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Research article

Lithium and valproate prevent methylphenidate-induced mania-like behaviors in the hole board test

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HIGHLIGHTS

- Lithium and valproate prevented the methylphenidate-induced hyperlocomotion in mice.
- Methylphenidate-treated mice mimic cardinal symptoms of mania in the hole board.
- Lithium prevented risk-taking and goal-directed behaviors induced by methylphenidate.

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ABSTRACT

Manic bipolar is diagnosed by psychomotor agitation, increased goal-directed activity, insomnia, grandiosity, excessive speech, and risky behavior. Animal studies aimed to modeling mania are commonly based in psychostimulants-induced hyperlocomotion. The exploration of other behaviors related with mania is mandatory to investigate this phase of bipolar disorder in animals. In this study, the hole board apparatus was suggested for evaluating mania-like behaviors induced by the psychostimulant methylphenidate. The treatment with methylphenidate (10 mg/kg, ip) increased locomotion in the open field test. The pretreatment with lithium (50 mg/kg, ip) and valproate (400 mg/kg, ip) significantly prevented the hyperlocomotion. In the hole-board test, methylphenidate increased interactions with the central and peripheral holes and the exploration of central areas. Lithium was more effective than valproate in preventing all the behavioral manifestations induced by the psychostimulant. These findings were discussed based on the ability of methylphenidate-treated mice mimicking two symptoms of mania in the hole board test: goal-directed action and risk-taking behavior. In conclusion, the results point to a new approach to study mania through the hole board apparatus. The hole board test appears to be a sensitive assay to detect the efficacy of antimanic drugs.

1. Introduction

Bipolar disorder is a chronic mental illness defined by the alternation of manic and depressive periods with euthymic or normal mood states between episodes [1]. The estimated lifetime prevalence of bipolar disorder in general population is around 4% [2]. The onset of first manic or depressive episode in young adulthood frequently occurs above the 25 years old [2]. It is still unknown the etiology of bipolar disorder, but probably genetic and environmental factors are involved [3,4].

Modeling bipolar disorder in animals is extremely challenging given the difficulty to infer mood states that mimics the clinical symptoms and cognitive deficits of human illness [5,6]. On top of the difficulties to modeling bipolar disorder in animals is the oscillating nature of the disease [7], in which patients alternate between episodes of depression and mania/hipomania [1]. While depressive symptoms include anhedonia, lack of motivation, loss of appetite, insomnia, motor retardation or agitation, fatigue, cognitive impairment, and suicidal thoughts, a manic episode is characterized by expansive or irritable mood, increased goal-directed activity, psychomotor agitation, excessive speech, grandiosity, insomnia, distractibility, involvement with risky activities and flight of ideas [1]. In this way, animal models for the entire scope of bipolar disorder are in fact non-existent and the common practice is to use distinct tests for depressive- and mania-like behaviors [5,6].

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Pharmacological treatment for bipolar disorder has two main scopes: episodes' treatment or maintenance. During depressive or manic episodes, the treatment aims to resolve an episode that is ongoing [8]. In this case, for acute mania, the pharmacological options of treatment include lithium or valproate plus an antipsychotic, while for acute bipolar depression, therapeutic options more frequently used are atypical antipsychotics [9]. In maintenance treatment, the focus is to delay the occurrence of future episodes, and minimize the severity of episodes that do occur [8]. Lithium and valproate are the most efficient monotherapies for the long-term treatment of bipolar disorder [9]. Thus, considering animal models of bipolar disorder, it is expected that these drugs can prevent and/or normalize the behavioral parameters which are mimicking a human bipolar episode [6,10].

