Original Research

Time-Dependent Effects of Buspirone versus Desipramine on the 5-Choice Serial Reaction Time Task in Rats Reared in Social Isolation: Implication of Early Life Experience and Motoric Impulsivity

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Abstract

Background: Early life social experience and the function of the central serotonin (5-Hydroxytryptophan, 5-HT) system are involved in development of behavioral impulsivity in which individuals act without forethought or before all necessary information is available. However, most of the evidence has been obtained from acute 5-HT manipulation, whereas, the present study aimed to investigate the effects of subchronic regimen targeting of $5\text{-}HT_{1A}$ receptors on motoric waiting impulsivity in socially isolated rats. **Methods**: A two-week protocol of buspirone (0.5 mg/kg/day) and desipramine (2.5 mg/kg/day) was employed for rats following social isolation rearing (IR) to examine their behavioral performance in a 5-choice serial reaction time task (5-CSRTT) during the treatment regimen. Responses in any one of the apertures prior to an informative signal were recorded as a premature response. **Results**: IR rats presented with more locomotor activity than socially reared (SR) rats. Buspirone progressively increased the baseline level of premature responding in a time-dependent manner that was not observed in IR rats. Both IR and SR rats exhibited less premature responding following acute buspirone challenge. For a subchronic desipramine regimen, IR rats followed the same trend of SR controls to increase the prematurity of baseline response. **Conclusions**: Buspirone but not desipramine-induced time-dependent effects of motoric waiting impulsivity can be reversed by IR, indicating a role for early life social experience on $5\text{-}HT_{1A}$ receptor-associated ability to control impulsiveness.

Keywords: 5-CSRTT; $5\text{-}HT_{1A}$ receptors; buspirone; desipramine; motoric waiting impulsivity; serotonin

1. Introduction

Impulsivity is an urge to perform a specific act following a stimulus caused by the physiological activation of a sense organ. Motoric impulsivity is a type of impulsivity in which individuals act without forethought or before all necessary information is available [1]. Increasing evidence reveals that disturbance of central serotonin (5-Hydroxytryptophan, 5-HT) functions leads to a variety of mental abnormalities, including behavioral impulsivity [2–4]. It is generally accepted that current evidence suggests a positive correlation between the neuronal activity of 5-HT and the ability to control impulsivity, at least in the domains of both cognitive impulsivity indexed by the preference toward large but delayed reward in the temporal discounting of reward task (TDRT) and motoric impulsivity indexed by the premature responding prior to information collection required in the 5-choice serial reaction time task (5-CSRTT) [5]. Most of the evidence supporting this proposition has been obtained from acute manipulation of 5-HT. Thus, it remains inconclusive as to the long-term or time-dependent effects of 5-HT on the behavioral phenotype of impulsivity, which is a role of great interest in its clinical use.

In clinical psychiatry, the time-dependent effect is crucial in the interpretation of pharmacological intervention with 5-HT-related agents. The current working hypothesis considers that the improvement of depressive mood is time-dependently associated with reduced sensitivity of pre-synaptic $5\text{-}HT_{1A}$ autoreceptors [6], possibly together with upgraded utility of post-synaptic $5\text{-}HT_{1A}$ receptors [7,8]. Consequently, the authors considered it worthwhile to investigate behavioral impulsivity following the manipulation of $5\text{-}HT_{1A}$ receptors.

Buspirone, a full agonist of presynaptic $5\text{-}HT_{1A}$ receptors and partial agonist of postsynaptic $5\text{-}HT_{1A}$ receptors, is currently employed as an anxiolytic drug. However, due to the unique profile of $5\text{-}HT_{1A}$ receptors, buspirone becomes potentially useful in rectifying mental problems beyond anxiety, for example, to facilitate the therapeutic onset of selective serotonin reuptake inhibitors (SSRIs). In a rodent model of impulsivity, buspirone helps regulate both cognitive impulsivity indexed by the TDRT [9] and motoric impulsivity indexed by the 5-choice serial reaction time task (5-CSRTT) [10]. In these two impulsive paradigms, buspirone functions distinctively in terms of the psychological nature of each task (i.e., cognitive versus motoric), the

longitudinal duration of the treatment regimen (i.e., acute versus two-week subchronic intervention), and elicits time-dependent, dissociative changes of 5-HT-related behavioral impulsivity.

Among the factors that influence impulsivity, early life socialization is one that can be practically approached in rodent study. Rats underwent isolation rearing (IR) by experiencing social deprivation from weaning by being reared individually; allowed to see and smell others, but not physically contact them [11]. IR rats are less impulsive than their socially reared (SR) controls in both cognitive and motoric impulsiveness, as shown by TDRT and 5-CSRTT testing, respectively [12,13]. For motoric waiting impulsivity, it has previously been demonstrated that in a time-dependent manner, a subchronic buspirone regimen increased the occurrence of premature activity, as opposed to its acute effect [10]. It is of interest to investigate whether IR may influence the buspirone effects in 5-CSRTT.

In the present study, adult IR rats were employed for the 5-CSRTT to obtain a profile of their motoric impulsivity. A 15-days buspirone/desipramine regimen was introduced in which both acute and subchronic effects of the drugs were examined. The use of desipramine, a relatively selective norepinephrine reuptake inhibitor (NRI) which is also used in treating impulsiveness [14,15], was contrasted with 5-HT$_{1A}$ effects of buspirone. The results of this study may provide new insight into early life experience and the clinical utility of 5-HT$_{1A}$ manipulations.

2. Materials and Methods

2.1 Animals

A total 56 male and weaned Sprague-Dawley rats were randomly assigned into SR group (2 rats/cage) and IR group (1 rat/cage) at 21 postnatal days (PD) and they did the 5-CSRTT training at PD56. After 5-CSRTT training, the rats were further assigned to saline, buspirone, or desipramine administrations. Therefore, there were 6 groups in the present study: SR-Saline (n = 10), IR-Saline (n = 10), SR-Buspirone (n = 9), IR-Buspirone (n = 9), SR-Desipramine (n = 9), and IR-Desipramine (n = 9). Note the data of group of SR-Saline and SR-buspirone had been used in our previous publication [10]. All rats were housed in the laboratory animal center (National Defense Medical Center, Taipei, Taiwan) with the humidity of (50% ± 5%) and the temperature of 25 °C (±1 °C), and maintain the 12 hour light and dark cycles (lights on started at 07:00 AM). The cage size is 46 × 24 × 21 cm^3. During the experiment, the rats received standard laboratory rodent chow diet (Ralston Purina, St. Louis, MO, USA) and sterile water. All efforts in the present study were reduce the number of animals used and made to minimize animal suffering during the experiments. This study were evaluated and approved by the National Defense Medical Center animal care committee (Taipei, Taiwan, IACUC-15-054), and we confirmed that all experiments were performed in accordance with the relevant guidelines and regulations of Taiwan. The simplified experimental design is illustrated in Fig. 1.

