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ORIGINAL INVESTIGATION

Chronic REM sleep deprivation leads to manic- and OCD-related behaviors, and decreases hippocampal BDNF expression in female rats

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Abstract

Background Rapid-eye movement (REM) sleep deprivation (SD) can induce manic-like behaviors in rodents. On the other hand, lithium, as one of the oldest drugs used in neuropsychiatric disorders, is still one of the best drugs for the treatment and control of bipolar disorder. In this study, we aimed to investigate the role of chronic short-term REM SD in the induction of manic-like behaviors in female rats.

Methods The rats were exposed to REM SD for 14 days (6 hours/day). Lithium was intraperitoneally injected at the doses of 10, 50, and 100 mg/kg. Results: REM SD induced hyperactivity and OCD-like behavior, and decreased anxiety, depressive-like behavior, and pain subthreshold. REM SD also impaired passive avoidance memory and decreased hippocampal brain-derived neurotrophic factor (BDNF) expression level. Lithium at the doses of 50 and 100 mg/kg partly and completely abolished these effects, respectively. However, lithium (100 mg/kg) increased BDNF expression level in control and sham REM SD rats with no significant changes in behavior.

Conclusions Chronic short-term REM SD may induce a mania-like model and lead to OCD-like behavior and irritability. In the present study, we demonstrated a putative rodent model of mania induced by chronic REM SD in female rats. We suggest that future studies should examine behavioral and mood changes following chronic REM SD in both sexes. Furthermore, the relationship between manic-like behaviors and chronic REM SD should be investigated.

Keywords REM sleep deprivation · Lithium · Mania · OCD · Pain perception · Brain-derived neurotrophic factor (BDNF)

Introduction

Mania or hypomania in full or subsyndromal forms is one of the most important features of bipolar disorder (Dubovsky 2015). The structure of mania has been based on three fundamental features in humans: euphoria, pressured speech, and hyperactivity (Kraepelin 1913). Comorbidity of mania with other disorders is common, particularly with attention deficit hyperactivity disorder (ADHD), followed by oppositional defiant disorder, agoraphobia, panic disorder, generalized anxiety disorder, alcohol dependence, and drug abuse (Kessler et al. 2005).

In rodents, hyperactivity has been approved as the most important feature of manic-like behavior (Valvassori et al. 2022; Wohr 2022). Although there are some methods using drugs to induce a rodent model of mania, however, drugs (for example, ketamine or amphetamine) can affect behavioral data and other cognitive functions. Also, a rodent model of mania without manipulation of mood processes by drugs may be more similar to a human model of mania. Rapid-eye movement (REM) sleep deprivation (SD) can induce manic-like behaviors in rodents. Previous study has reported that REM SD induces hyperactivity and decreases depressive-like behavior in rodents (Chen et al. 2022). Furthermore, it has been shown that 36 hours paradoxical SD leads to manic-like behaviors in male mice (Dal-Pont et al. 2019).

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The pathophysiology of mania is not completely understood. Three neurotransmitters have been considered as the most important neurotransmitters involved in the pathophysiology and treatment of mood disorders including norepinephrine, dopamine, and serotonin (Miklowitz and Johnson 2006). Furthermore, low levels of norepinephrine and dopamine are closely related to depression models, while mania is related to high levels of norepinephrine and dopamine. In addition, both mania and depression are tied to low levels of serotonin, a neurotransmitter that regulates the level and function of norepinephrine and dopamine (Alex and Pehek 2007; Szabo and Blier 2002). It has been suggested that mood disorders should be explained by changes in the level of neurotransmitters in the synaptic cleft. However, this hypothesis may not be accurate, as the time course of drug responses suggests that altered receptor sensitivity is more likely responsible for symptom stabilization than changes in absolute neurotransmitter levels (Thase et al. 2002). Therefore, drugs that change both neurotransmitter level and receptor sensitivity can be more useful.

Lithium is one of the most effective drugs for the treatment of bipolar disorder and mania. Previous studies have shown that lithium reverses manic-like behaviors induced by ketamine in rodents (Ettenberg et al. 2020; Gao et al. 2021). It has also been reported that lithium treatment attenuates ketamine-induced manic-like behavior in male rats (Krug et al. 2019). Although the molecular mechanisms underlying the therapeutic effects of lithium have not been well investigated, it appears that lithium can reverse mania by increasing protein kinase B (Akt), and phosphorylation and inhibition of glycogen synthase kinase-3 (GSK-3) activity (Beaulieu et al. 2004; Liu et al. 2013). Studies have shown that overexpression of GSK-3beta leads to manic-like behaviors in mice (Prickaerts et al. 2006). In addition, it has been shown that brain-derived neurotrophic factor (BDNF) is involved in the antimanic effect of lithium (Gideons et al. 2017).