Different experimental approaches including animal models that singly evaluate each phase of bipolar disorder, *i.e.*, depression and mania, have been used. Modeling depression is similar to what happen in the context of experimental major depression, in which behavioral despair tests, such as forced swimming test and tail suspension, can be used [11]. Differently, modeling mania may be more challenging since many symptoms are exclusively observed in human beings, which limit the approach [12,13]. The induction of hyperactivity in response to drugs that modulate dopaminergic activity is the most common [14]. The psychostimulant methylphenidate has been reported as a pharmacological tool to induce hyperactivity related to a manic-like state in mice [15–18]. However, psychostimulants-induced hyperlocomotion cannot be directly addressed to mania, once this manifestation can be observed in animal models of other psychiatric disorders, *i.e.* schizophrenia [19].

Mimicking one or more of mania symptoms in rodents rather than hyperactivity would be mandatory to refine the investigation of the biological basis and the treatment targets of this psychiatric disorder. In this context, the present study aimed to propose the hole board test as a novel tool to study mania-like behaviors in mice. The first-line mood stabilizers lithium and valproate were used to pharmacologically validate the methylphenidate-induced behaviors in the open-field and hole board tests.

2. Material and methods

2.1. Animals

Experiments were conducted using male Swiss mice breaded at the Federal University of Rio Grande do Norte (Natal, Brazil) (12–16 weeks old, 28–35 g). Mice were housed in plastic cages (41 × 34 × 16 cm) in groups of maximum 13 per cage under standard conditions (22 °C;12-h light:12-h dark cycle, lights on at 6:00 am) with food and water *ad libitum*. A total number of 160 mice were used to develop this study. All experiments were conducted in accordance with Brazilian Law No. 11.714/2008 for care and use of experimental animals. The protocol was approved by Ethic Committee for Animal Use of Federal University of Rio Grande do Norte (Licenses No. 040/2012; 041/2014). This study is reported following the ARRIVE guidelines [20].

2.2. Drugs and treatments

Methylphenidate (Novartis Biociências S.A., São Paulo, Brazil), sodium valproate (Sanofi S.A., São Paulo, Brazil) and lithium (Sigma-Aldrich Corporation, St. Louis, MO, EUA) were used. All the drugs were dissolved in saline solution. Methylphenidate (10 mg/kg) was administrated 15 min prior to the tests, while sodium valproate (400 mg/kg) and lithium (50 mg/kg) were injected 30 min before methylphenidate injection. All the drugs were intraperitoneally (ip) administrated in a volume of 10 ml/kg and were freshly prepared before experiments. Control groups were treated with saline solution following the same schedule described to treatment groups. The drugs employed in this study have been previously reported in the literature, either to induce mania-like behavior (methylphenidate) or to prevent it in rodents (sodium valproate and lithium) [16–18].

2.3. Methylphenidate-induced hyperlocomotion in the open-field test

Hyperlocomotion induced by methylphenidate was measured in the open-field apparatus, which consisted of a wooden box covered with black impermeable formica (40 × 40 × 40 cm). The test room had a controlled illumination (dimly-light condition; approx. 50 lx at the center of the apparatus). Each mouse was placed in the center of the apparatus and the distance travelled (in meters) were measured by a video camera connected to an automated activity monitoring system (AnyMaze, Stoelting Co., Wood Dale, IL, USA) for a period of 30 min. After the behavioral evaluation of each mouse, the arena was wiped with water-alcohol (5%) solution.

2.4. Hole board test

Measures of hole board parameters were performed in a wooden box (40 × 40 × 35 cm) with 16 holes (3 cm of diameter) on the ground: 4 in the center and 12 in the periphery of the board. The board was suspended 5 cm to the floor. Detailed description of the hole board apparatus is illustrated in Fig. S1. Each animal was evaluated for a period of 10 min. During this time, the frequency of interactions with the central and peripheral holes, the time spent in (in s) and the distance moved (in meters) in the central area was measured. Behaviors like sniffing or poking the hole for at least 1 s were recorded as interactions with the holes. The distance moved and the time spent in the central area was recorded by a video camera connected to an automated activity monitoring system (AnyMaze, Stoelting Co., Wood Dale, IL, USA). The interactions with the holes were manually recorded by an experienced observer who was blind with respect to the treatment conditions.