2.2 Drugs

Buspirone (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in saline and the rats were intraperitoneally (i.p.) injected buspirone with 0.5 mg/kg. Desipramine (Sigma-Aldrich, St. Louis, MO, USA) was dissolved in deionised water and the rats were received 2.5 mg/kg desipramine by subcutaneous injection. The rats were received buspirone or desipramine once per day during the 15-day 5-CSRTT paradigm. The acute administration was be arranged on the Day 1 and Day 15, in which the buspirone, desipramine, and saline were administrated 60, 30, 30 min before the 5-CSRTT, respectively. The subchronic regimen was be arranged daily from Day 2 to Day 14, and all drugs were be administrated 30 min after 5-CSRTT. The doses chosen for buspirone (0.5 mg/kg) and desipramine (2.5 mg/kg) were based on the literatures that the drugs at these doses showed high sensitive to exert effects on the premature responding of the 5-CSRTT [10,16,17].

2.3 Locomotor Activity

Locomotor activity was measured when the rats 8 weeks old. The distance travelled was summed up every 5 min within a total 60 min test by the software of Activity Monitor® 5 (Med Associates, Inc., Fairfax, VT, USA). The apparatus of locomotor activity (Med Associates, Inc., Fairfax, VT, USA) was a Plexiglass chambers (43 × 43 × 30 cm^3) equipped with 16 photodetectors I/R array and corresponding light sources that emitted photobeams 4.5 cm above the floor of chamber and 3 cm apart from each other.

2.4 5-CSRTT

The 5-CSRTT training procedure was similar to our previously studies [13,18,19]. The size of 5-CSRTT chamber (TSE Systems GmbH, Bad Homburg, Germany) was 25 × 31 × 33 cm^3. Each session started when the 5-CSRTT chamber light on, and the initiate trial was began after the rats nose poked the magazine, 5 s [inter-trial interval (ITI)] later, a light which at the rear of one of the five response apertures was briefly illuminated.

A correct response was recorded when rats responded to the illumination aperture within a limited illumination period of the hole, then the reward of a food pellet was delivered to the magazine. An incorrect response was recorded when rats responded to a non-illuminated aperture, and it was punished by a 5 s timeout period accompanied by the chamber light extinguished. A session was stopped after 30 min or 100 completed trials, it depended on which came first.

The percentage of accuracy was collected by the following formula: [correct responses/(correct responses + incorrect responses)]. The percentage of omission was collected by the following formula: (the trials of no response
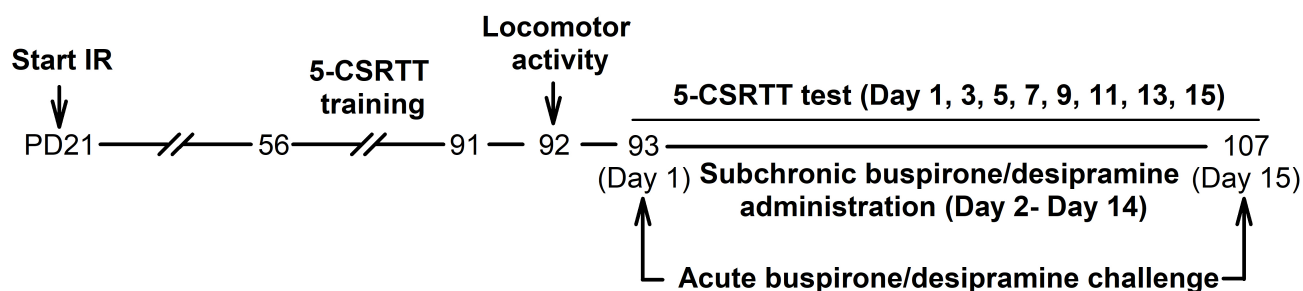
Fig. 1. The simplified experimental design. PD, postnatal days; IR, isolation rearing; 5-CSRTT, five-choice serial reaction time task.

during an ITI/total trial). Premature was recorded when rats "first" responded to any one of the apertures prior to any apertures illumination. Correct latency was means the time duration from an aperture illumination to the rats responded to the correct hole. Collect latency was means the time duration from the rats responded to the correct hole to they take the reward food pellet.

2.5 Statistical Analysis

In the present study, three-way Analysis of Variance (ANOVA) was employed in the data of subchronic treatment with two between-subjects factors of rearing (SR and IR) and treatment (saline and buspirone or saline and desipramine), and a within-subjects factor of time. Two-way ANOVA was used in the data of locomotor activity and acute treatment with between-subjects factor of rearing (SR and IR) or treatment (saline and buspirone or saline and desipramine), or within-subjects factor of time. p-values of <0.05 were defined as statistically significant, the statistically significant main effects were subjected to Bonferroni post-hoc test; and the statistically significant interactions were further split for found simple main effect. All the statistical analyses were used by SPSS 16.0 for Windows software (Chicago, IL, USA).

3. Results

3.1 IR Effect on the Locomotor Activity

The effect of early life social deprivation was validated by characteristically hyperactivity of IR rats in the locomotion test ($F_{1,20} = 61.472$, $p < 0.001$) (Fig. 2).

3.2 The Effects of Subchronic Buspirone Treatment on 5-CSRTT Performances

For the percentage of accuracy, there were no significant effects (Fig. 3A). For the percentage of omission, the data showed a significant interaction between time and treatment ($F_{5,170} = 7.915$, $p < 0.001$), and further analysis indicated significant difference between the SR-Saline and SR-Buspirone ($F_{1,18} = 11.366$, $p < 0.001$), and IR-Saline and IR-Buspirone ($F_{1,16} = 15.298$, $p < 0.001$) on Day 3 (Fig. 3B). For the premature response, the data showed significant interactions between time and treatment ($F_{5,90} =$
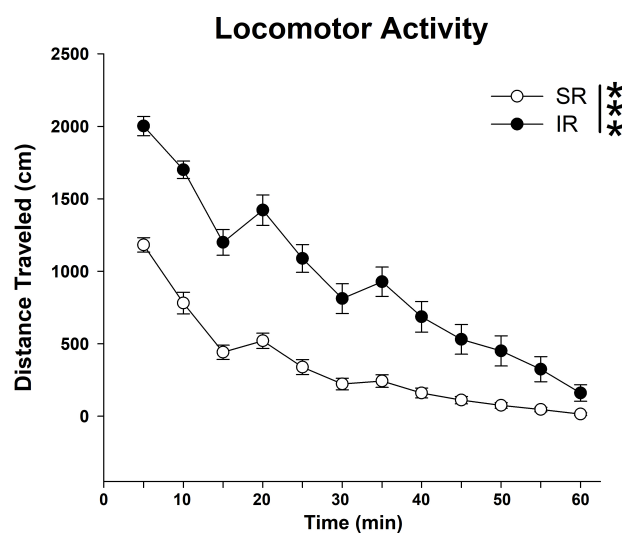
Fig. 2. The locomotor activity after IR and SR. Two-way ANOVA was employed for statistical analysis with a between-subjects factor of rearing (SR and IR) and a within-subjects factor of time. The data represent the mean ± SEM. n = 12 for each group. ***$p < 0.001$, SR group vs. IR group.

