Behavioural Brain Research 343 (2018) 61–70

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Assessment of impulsivity in adolescent mice: A new training procedure for a 3-choice serial reaction time task

Hitomi Sasamori[a], Yu Ohmura[b,*], Takuya Kubo[c], Takayuki Yoshida[b], Mitsuhiro Yoshioka[b]

[a] Hokkaido University School of Medicine, N15 W7 Kita-ku, Sapporo 060-8638, Japan
[b] Department of Neuropharmacology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, N15 W7 Kita-ku, Sapporo 060-8638, Japan
[c] Graduate School of Environmental Earth Science, Hokkaido University, Sapporo 060-0810, Japan

ARTICLE INFO

Keywords:
Development
C57BL/6N
Behavioral inhibition
Executive function

ABSTRACT

Immaturity in impulse control among adolescents could result in substance abuse, criminal involvement, and suicide. The brains of adolescents and adults are anatomically, neurophysiologically, and pharmacologically different. Therefore, preclinical models of adolescent impulsivity are required to screen drugs for adolescents and elucidate the neural mechanisms underlying age-related differences in impulsivity. The conventional 3- or 5-choice serial reaction time task, which is a widely used task to assess impulsivity in adult rodents, cannot be used for young mice because of two technical problems: impaired growth caused by food restriction and the very long training duration. To overcome these problems, we altered the conventional training process, optimizing the degree of food restriction for young animals and shortening the training duration. We found that almost all basal performance levels were similar between the novel and conventional procedures. We also confirmed the pharmacological validity of our results: the 5-hydroxytryptamine 2C (5-HT_{2C}) receptor agonist Ro60-0175 (0.6 mg/kg, subcutaneous) reduced the occurrence of premature responses, whereas the 5-HT_{2C} receptor antagonist SB242084 (0.5 mg/kg intraperitoneal) increased their occurrence, consistent with results of previous studies using conventional procedures. Furthermore, we detected age-related differences in impulsivity using the novel procedure: adolescent mice were found to be more impulsive than adult mice, congruent with the results of human studies. Thus, the new procedure enables the assessment of impulsivity in adolescent mice and facilitates a better understanding of the neurophysiological/pharmacological properties of adolescents.

1. Introduction

Many studies have shown that adolescents are more impulsive than adults [1–4]. As is well known, a higher impulsivity is a risk factor for criminal involvement, substance abuse, and suicide [5–8]. Thus, increased impulsivity in adolescents could lead to various problems, such as risky driving and substance abuse [9–11]. In addition, deficits in impulse control are often observed in psychiatric disorders that mainly occur in adolescents, such as attention-deficit/hyperactivity disorder [12] and schizophrenia [13].

To address these issues, it is important to screen potential anti-impulsivity drugs and understand the neural mechanisms of age-related differences in impulsivity. To this end, preclinical models using rodents are useful, especially mouse models, as many transgenic mouse models have already been developed.

The 5-choice serial reaction time task (5-CSRTT) [14] and 3-choice serial reaction time task (3-CSRTT) [15] have been used widely to assess impulsivity in adult rodents. In these tasks, a light is briefly flashed through one of the 5 or 3 holes and animals are required to make a nose-poke response in the lit hole (*i.e.*, the correct response) to get a food pellet. Nose-poke responses before the presentation of the light stimulus are termed premature responses and are considered an impulsive action. Responses, including premature responses, other than the correct response result in a time-out period. Such tasks have helped scientists to find various pro/anti-impulsivity drugs [16–19] and elucidate the neural mechanisms of impulsive behavior in adult animals [20,21].

However, these findings from these tasks cannot be simply extrapolated to adolescents for two reasons. First, the side effects of several medications, including suicidal tendency associated with use of antidepressants, are age-dependent [22,23]. Second, neurophysiological evidence suggests that the prefrontal cortex, which plays a pivotal role in impulse control, does not fully develop until the age of 25 [24].

Therefore, formulating a task that can assess impulsivity in adolescent mice is imperative. Conventional protocols of 5-CSRTT/3-CSRTT cannot be used in young mice for two reasons: first, the usual

* Corresponding author.
E-mail address: gwd0701@yahoo.co.jp (Y. Ohmura).

https://doi.org/10.1016/j.bbr.2018.01.014
Received 10 September 2017; Received in revised form 26 December 2017; Accepted 15 January 2018
Available online 31 January 2018