2.5. Statistical analysis

Data were analyzed using Student *t*-test or one-way ANOVA followed by Duncan's test, as specified in the legends, and were presented as mean ± SEM of n animals. Differences were considered significant when $p < 0.05$. All statistical analyses were performed using the softwares Prism version 5.0 (Graphpad Software Inc, San Diego, USA) and Statistica version 7.0 (Statsoft Inc, Tulsa, USA).

3. Results

3.1. Effect of methylphenidate on the mouse exploratory behavior in the open field and hole board tests

As shown in the Table 1, the behavioral pattern of mice treated with methylphenidate was significantly different from the exhibited by controls in the open field and hole board tests. Treatment with the psychostimulant drug significantly increased the cumulative distance travelled in the open field test ($t = 5.32$, $df = 15$, $p < 0.05$). Concerning the hole board assay, methylphenidate induced a significant increase in the central and peripheral holes interaction (central interactions: $t = 2.59$, $df = 28$, $p < 0.05$; peripheral interactions: $t = 2.27$, $df = 28$, $p < 0.05$). In addition, methylphenidate-treated mice explored more the central areas of the hole board compared to saline group (central distance

Table 1
Effects of methylphenidate administration (10 mg/kg, ip) on mouse behaviors measured in the hole board and open field tests.

	Open field	Hole board			
	Total distance travelled	Central hole interactions	Peripheral hole interactions	Center time (s)	Central distance moved (m)
Saline	40.5 ± 5.8	17.3 ± 1.4	69.7 ± 3.4	36.7 ± 3.5	1.8 ± 0.2
Methylphenidate	183.7 ± 19.4*	29.1 ± 3.8*	87.0 ± 6.1*	54.4 ± 8.5#	4.1 ± 0.6*

Data are the mean ± SEM of 8–9 mice/group (open field test) and 15 mice/group (hole board test). *p < 0.05 and #p = 0.09 according to unpaired Student *t*-test.