4.809, $p = 0.001$) and between rearing condition and treatment ($F_{5,90} = 9.62$, $p = 0.004$), and further analysis indicated significant differences between the SR-Saline and SR-Buspirone on Day 5 ($F_{1,18} = 7.478$, $p < 0.007$), Day 7 ($F_{1,18} = 12.324$, $p < 0.001$), Day 9 ($F_{1,18} = 7.688$, $p < 0.007$), Day 11 ($F_{1,18} = 17.405$, $p < 0.001$), and Day 13 ($F_{1,18} = 12.413$, $p < 0.001$) (Fig. 3C). For the correct latency, the data showed a significant interaction among time and rearing condition and treatment ($F_{5,90} = 2.902$, $p = 0.021$), and further analysis indicated a significant difference between the SR-Saline and SR-Buspirone on Day 3 ($F_{1,18} = 27.865$, $p < 0.001$) (Fig. 3D). For the collect latency, the data showed significant interactions between time and treatment ($F_{5,90} = 8.426$, $p < 0.001$) and between rearing condition and treatment ($F_{5,90} = 5.111$, $p = 0.03$), and further analysis indicated significant differences between the SR-Saline and SR-Buspirone on Day 3 ($F_{1,18} = 9.331$, $p < 0.003$), and between the IR-Saline and IR-Buspirone on Day 3 ($F_{1,16} = 22.950$, $p < 0.001$), Day 5

($F_{1,16} = 5.160$, $p < 0.025$), and Day 7 ($F_{1,16} = 8.019$, $p < 0.006$) (Fig. 3E).

3.3 The Effects of Subchronic Desipramine Treatment on 5-CSRTT Performances

For the percentage of accuracy, there were no significant effects (Fig. 4A). For the percentage of omission, ANOVA showed significant interactions between time and treatment ($F_{5,170} = 6.826$, $p < 0.001$) and between rearing condition and treatment ($F_{5,170} = 4.317$, $p = 0.045$), and further analysis indicated a significant difference between the SR group and IR group ($F_{5,170} = 8.544$, $p < 0.010$), and the data also exhibited significant differences between the SR-Saline and SR-Desipramine ($F_{1,18} = 5.706$, $p < 0.029$), IR-Saline and IR-Desipramine ($F_{1,16} = 14.081$, $p < 0.001$) on Day 3 (Fig. 4B). For the premature response, ANOVA showed a significant interaction between time and treatment ($F_{5,90} = 9.759$, $p < 0.001$), and further analysis indicated a difference between the SR group and IR group ($F_{5,170} = 9.851$, $p < 0.001$), and the data also exhibited significant differences between the SR-Saline and SR-Desipramine on Day 11 ($F_{1,18} = 7.783$, $p < 0.01$) and Day 13 ($F_{1,18} = 8.891$, $p < 0.01$), and between the IR-Saline and IR-Desipramine on Day 11 ($F_{1,16} = 9.122$, $p < 0.01$) and Day 13 ($F_{1,16} = 7.040$, $p < 0.010$) (Fig. 4C). For the correct latency, there were no significant effects (Fig. 4D). For the collect latency, the data showed a significant interaction between time and treatment ($F_{5,90} = 7.937$, $p < 0.001$), and further analysis indicated significant differences between the SR-Saline and SR-Desipramine on Day 3 ($F_{1,18} = 10.402$, $p < 0.01$), and Day 5 ($F_{1,18} = 7.918$, $p < 0.01$), and between the IR-Saline and IR-Desipramine on Day 3 ($F_{1,18} = 8.268$, $p < 0.01$) (Fig. 4E).

3.4 The Effects of Acute Buspirone Administration on 5-CSRTT Performances

For the percentage of accuracy, ANOVA exhibited a significant effect of time ($F_{2,34} = 4.395$, $p = 0.02$), further analysis showed a significant difference between baseline and pre-chronic conditions ($p = 0.016$) (Fig. 5A). For the percentage of omission, ANOVA exhibited a significant effect of time ($F_{2,34} = 23.739$, $p < 0.001$), further analysis showed a significant difference between baseline and pre-chronic ($p = 0.002$), and between baseline and post-chronic conditions ($p < 0.001$) (Fig. 5B). For the premature response, ANOVA showed a significant difference of time ($F_{2,34} = 15.205$, $p < 0.001$) and rearing condition ($F_{1,17} = 13.356$, $p = 0.002$), further analysis showed a significant difference between baseline and pre-chronic ($p = 0.027$), and between baseline and post-chronic conditions ($p = 0.032$) (Fig. 5C). For the correct latency, ANOVA exhibited a significant difference of time ($F_{2,34} = 22.336$, $p < 0.001$) and rearing ($F_{1,17} = 23.390$, $p < 0.001$), further analysis showed significant differences between baseline and pre-chronic conditions ($p < 0.001$), baseline and post-chronic (p

< 0.001), and pre-chronic and post-chronic conditions ($p = 0.002$) in the SR group (Fig. 5D). For the collect latency, the data exhibited a significant difference of time ($F_{2,34} = 38.144$, $p < 0.001$), further analysis showed significant differences in the SR group between baseline and pre-chronic ($p < 0.001$), and baseline and post-chronic conditions ($p < 0.001$), and in the IR group between baseline and post-chronic ($p < 0.001$), and pre-chronic and post-chronic conditions ($p = 0.006$) (Fig. 5E).

### 3.5 The Effects of Acute Desipramine Administration on 5-CSRTT Performances

For the percentage of accuracy, ANOVA exhibited a significant effect of time ($F_{2,34} = 5.290$, $p = 0.01$), further analysis showed a significant difference between baseline and pre-chronic conditions ($p = 0.008$) (Fig. 6A). For the percentage of omission, ANOVA exhibited a significant effect of time ($F_{2,34} = 13.033$, $p < 0.001$), further analysis showed a significant difference between baseline and pre-chronic conditions ($p < 0.001$), and between baseline and post-chronic conditions ($p = 0.006$) (Fig. 6B). For the premature response, ANOVA showed a significant difference of rearing condition ($F_{1,17} = 6.092$, $p < 0.024$) (Fig. 6C). For the correct latency, ANOVA exhibited a significant difference of time ($F_{2,34} = 9.927$, $p < 0.001$), further analysis showed significant differences between baseline and pre-chronic conditions ($p < 0.001$), and baseline and post-chronic conditions ($p = 0.006$) (Fig. 6D). For the collect latency, the data exhibited significant differences in the SR group between baseline and pre-chronic ($p < 0.001$), and pre-chronic and post-chronic conditions ($p < 0.001$), and in the IR group between baseline and post-chronic ($p = 0.023$), and pre-chronic and post-chronic conditions ($p = 0.004$) (Fig. 6E).

4. Discussion

The present study examined the behavioral effects of buspirone/desipramine on the performance of the 5-CSRTT test in IR rats. Three major findings were obtained: (i) IR rats exhibited more locomotor activity than SR rats. (ii) IR rats behaved differently when compared with their SR controls. It was found that buspirone progressively increased the baseline level of premature responding in a time dependent manner in SR but not IR rats. (iii) Both IR and SR rats exhibited less premature responding following acute buspirone challenge. (iv) During the subchronic desipramine regimen, IR rats exhibited the same trend of SR controls to increase their baseline premature responding. These results suggest that early life social experience is involved in the functions of 5-HT$_{1A}$ receptors that regulate impulsivity.