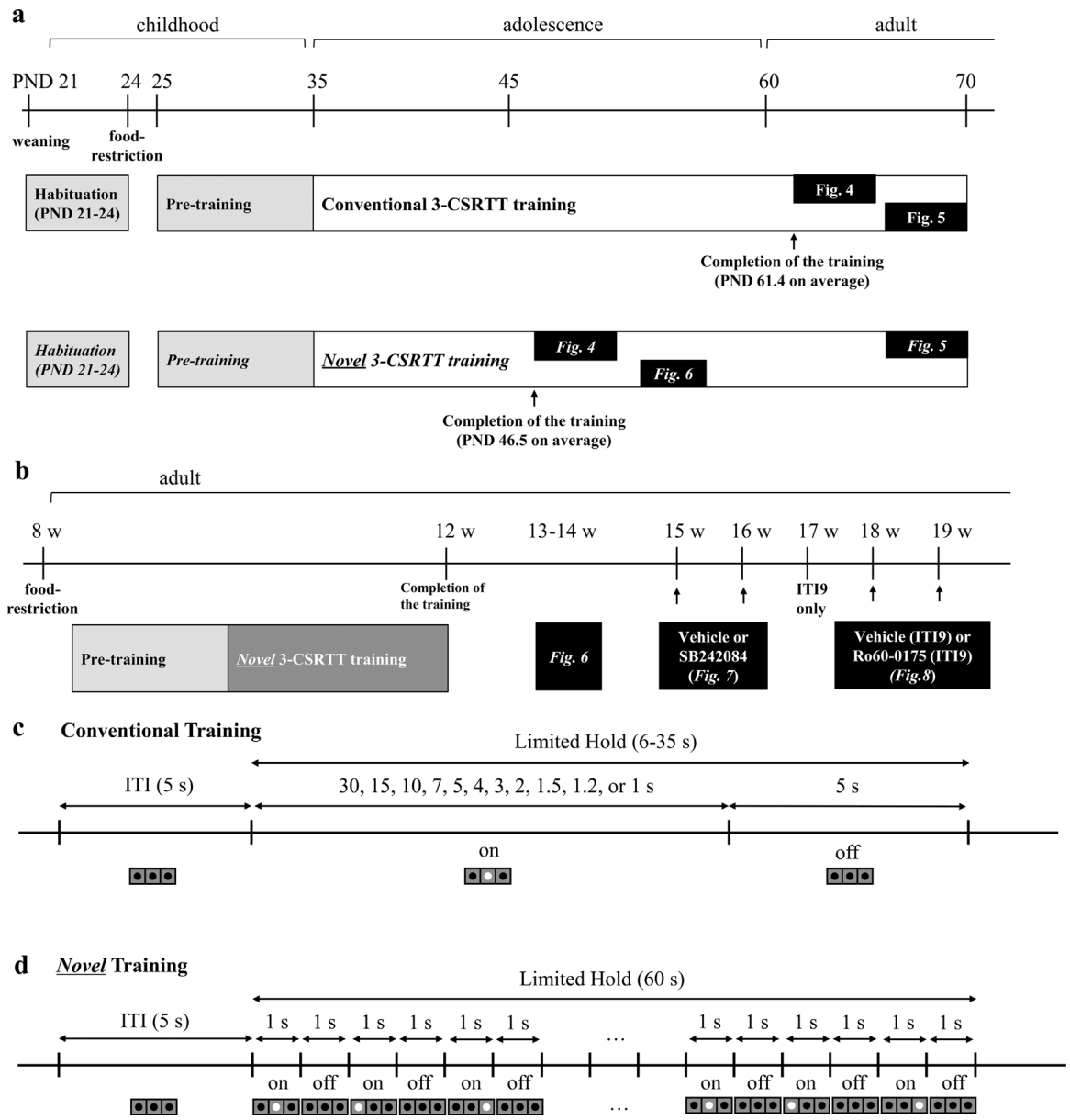

Fig. 1. Schematic representation of the experimental design. (a) Thirty-seven mice for the adolescent 3-CSRTT experiment underwent the habituation (PNDs 21–24) and pre-training procedures. Among these mice, 23 underwent the novel training procedure and 14 underwent the conventional training procedure. When the adolescent mice achieved a stable performance (see 2.3.3 *Common components of the conventional and novel 3-CSRTT training procedures*), training was considered complete. Please note that the time frames of the trainings shown in the figure are based on the number of days (conventional 37.4 ± 9.9, novel 22.5 ± 7.2 days, mean ± 1SD) and not the number of sessions (see Fig. 3). In rodents, "childhood" loosely refers to PND 21–35, "adolescence" refers to PND 36–59, and "adulthood" refers to PND 60–90 [43,44]. PND, postnatal days. The black bars reflect the experimental time points for each figure. (b) Twelve adult mice underwent the habituation, pre-training, and novel training procedures. When the adolescent mice achieved a stable performance (see 2.3.3 training was considered complete. The black bars reflect the experimental time points for each figure. (c) In the conventional procedure, the stimulus duration was gradually decreased (30, 15, 10, 7, 5, 4, 3, 2, 1.5, 1.2, and 1 s) when the mouse attained the criteria for progression, as described in Methods Section 2.3.4 (d) In the novel training procedure, one of the holes was turned on for 1 s and then turned off for 1 s. The cycle was repeated for up to 60 s in each trial. When a mouse correctly made a nosepoke response into the lit hole, the trial ended and a reward pellet was delivered. Responses to non-illuminated holes during the limited hold had no consequence (see 2.3.5).

food restriction procedure in 5-CSRTT/3-CSRTT could disrupt the normal growth of mice during adolescence. Second, conventional protocols of 5-CSRTT/3-CSRTT do not enable us to conduct experiments in adolescent mice because 6–9 weeks are required to complete training [25,26] and mice reach adolescence approximately 5 weeks after weaning (Fig. 1a).

To solve these problems, we established a novel training procedure for the 3-CSRTT in mice with two revisions compared with the previous training procedure. First, we optimized the degree of food restriction for younger mice, allowing them to grow normally and be motivated enough to perform tasks. Second, we decreased the number of sessions required to complete the training. We introduced unpunished training sessions (*i.e.* without a time-out period), with many chances to detect a brief light stimulus during the usual training procedure. We confirmed that the basal performance levels were similar between the novel and conventional procedures. Further, we examined whether our methods could detect age-related differences in impulsivity in mice, as is deducible in the case of humans. We also confirmed the validity of the