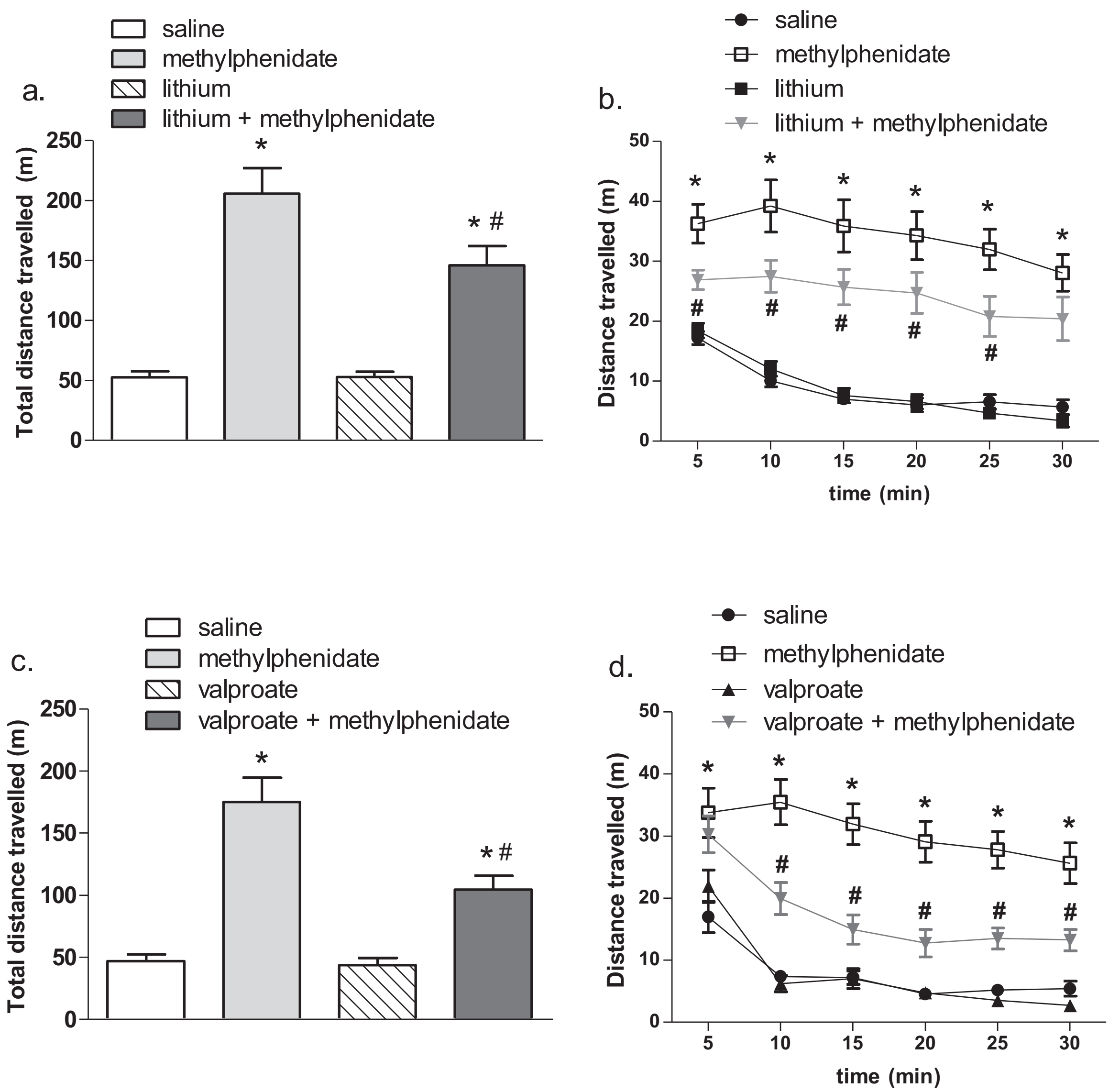

Fig. 1. Effects of the pretreatment with lithium 50 mg/kg (a,b) and valproate 400 mg/kg (c,d) and on the total distance travelled in mice treated with methylphenidate 10 mg/kg in the open field test. Data are the mean ± SEM of 12–13 mice/group. *p < 0.05 vs. saline and #p < 0.05 vs. methylphenidate according to ANOVA, Duncan's *post-hoc* test.

moved: t = 3.37, df = 28, $p < 0.05$; time spent in the center: t = 1.75, df = 28, p = 0.09).

3.2. Lithium and valproate prevented methylphenidate-induced hyperlocomotion in the open field test

The treatment with methylphenidate induced an increase in the total distance travelled compared with control mice (Fig. 1a, 1b; $p < 0.05$). The pretreatment with lithium and valproate partially prevented the methylphenidate-induced hiperlocomotion (Fig. 1a, $F_{(3,47)} = 28.97$, $p < 0.05$; Fig. 1b, $F_{(3,47)} = 28.39$, $p < 0.05$). It is worth mentioning the pretreatment with lithium and valproate *per se* did not affect the mouse total distance travelled in the open field test (Fig. 1a, 1b; $p > 0.05$).

3.3. Lithium and valproate prevented the methylphenidate-induced increase of mouse exploratory behavior in the hole board test

Fig. 2 shows the effects of lithium on the methylphenidate-induced increase of exploration in the hole board test. The administration of lithium prevented the increased interactions