Compared with SR rats, IR rats presented more locomotor activity but less premature responding, demonstrating the different natures of these two conditions. Although hyperactive locomotion and premature responding are both considered behavioral output, each has its own working
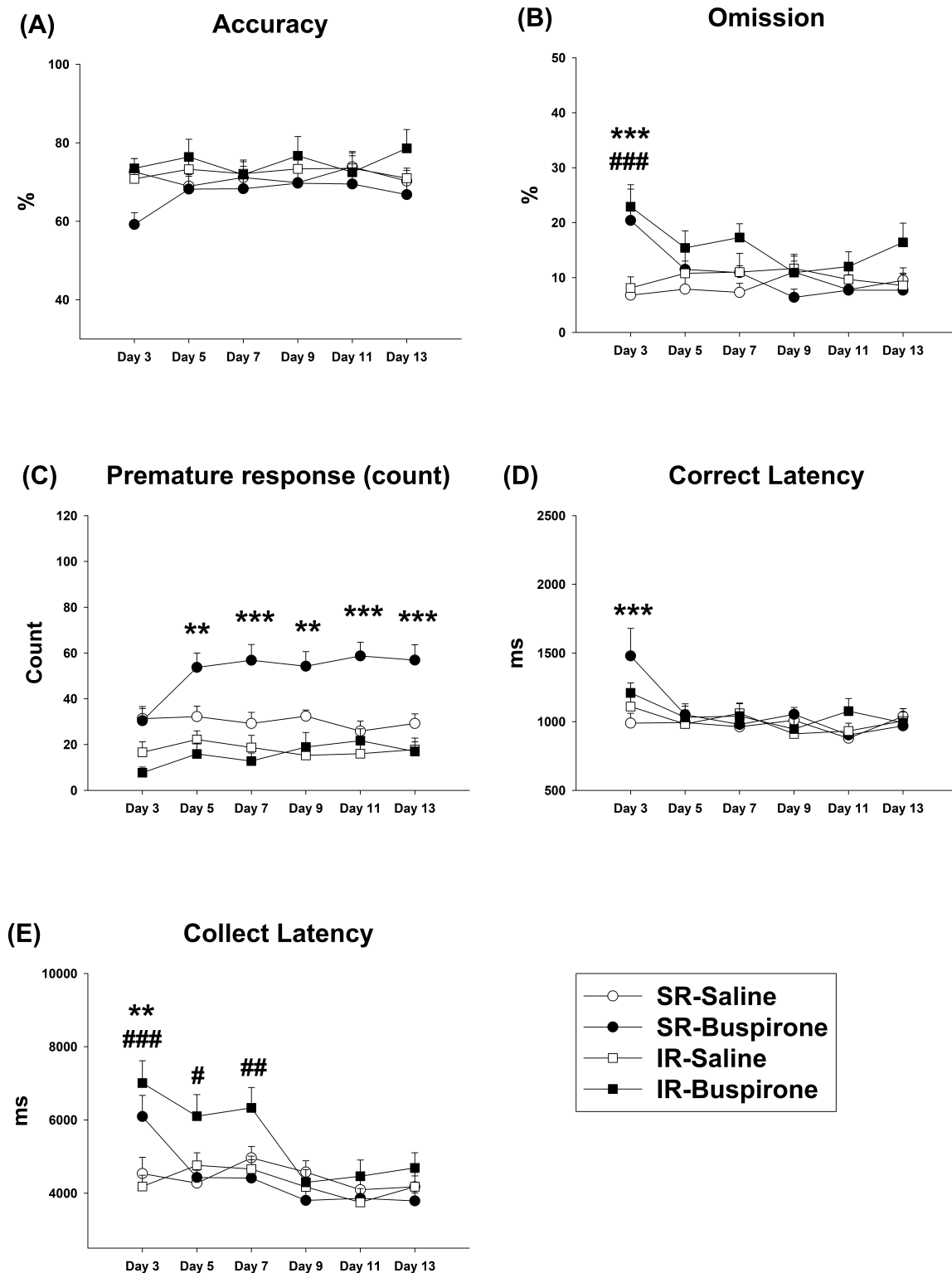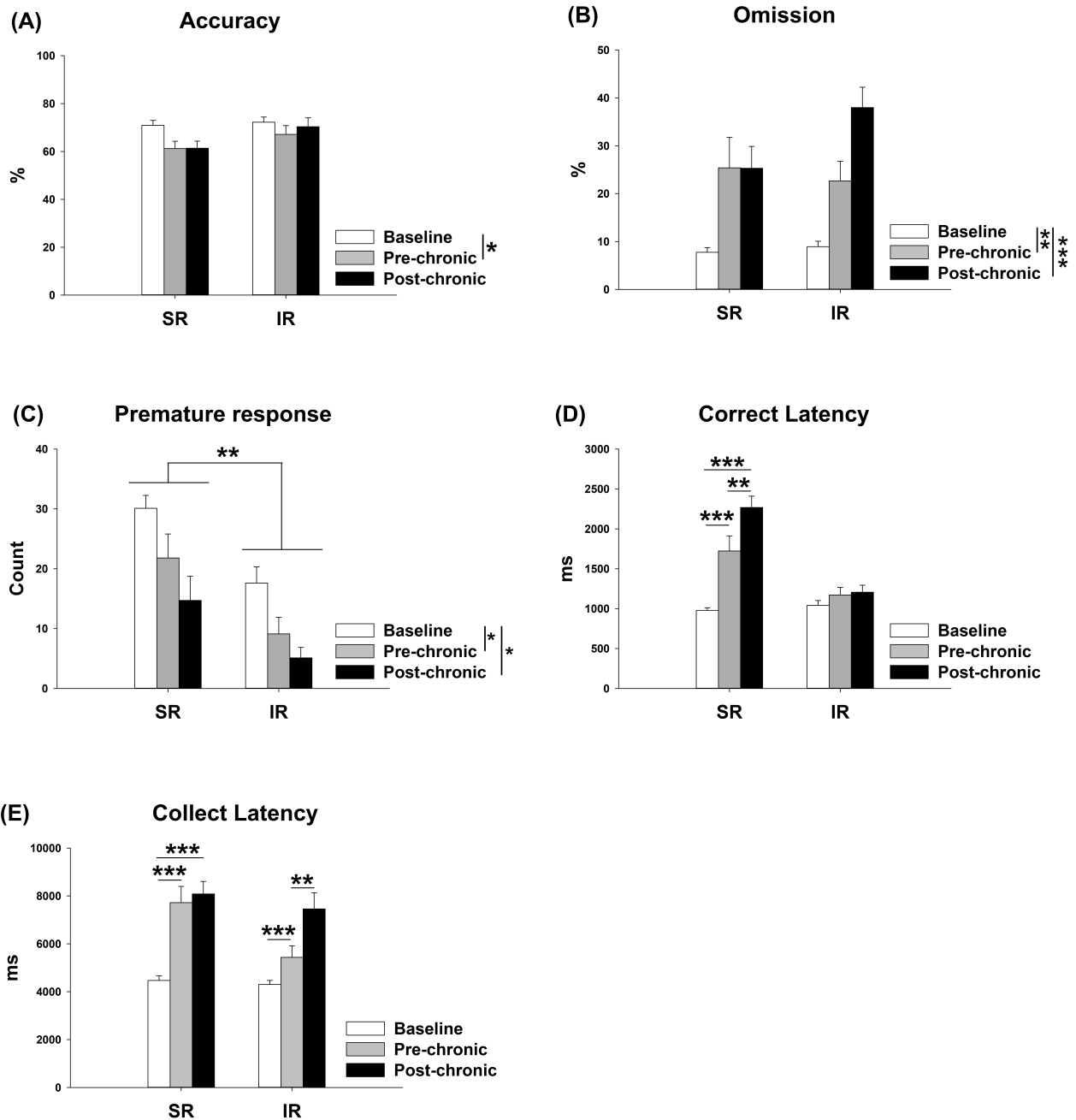
Fig. 3. The performances of IR and subchronic buspirone administration on the 5-CSRTT. (A) The percentage of accuracy. (B) The percentage of omission. (C) The premature response. (D) The correct latency. (E) The collect latency. Three-way ANOVA was employed for statistical analysis with between-subjects factors of rearing (SR and IR) and treatment (saline and buspirone), and a within-subjects factor of time. The data represent the mean $\pm$ SEM. n = 10 for SR-Saline group and SR-buspirone group, n = 9 for IR-Saline group and IR-buspirone group. $**p < 0.01$, $***p < 0.001$, SR-Saline group vs. SR-buspirone group; $\#p < 0.05$, $\#\#p < 0.01$, $\#\#\#p < 0.001$, IR-Saline group vs. IR-buspirone group.
