phencyclidine or MK-801. Dizocilpine (MK-801) is an NMDA glutamate receptor antagonist that induces

* Corresponding author at: Primate Center and Laboratory of Neurosciences and Behavior, Department of Physiological Sciences, Institute of Biology, University of Brasília, CEP 70910-900, Brasilia, DF, Brazil.
E-mail address: rsmaior@unb.br (R.S. Maior).

http://dx.doi.org/10.1016/j.bbr.2016.08.043
0166-4328/

schizophrenic-like effects, including deficits in working memory [29,32] and social behaviors [18,37]. Although, to our knowledge, its effects on visual illusions have yet to be tested directly, there are several indications that MK-801 disrupts sensory processing. In both rodents and primates, MK801 impaired visuo-spatial processing [4,19] and changes in sensory gating, as evidenced by acoustic prepulse inhibition studies [23]. Therefore, we tested the effects of MK-801 in capuchin monkeys performing a MLI task based on the procedure employed by Suganuma et al. [27]. The results are discussed in terms of a potential tool for screening novel anti- psychotic compounds.

2. Materials and methods

2.1. Subjects

Five adult (10–20 years old) capuchin monkeys (*Sapajus* spp.) were employed in this study, 3 females and 2 males, weighing between 2 and 5 kg. They were housed in pairs or triads at the Primate Center of the University of Brasilia, Brazil, with home-cages (4 m long, 2.9 m wide and 2 m high) being provisioned with natural substrate, rope swings and nest boxes. The animals were tested in their own home-cages under natural light and temperature conditions. They were separated from the rest of their group only during the training or test sessions (see Procedure below), but no head or body restrained was enforced. They all had prior experience with touchscreen monitors, yet none had been previously exposed to the drug tested. The subjects had free access to food and water, except during the experimental sessions. All procedures herein complied with the Brazilian regulations for the scientific use of laboratory animals (Lei Arouca 11.794/2008), as well as the CONCEA/Brazil and NIH/USA guidelines for the care and use of laboratory animals, and were approved by the Animal Ethics Committee of the University of Brasilia (46077/2014).

2.2. Apparatus and computer program

A laptop (Sony® Vaio®, SVE141D11X, Brazil) connected to a 15 in. touchscreen monitor (Bematech®, USA) was used for data collection. The apparatus was set up inside a portable wooden cart that had a square opening in the front for the monitor to face the subjects and an opening in the back so that the laptop faced the experimenters. All training and test tasks were created and run using the e-Prime 2.0 software (Psychology Software Tools Inc®, USA), with the subject's response accuracy being recorded on each session.

2.3. Drug

MK-801 (5.6 μg/kg, Sigma-Aldrich, Brazil) was dissolved in a 1:19 solution of Tween 80 (SigmaAldrich, Brazil) and phosphate-buffered saline, and injected intramuscularly (i.m.) in a volume of 1 mL/kg. To reduce possible ataxic effects, the dose was based on previous studies with nonhuman primates [3,7,23].

2.4. Procedure

The procedures were conducted five days a week, between 2 and 6 pm, being divided into three stages: an initial training period, the determination of each subject's Point of Subjective Equality (PSE) with and without arrowheads, and lastly a test stage. On all three stages, 5 mm thick straight horizontal black lines on a white background were used as stimuli. These lines were 20–105 mm in length, with or without arrowheads at the extremities. When present, the length of the arrowheads was 25% of the length of the respective line, forming a 45° angle for outward-pointing arrowheads and 135° for inward-pointing arrowheads. Correct and incorrect responses from the subjects on each task were immediately followed by distinct (0.5 s) buzzer tones. Each correct response was also rewarded with a raisin provided manually to the subject by one of the experimenters.

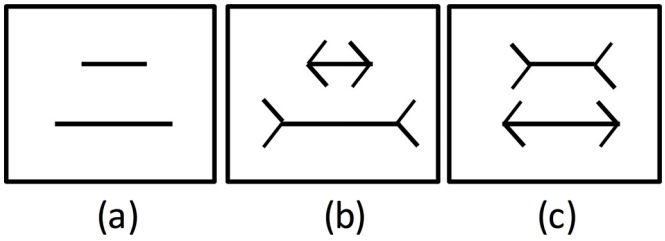

Fig. 1. Example of stimuli used during training and test phases. (a) Pair of lines without arrowheads; (b) and (c) pair of lines with arrowheads. For PSE determination and test phases, (b) was used as 'neutral pair' and (c) 'illusion pair'.

2.4.1. Training

Subjects were trained for several weeks to select the shortest line in each stimulus pair (with or without arrowheads) presented on the touchscreen monitor (Fig. 1a-c). Subsequently, the point of subjective equality (PSE) was determined for each animal. The PSE was operationally defined as the difference whereby the subject's performance reached chance level.

2.4.2. Point of subjective equality

2.4.2.1. PSE without arrowheads. We initially calculated the percentage of correct responses required per session using a binomial test with a 95% confidence limit (CI) of a random performance (50%) based on the total number of trials per session. As each session consisted of 60 trials, the upper CI was set at 63.19% per session; i.e.: 38 correct responses in 60 trials. On any given session, the length difference between the two lines presented was the same on all trials (Fig. 1a). On the subject's first session, the pair of lines had a 50% length difference (90/45 mm). If the subject attained the calculated percentage of correct responses on this session, the difference in length between the two lines was reduced by 10 percentage points (p.p.) on the next session (e.g.: 50–10 = 40%). If the criterion was not reached within the first session, the same length difference was repeated on the subsequent session. If the criterion was still not reached, the subject's third session tested the last length difference it had achieved the upper CI minus 2 p.p. (e.g.: if upper CI was attained at 50% but not at 40% difference, the next session would use a 48% (50%–2 p.p.) length difference between lines). The procedure was then repeated with successive 2 p.p. decrements at each session, until the subject failed to reach the upper CI on two consecutive sessions. The last length difference in which the calculated percentage of correct responses was reached was set as the subject's PSE without arrowheads (e.g.: if it failed at a 44% difference, then 'PSE without arrowheads' for this subject would be set at 46% length difference between lines).

2.4.2.2. PSE with arrowheads. In this phase, each session consisted of 60 trials: 30 with 'illusion pairs' and 30 with 'neutral pairs'. For the latter, the direction of the arrowheads accentuated the length difference between the two lines (Fig. 1b), whereas it decreased that of the 'illusion pair' (Fig. 1c). Only 'illusion pairs' were used to determine each subject's PSE with arrowheads and as such the upper CI was set at 68.7% per session (21 correct responses in 30 trials). A given length difference was tested on four consecutive sessions, held at 24 h intervals. The first line pair tested was the 90/45 mm, corresponding to a 50% difference in length between the two lines. If the subject attained the upper CI on all four sessions, the subsequent four sessions used a pair of lines with a 10