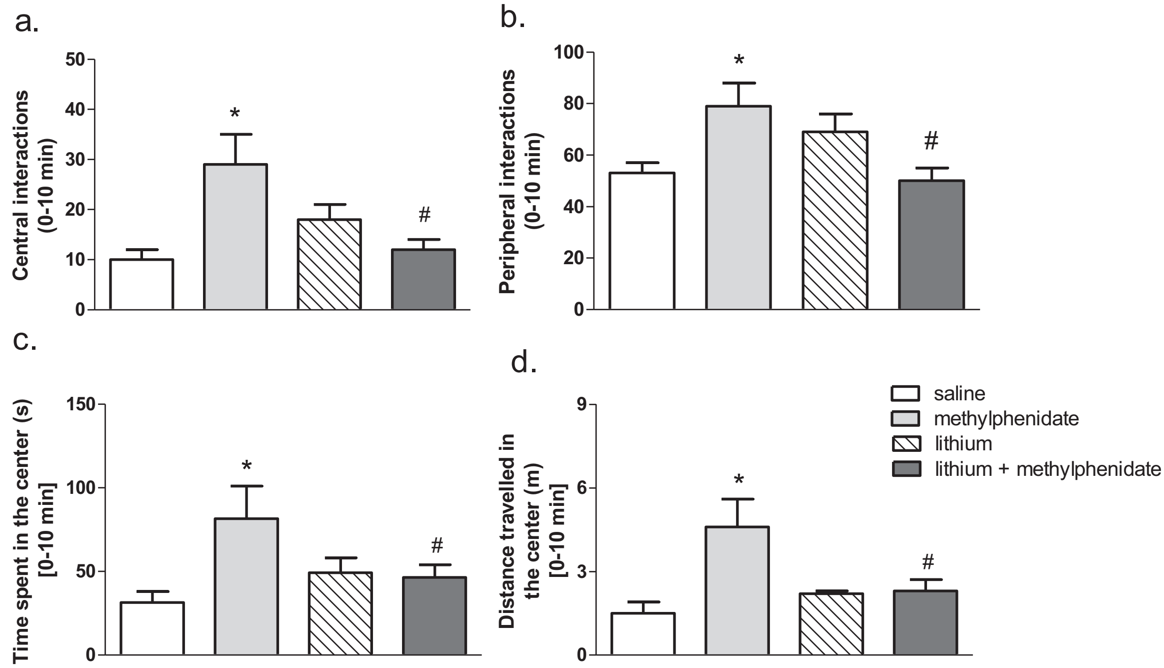

Fig. 2. Effects of the pretreatment with lithium 50 mg/kg on the interactions with central (a) and peripheral holes (b), and on the time spent in (c) and distance travelled in the center areas (d) in mice treated with methylphenidate 10 mg/kg in the hole board test. Data are mean ± SEM of 6–7 mice/group. *p < 0.05 vs. saline and #p < 0.05 vs. methylphenidate according to ANOVA, Duncan's test.

with the holes induced by methylphenidate (central holes: Fig. 2a, $F_{(3,23)} = 5.78$, $p < 0.05$; peripheral holes: Fig. 2b, $F_{(3,23)} = 4.49$, $p < 0.05$). Additionally, lithium was also able to prevent the increased time spent in and distance travelled in the central areas of the apparatus (time spent in central areas: Fig. 2c, $F_{(3,23)} = 3.21$, $p < 0.05$; distance travelled in the center: Fig. 2d, $F_{(3,23)} = 4.90$, $p < 0.05$). Interestingly, lithium was inactive *per se* in all behavioral parameters analyzed in the hole board test (Fig. 2a-d; $p > 0.05$).

Fig. 3 illustrates the pretreatment with valproate on the effects of methylphenidate in the exploration of the hole board apparatus. The preventive effect of valproate in the methylphenidate-induced increase of central, but not peripheral, holes is illustrated in Fig. 3 (Fig. 3a, $F_{(3,40)} = 6.40$, $p < 0.05$; Fig. 3b, $F_{(3,40)} = 7.83$, $p > 0.05$). In addition, the administration of valproate *per se* reduced the exploration of peripheral holes of the board (Fig. 3b, $p < 0.05$). Concerning the time spent in and the distance travelled in the central areas, the pretreatment with valproate was not effective in preventing the methylphenidate-induced effects (time spent in central areas: Fig. 3c, $F_{(3,40)} = 1.42$, $p > 0.05$; distance travelled in the center: Fig. 3d, $F_{(3,40)} = 8.28$, $p < 0.05$). The treatment with valproate *per se* did not affect the central exploration of the board (Fig. 3c, 3d; $p > 0.05$).