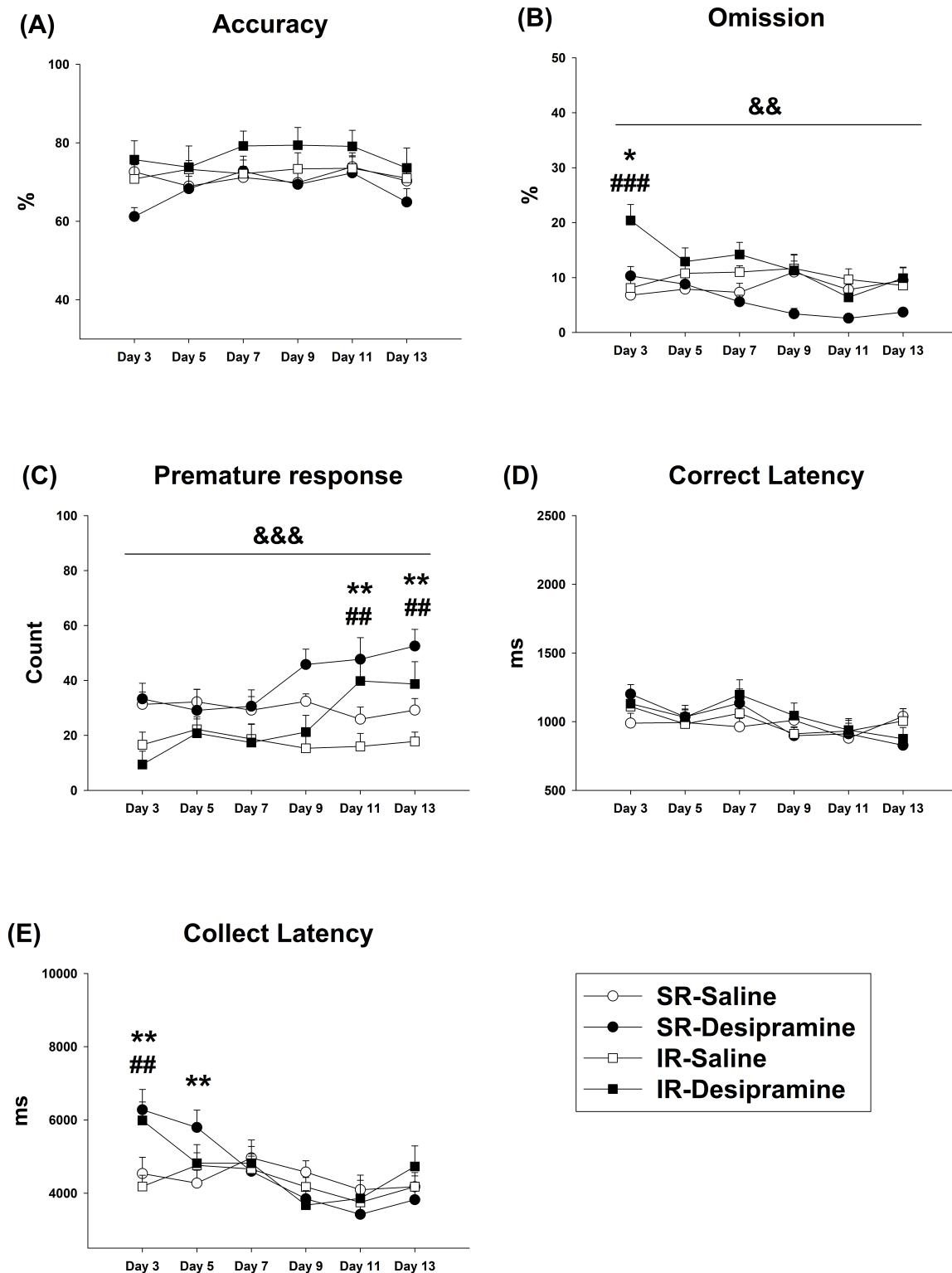
Fig. 4. The performances of IR and subchronic desipramine administration on the 5-CSRTT. (A) The percentage of accuracy. (B) The percentage of omission. (C) The premature response. (D) The correct latency. (E) The collect latency. Three-way ANOVA was employed for statistical analysis with between-subjects factors of rearing (SR and IR) and treatment (saline and desipramine), and a within-subjects factor of time. The data represent the mean $\pm$ SEM. n = 10 for SR-Saline group and SR-desipramine group, n = 9 for IR-Saline group and IR-desipramine group. *$p < 0.05$, **$p < 0.01$, SR-Saline group vs. SR-desipramine group; ##$p < 0.01$, ###$p < 0.001$, IR-Saline group vs. IR-desipramine group; &&$p < 0.01$, &&&$p < 0.001$, SR group vs. IR group.

Acute buspirone administration

(A) Accuracy

(B) Omission

(C) Premature response

(D) Correct Latency
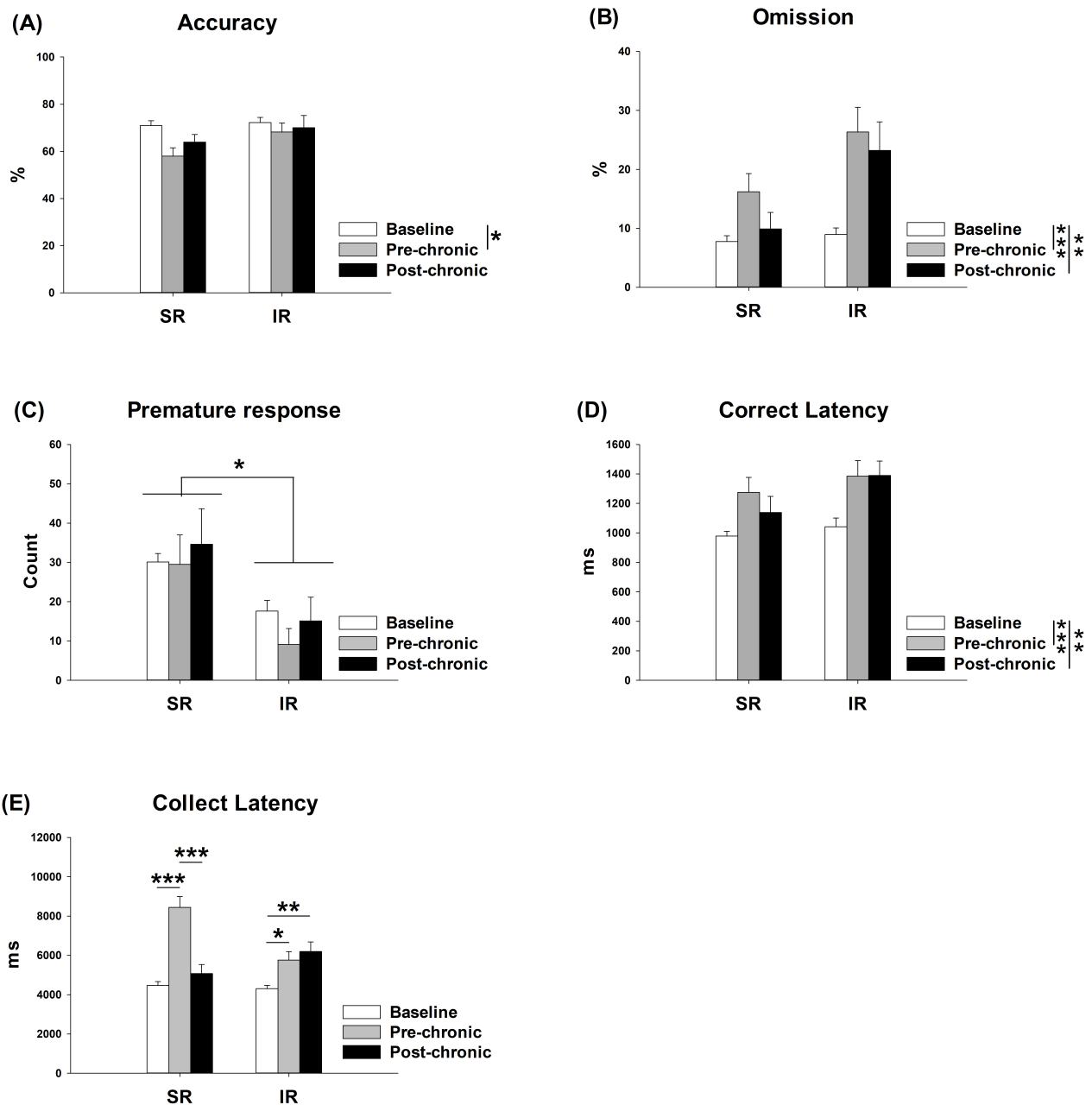
(E) Collect Latency

Fig. 5. The acute effects of buspirone before (i.e., Day 1) and after (i.e., Day 15) the subchronic regimen on the 5-CSRTT performances in IR and SR rats. (A) The percentage of accuracy. (B) The percentage of omission. (C) The premature response. (D) The correct latency. (E) The collect latency. Two-way ANOVA was employed for statistical analysis with a between-subjects factor of rearing (SR and IR) and a within-subjects factor of time. The data represent the mean $\pm$ SEM. n = 10 for SR-Saline group and SR-buspirone group, n = 9 for IR-Saline group and IR-buspirone group. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

mechanism. Locomotor activity is a non-specific behavioral output and the hyperactive characteristic of IR rats can be used to validate the success of the IR paradigm [20], whereas premature responding is a specific index that reflects the ability to control motoric impulsiveness.

Rats subject to repeated buspirone treatment exhibited greater baseline premature responding in the 5-CSRTT case, indicating they were more motorically impulsive, a different response to that of the acute effect of the drug [10]. Concordant with this behavioral finding, Newman

Acute desipramine administration

Fig. 6. The acute effects of desipramine before (i.e., day 1) and after (i.e., day 15) the subchronic regimen on the 5-CSRTT performances after IR and SR. (A) The percentage of accuracy. (B) The percentage of omission. (C) The premature response. (D) The correct latency. (E) The collect latency. Two-way ANOVA was employed for statistical analysis with a between-subjects factor of rearing (SR and IR) and a within-subjects factor of time. The data represent the mean $\pm$ SEM. n = 10 for SR-Saline group and SR-desipramine group, n = 9 for IR-Saline group and IR-desipramine group. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

and colleagues [21] demonstrated at a cellular level that long-term administration of buspirone reduced the 5-HT inhibition of forskolin-stimulated adenylate cyclase activity in rat hippocampal membranes, similar to the chronic effect of fluoxetine, a well-documented SSRI. It should be noted that in clinical application, although SSRIs have been used for their anti-impulsivity effect, the contribution of 5-HT$_{1A}$ receptors appears debatable [22]. Taken together, the buspirone-increased motoric impulsivity observed in the present study appears related to a postsynaptic action, which differs with that of SSRIs. Further, the above buspirone effect is unlikely to be explained by any

of the anxiolytic properties of the drug, given the fact that high motoric impulsivity is in general directly related to the clinical severity of generalized anxiety disorder [23]. The buspirone effect was also unlikely explained by any secondary effects following the changes of other variables of the 5-CSRTT, such as accuracy, omission, and latency, as in general the subjects remained unaffected for the duration of the treatment.

The most important finding in the present study is that the above subchronic buspirone effects disappeared in rats during the ongoing IR paradigm as revealed by significant statistical interactions between rearing condition and treatment. IR rats exhibited greater impulsiveness than SR rats during the subchronic buspirone treatment. The underlying mechanism can be complicated, but it at least relates to (i) the IR-induced greater ability to inhibit the 'waiting impulsivity' not only in motoric impulsivity as shown in the present study but also the cognitive impulsivity of TDRT as well [13], (ii) a developmentally specific phenomenon because it did not occur in the IR case but only with the re-socialization protocol [24]. In other words, the ongoing/continuous social isolation following the critical period of rats, as it influences the IR-impaired ability of prepulse inhibition of the startle reflex [20], and is crucial as well to ensure the IR effect of inhibiting impulsiveness. The experience of long-term, ongoing social isolation has been usually considered adverse or negative. Why IR rats exhibit a greater ability to control their impulsiveness is paradoxically intriguing. What is 'lacking' following IR across the adolescent period is crucial, in which playfighting (also known as 'social play') and activities including pouncing and pinning are critical to the development of motoric/cognitive functions [25,26]. Lack of these activities may develop a behavioral strategy of less risk-taking or impulsiveness.