Representative group occupancy plots illustrate the mouse behavioral pattern in the hole board apparatus. Control mice trended to spend more time in the arena's corns. By contrast, methylphenidate-treated animals explored equally central and peripheral areas of the apparatus. Interestingly, the treatment with lithium and valproate attenuated the methylphenidate-induced central occupancy area of the board (Fig. S2).

4. Discussion

Preclinical studies aimed to modeling mania are commonly based in psychomotor agitation assessed by the increase in spontaneous locomotion [12,13]. However, manic episodes experienced by bipolar patients display a rich panel of symptoms [1]. Preclinical studies aimed to mimicking the symptoms experienced by bipolar patients could give additional information about the biological basis and pharmacological targets for bipolar mania [14]. In this study we evaluate the classical methylphenidate-induced hyperlocomotion in the open field test. In addition, we proposed the hole board apparatus as a novel approach to model other nuances of mania than hyperlocomotion.

To find the best experimental conditions and ensure that the pharmacological treatment would be effective either to induce hyperlocomotion with methylphenidate or prevent it with mood stabilizers the open field test was performed. Corroborating the data from literature [16–18,21], the administration of methylphenidate increased the total distance travelled by rodents. The administration of lithium counteracted methylphenidate induced hyperlocomotion have been previously reported [17,18]. Regarding valproate, Barbosa and colleagues [16] described antimanic-like effects of this drug in mice only after repeated administrations (14 days). Based on these findings, we adopted the same doses of lithium and valproate employed in the open field test to counteract the behavioral actions of methylphenidate in the hole board apparatus.

In our study, methylphenidate increased hole interactions on the hole board apparatus both centrally and peripherally. This behavior indicates a unique pattern of over-activity induced by methylphenidate which resembles the goal-direct object behavior observed in manic patients [22–24]. Literature findings showed that selective genetic and pharmacologic inhibition of the dopamine transporter in mice evoked hyperlocomotion and increased goal-directed object activity, assessed by the increase in hole interactions [24]. Our findings indicated that the pretreatment with lithium and valproate significantly blocked the interaction with central holes. However, lithium was also able to prevent the increased interactions with the peripheral holes of the board, thus showing a more robust antimanic effect for lithium than valproate in the hole board test.

In this study, methylphenidate increased the central exploration of the board as observed by the increase of time spent in and distance travelled in the center. When expose to novelty, as the