The data also revealed that the premature responding of the buspirone treated rats gradually increased to reach its maximal level on Day 7. This time-dependent effect fits the desensitization hypothesis of the somatodendritic $5HT_{1A}$ autoreceptors in the dorsal raphe nucleus [27,28]. The data also support the idea that the chronic effect via 5-HT_{1A} receptors on impulsivity or inhibitory response control is task-dependent. In cognitive impulsivity indexed by TDRT, rats become less impulsive [9], whereas in motoric impulsivity indexed by 5-CSRTT (i.e., the present study), they are more impulsive. As buspirone serves as a full agonist of presynaptic 5-HT_{1A} receptors and a partial agonist of postsynaptic 5-HT_{1A} receptors, the overall long-term effects need to take effect terminal areas in the brain, particularly the prefrontal cortex [9], one of the main sites of 5-HT_{1A} postsynaptic receptors, a fact highly relevant to inhibitory response control [29]. IR reversed the long-term buspirone effect on waiting impulsivity implying that early life social experience may contribute to adjustment of the profile of 5-HT_{1A} receptors. IR may induce considerable

change of neural substrates in an area-dependent manner. In IR rats, serotonin receptors were found presynaptically down-regulated and postsynaptically up-regulated [30,31]. It is possible that, to a degree, the IR profile is reminiscent of the long-term antidepressant effects of 5-HT associated medicines used to both down-regulate the presynaptic (such as SSRIs), but strengthen the postsynaptic functions (such as vortioxetine, see Celada *et al.*, 2013 [32]).

In contrast to its long-term effect to increase baseline premature responding, acute buspirone, whether administered either before or after the subchronic regimen, tended to reduce the reactivity of responding. Note that in neurochemical terms, the acute effect of buspirone did not alter synaptic 5-HT efflux, it was decreased in ventral hippocampus but increased in medial prefrontal cortex [9]. As reduced 5-HT function is in general considered to disrupt impulse control, this discrepancy needs to be solved by mechanisms other than area-based neurochemical change. Alternatively, it is possible that this is because of impairment of motoric readiness (or agility, thus lengthening of the magazine latency to retrieve the reward) following the acute effect of buspirone, as seen in the present study. Further, as this effect was also counteracted by IR, it implies that early life social experience contributes to the buspirone-induced motoric reactivity.

In the present study, desipramine was used to compare the effects of buspirone that represented distinctive pharmacological manipulations, i.e., NRI versus 5-HT_{1A} receptor partial agonism. Results revealed that desipramine had no effect on the motoric impulsivity if given acutely. However, after repeated administration, both SR and IR rats exhibited greater premature responding. Previous studies have revealed that the acute effect of NRIs (for example, desipramine and atomoxetine) tend to either enhance inhibitory control or reduce the motoric impulsivity [16,17,19], possibly via modulation of prefrontal Norepinephrine (NE) neurons [33]. So far there is no evidence for the long-term effect of desipramine on the impulsivity profile of the 5-CSRTT. Result presented here, show that IR rats followed the same trend as SR controls, i.e., to increase their baseline premature responding following the subchronic desipramine regimen. This suggests that early life social experience is not involved in NRI-related motoric impulsivity, highlighting a specific effect of IR on the 5-HT_{1A} receptor involved regulation of motoric impulsivity.

In terms of clinical implication, results reported here suggest that early life social experience should be taken into account when accessing motoric waiting impulsivity, particularly when it comes to the pharmacological manipulation of 5-HT_{1A} receptors. In fact, impairment of impulse control is not only a key symptom in impulse control disorders [34], but also appears often in other psychiatric disorders, for example, mood disorders such as bipolar disorder and anxiety disorders such as obsessive compulsive disor-

der [35,36]. With its unique effects on both presynaptic and postsynaptic 5-HT$_{1A}$ receptors, buspirone is employed in clinical psychiatry to facilitate an antidepressant response [32,37].

Several limitations should be addressed in the interpretation of the results. First, there was a lack of dose-response curve to validate the data. Second, a two-week subchronic regimen was employed in the present study, but a longer period of intervention is suggested. Finally, as protein expression of 5-HT$_{1A}$ receptors was not measured in the present study, the specificity of IR effect on 5-HT$_{1A}$ associated behavioral impulsivity needs to be identified in more detail. For example, it can be examined through clarifying the role of presynaptic versus postsynaptic receptors in rats with 5-HT depletion by 5,7-Dihydroxytryptamine (5,7-DHT) [38,39].

5. Conclusions

The present study demonstrated that social isolation during early life reversed buspirone but not desipramine-induced time-dependent effects of motoric waiting impulsivity, indicating a role for early life social experience in 5-HT$_{1A}$ receptor-associated ability to control impulsiveness.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

CST and YPL designed the study and wrote the protocol. YWL performed the experiment. CST and YPL worked for the clinical interpretation. CCL and YWL worked for the data analysis. CCL and YPL worked for writing drafts of the manuscript. All authors contributed to editorial changes in the manuscript. All au- thors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Ethics approval had been granted by the Laboratory Animal Center from the National Defense Medical Center, Taiwan (IACUC-15-054).

Acknowledgment

Not applicable.

Conflict of Interest

Che-Se Tung is serving as one of the Editorial Board members of this journal. We declare that Che-Se Tung had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel. The other authors declare no conflict of interest.

References

[1] Dong L, Wang S, Li Y, Zhao Z, Shen Y, Liu L, *et al*. RU486 Reverses Emotional Disorders by Influencing Astrocytes and Endoplasmic Reticulum Stress in Chronic Restraint Stress Challenged Rats. Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology. 2017; 42: 1098–1108.

[2] Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK. Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sciences. 1983; 33: 2609–2614.

[3] Soubrié P. Reconciling the role of central serotonin neurons in human and animal behavior. Behavioral and Brain Sciences. 1986; 9: 319–335.

[4] Evenden JL, Ryan CN. The pharmacology of impulsive behaviour in rats VI: the effects of ethanol and selective serotonergic drugs on response choice with varying delays of reinforcement. Psychopharmacology. 1999; 146: 413–421.

[5] Jones JA, Zuhlsdorff K, Dalley JW. Neurochemical substrates linked to impulsive and compulsive phenotypes in addiction: A preclinical perspective. Journal of Neurochemistry. 2021; 157: 1525–1546.

[6] Blier P. Pharmacology of rapid-onset antidepressant treatment strategies. The Journal of Clinical Psychiatry. 2001; 62: 12–17.

[7] Savitz J, Lucki I, Drevets WC. 5-HT(1A) receptor function in major depressive disorder. Progress in Neurobiology. 2009; 88: 17–31.