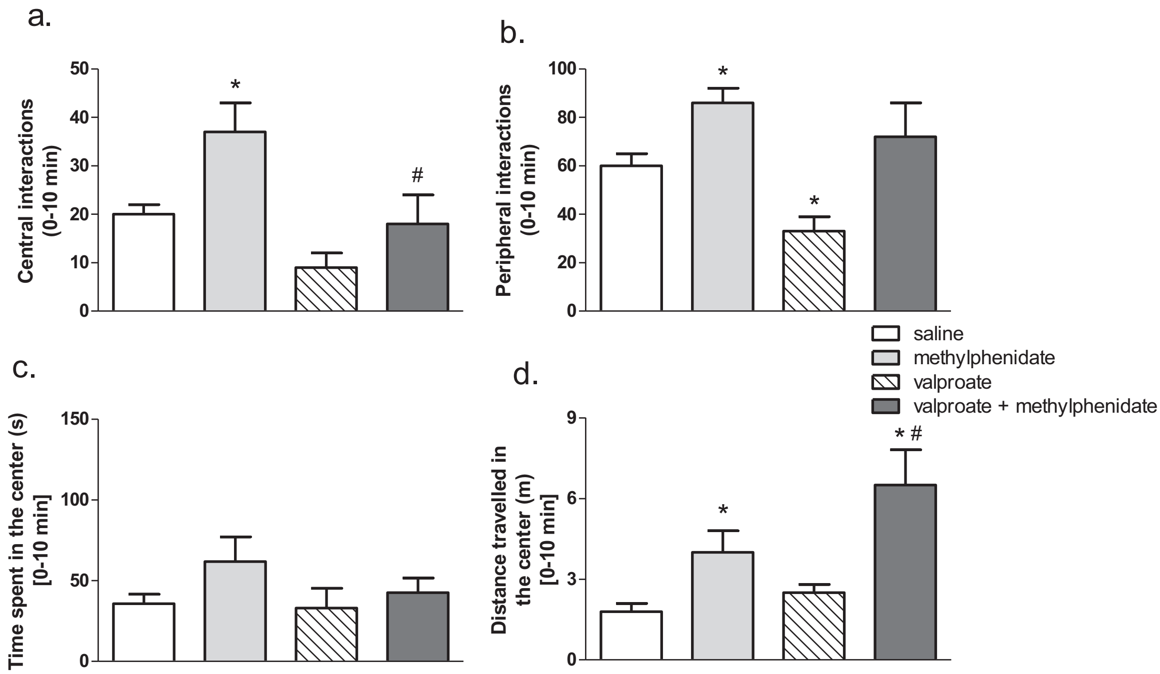

Fig. 3. Effects of the pretreatment with valproate 400 mg/kg on the interactions with central (a) and peripheral holes (b), and on the time spent in (c) and distance travelled in the center areas (d) in mice treated with methylphenidate 10 mg/kg in the hole board test. Data are mean ± SEM of 9–12 mice/group. *p < 0.05 vs. saline and #p < 0.05 vs. methylphenidate according to ANOVA, Duncan's test.

hole board apparatus, rodents tend to avoid unprotected areas, such as the center, due their natural fear of predation [25]. Therefore, the increased exploration of the central area of the board by methylphenidate-treated mice could be interpreted as risk-taking behavior. Similar effects have been recently reported in the literature in rats chronically treated with amphetamine in the elevated plus maze test [26]. Interestingly, in our study, the treatment with lithium, but not valproate, was able to prevent the increase in risk-taking behavior induced by methylphenidate. The ineffectiveness of valproate in counteracting this behavioral parameter corroborates its clinical profile, since this drug, despite been an alternative to treat mania, is less effective than lithium [8]. Lithium is considered a gold-standard mood stabilizer; however significant side effects, nephrotoxicity and a narrow therapeutic window are reported, thus limiting the prescriptions and adhesion to the treatment. Lithium is usually prescribed as initial monotherapy for bipolar disorder patients, because it is probably effective against both manic and depressive relapse, although it is more effective than other mood stabilizers in preventing mania [9]. In this context, the proposed hole board test has the advantage to discriminate the efficacy of distinct mood stabilizers, such as lithium and valproate, currently used in bipolar patients.

In this study, control mice showed markedly preference in moving through the periphery of the apparatus (Fig. S2). Differently, methylphenidate-treated mice have not shown any tendency of preference, which reflects the propensity to risk-taking behavior induced by the psychostimulant. The pretreatment with lithium and valproate reduced the occupancy to central areas compared to methylphenidate administration. Thus, the illustration of behavioral pattern using occupancy plots is a didactic tool to reinforce the treatment efficacy in the exploration of the central zone in hole board test.

Taking together, we proposed to use the hole board test in methylphenidate-treated mice as an alternative or a complementary assay to the open field test to investigate the bipolar mania aspects. The hole board test enable quantitative assessments of two important nuances of mania: goal-directed activity and risky behavior, in contrast to the spontaneous locomotion assessed in the open field test.

5. Conclusions

Present findings support the hole board as a potential tool to assess methylphenidate-induced mania-like behaviors in mice, since risk-taking and goal-directed behaviors were objectively quantifiable in this test. Indeed, the clinical drugs currently used for bipolar mania are able to prevent in a distinct way the appearance of mania-like behaviors in methylphenidate-treated mice. Thus, suggesting higher sensitivity of the hole board test compared to open field in discriminating the efficacy of mood stabilizers. Finally, the hole board test is a no onerous and easily executed assay, which means that it could be adopted together or as an alternative to the open field test to assess a panel of behaviors related to mania.

6. Conflict of interests

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2016.06.044.

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