[8] Dale E, Pehrson AL, Jeyarajah T, Li Y, Leiser SC, Smagin G, *et al*. Effects of serotonin in the hippocampus: how SSRIs and multimodal antidepressants might regulate pyramidal cell function. CNS Spectrums. 2016; 21: 143–161.

[9] Liu YP, Wilkinson LS, Robbins TW. Effects of acute and chronic buspirone on impulsive choice and efflux of 5-HT and dopamine in hippocampus, nucleus accumbens and prefrontal cortex. Psychopharmacology. 2004; 173: 175–185.

[10] Lu CL, Ku YC, Lo SM, Peng CH, Tung CS, Lin YW, *et al*. Acute and subchronic effects of buspirone on attention and impulsivity in the five-choice serial reaction time task in rats. Neuroscience Letters. 2013; 556: 210–215.

[11] Robbins TW. Neurobehavioural sequelae of social deprivation in rodents revisited: Modelling social adversity for developmental neuropsychiatric disorders. Journal of Psychopharmacology (Oxford, England). 2016; 30: 1082–1089.

[12] Hellemans KGC, Nobrega JN, Olmstead MC. Early environmental experience alters baseline and ethanol-induced cognitive impulsivity: relationship to forebrain 5-HT1A receptor binding. Behavioural Brain Research. 2005; 159: 207–220.

[13] Liu YP, Wilkinson LS, Robbins TW. 'Waiting impulsivity' in isolation-reared and socially-reared rats: effects of amphetamine. Psychopharmacology. 2017; 234: 1587–1601.

[14] Wiley JL, Compton AD, Golden KM. Separation of drug effects on timing and behavioral inhibition by increased stimulus control. Experimental and Clinical Psychopharmacology. 2000; 8: 451–461.

[15] Bizot JC, David S, Trovero F. Effects of atomoxetine, desipramine, d-amphetamine and methylphenidate on impulsivity in juvenile rats, measured in a T-maze procedure. Neuroscience Letters. 2011; 489: 20–24.

[16] Paine TA, Tomasiewicz HC, Zhang K, Carlezon WA, Jr. Sensitivity of the five-choice serial reaction time task to the effects of various psychotropic drugs in Sprague-Dawley rats. Biological Psychiatry. 2007; 62: 687–693.

[17] van Gaalen MM, Brueggeman RJ, Bronius PFC, Schoffelmeer ANM, Vanderschuren LJMJ. Behavioral disinhibition requires dopamine receptor activation. Psychopharmacology. 2006; 187: 73–85.

[18] Liu YP, Tung CS, Lin YL, Chuang CH. Wake-promoting agent modafinil worsened attentional performance following REM sleep deprivation in a young-adult rat model of 5-choice serial reaction time task. Psychopharmacology. 2011; 213: 155–166.

[19] Liu YP, Huang TS, Tung CS, Lin CC. Effects of atomoxetine on attention and impulsivity in the five-choice serial reaction time task in rats with lesions of dorsal noradrenergic ascending bundle. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2015; 56: 81–90.

[20] Liu YP, Kao YC, Tung CS. Critical period exists in the effects of isolation rearing on sensorimotor gating function but not locomotor activity in rat. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2011; 35: 1068–1073.

[21] Newman ME, Shapira B, Lerer B. Regulation of 5-hydroxytryptamine1A receptor function in rat hippocampus by short- and long-term administration of 5-hydroxytryptamine1A agonist and antidepressants. The Journal of Pharmacology and Experimental Therapeutics. 1992; 260: 16–20.

[22] De Vry J. 5-HT1A receptor agonists: recent developments and controversial issues. Psychopharmacology. 1995; 121: 1–26.

[23] Pierò A. Personality correlates of impulsivity in subjects with generalized anxiety disorders. Compr Psychiatry. 2010; 51: 538–545.

[24] Baarendse PJJ, Counotte DS, O'Donnell P, Vanderschuren LJMJ. Early social experience is critical for the development of cognitive control and dopamine modulation of prefrontal cortex function. Neuropsychopharmacology. 2013; 38: 1485–1494.

[25] Takahashi LK, Lore RK. Play fighting and the development of agonistic behavior in male and female rats. Aggressive Behavior. 1983; 9: 217–227.

[26] Byers JA, Bekoff M. Social, spacing, and cooperative behavior of the collared peccary, Tayassu tajacu. Journal of Mammalogy. 1981; 62: 767–785.

[27] Blier P, de Montigny C. Current advances and trends in the treatment of depression. Trends in Pharmacological Sciences. 1994; 15: 220–226.

[28] Yocca FD. Neurochemistry and neurophysiology of buspirone and gepirone: interactions at presynaptic and postsynaptic 5-HT1A receptors. Journal of Clinical Psychopharmacology. 1990; 10: 6S–12S.

[29] Dalley JW, Cardinal RN, Robbins TW. Prefrontal executive and cognitive functions in rodents: neural and neurochemical substrates. Neuroscience and Biobehavioral Reviews. 2004; 28: 771–784.

[30] Bickerdike M, Wright I, Marsden C. Social isolation attenuates rat forebrain 5-HT release induced by KCl stimulation and exposure to a novel environment. Behavioural Pharmacology. 1993; 4: 231–236.

[31] Wright IK, Ismail H, Upton N, Marsden CA. Effect of isolation rearing on 5-HT agonist-induced responses in the rat. Psychopharmacology. 1991; 105: 259–263.

[32] Celada P, Bortolozzi A, Artigas F. Serotonin 5-HT1A receptors as targets for agents to treat psychiatric disorders: rationale and current status of research. CNS Drugs. 2013; 27: 703–716.

[33] Bari A, Robbins TW. Inhibition and impulsivity: behavioral and neural basis of response control. Prog Neurobiol. 2013; 108: 44–79.

[34] Tahir T, Wong MM, Maaz M, Naufal R, Tahir R, Naidoo Y. Pharmacotherapy of impulse control disorders: A systematic review. Psychiatry Research. 2022; 311: 114499.

[35] Santana RP, Kerr-Gaffney J, Ancane A, Young AH. Impulsivity in Bipolar Disorder: State or Trait? Brain Sciences. 2022; 12: 1351.

[36] Eskander N, Emamy M, Saad-Omer SM, Khan F, Jahan N. The Impact of Impulsivity and Emotional Dysregulation on Comorbid Bipolar Disorder and Borderline Personality Disorder. Cureus. 2020; 12: e9581.

[37] Sussman N. Anxiolytic antidepressant augmentation. The Journal of Clinical Psychiatry. 1998; 59: 42–50.

[38] Chang KJ, Chen YJ, Chung JY, Lin CC, Liu YP. Effects of 5HT1A Activation on Depression Profile Following 5-HT Depletion in Rats Lacking Social Attachment Since Weanling. Psychiatry Investigation. 2018; 15: 1000–1006.

[39] Tai YM, Ko CY, Lin CC, Wan YY, Chung JY, Liu YP. Effects of 5HT1A Activation on Gating Profile Following 5HT Depletion in Rats Lacking Social Attachment Since Weanling. Psychiatry Investigation. 2018; 15: 193–199.

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