BDNF is the most important neurotrophin in the central nervous system (CNS) (Huang and Reichardt 2001; Yamada and Nabeshima 2003). Neurotrophins are critical modulators of neural survival, development, function, and plasticity (McAllister et al. 1999; Sofroniew et al. 2001). BDNF may be involved in the pathophysiology of mania and the therapeutic effects of lithium. Previous studies have shown that both manic and depressive states in patients with bipolar disorder are significantly related to reduced BDNF serum level (Fernandes et al. 2015; Tunca et al. 2014). While, lithium treatment can elevate BDNF serum level in bipolar patients (de Sousa et al. 2011), and BDNF level in different parts of the rat brain (Fukumoto et al. 2001; Jornada et al. 2010).

According to the mentioned findings, in the present study, we aim to investigate the potential effect of chronic REM SD on the induction of manic-like behaviors and hippocampal BDNF level in female rats.

Material and method

Animals

Seventy-two female Wistar rats (170-180g, 7-8 weeks old) were used in this study. The rats were housed six per Plexiglas cage (25*50*25cm), and a 12h:12h light/dark cycle (lights on at 7:00h) and stable temperature (22±1°C) were observed. Each experimental group consisted of six female rats. All the rats were born and bred in Cognitive Neuroscience Lab, Medicinal Plants Research Center, Institute of Medicinal Plants, ACECR, Karaj, Iran. Also, all the rats had free access to food and water and all the experiments were done during the light hours (9:00 a.m. to 3:00 p.m.). Our experimental protocol was designed in accord with National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals (2011).

Drug

Lithium chloride was purchased from Tehrandarou Company, Tehran, Iran. Lithium was dissolved in normal saline and intraperitoneally injected at the doses of 10, 50, and 100 mg/kg. Lithium doses were selected based on previous studies (Rygula et al. 2015).

REM SD apparatus

REM SD apparatus (the multiple-platform apparatus, Tajhiz-Gostar Omid Iranian Co, Tehran, Iran) was used to induce REM SD. The multiple platform apparatus was a water tank (90×50×50 cm) with several circular platforms with 7 cm diagonal. The surface of the platforms was 2 cm above the water. The rats were placed in the apparatus and during the experiment, they were free to move through the tank. When the rats fell asleep, and when the REM phase began, they fell into the water and woke up (due to REM-induced muscles relaxation). This process induced REM SD in rats. Note that, platforms with a larger diagonal (15 cm) were provided for sham of REM SD rats, in which the rats had normal sleep. The temperature of the water was standard and monitored during the experiment (Javad-Moosavi et al. 2020; Lahimgarzadeh et al. 2022). Duration of REM SD was 6h for 14 days. Note that, this apparatus had a limitation. In addition to complete deprivation of REM sleep, non-REM sleep is also decreased about 30% during using this apparatus (Machado et al. 2004).

Open field test

The open field test (OFT) (Tajhiz-Gostar Omid Iranian Co, Tehran, Iran) was used to assess locomotor activity of

rats. This apparatus consisted of clear perspex container box (height: 30×30×40cm) divided into 16 equal-sized squares. Locomotor activity was evaluated as distance traveled (cm) during 300s (Mahdavi et al. 2021). Although which behavior in OFT measures anxiety is controversial, anxiety level was measured by recording the time spent in the four middle squares of the field (a preference to stay close to the walls of the field considered as anxiety) (Ennaceur 2014).

Marble burying test

Marble burying test is used to assess obsessive-compulsive disorder (OCD)-like behavior in rodents. In this test, standard glass toy marbles (assorted styles and colors, 15 mm diameter, 5-6 g in weight) gently put on the surface of the bedding in 2 rows of 5 marbles (10 marbles). Note that, marble burying test involves the placement of any number of marbles (usually between 4 and 25, depending on the zone configuration of the marble-burying arena) (de Brouwer et al. 2019). The duration of the test was 30 minutes. More buried marbles were considered as OCD-like behavior.

Hot plate apparatus

Hot plate apparatus measures the pain subthreshold in rodents. This apparatus was a sheet getting hot by electric current (Tajhiz-Gostar Omid Iranian Co, Tehran, Iran). At first, hot plate sheet was cleaned by ethanol 70%. Then, each rat was placed on the hot sheet. The start time was determined and as soon as the rats started to lick their paws or change their steps, the pain subthreshold was recorded. The temperature of the apparatus was set at 50 °C. The cut-off time was 100 seconds (Mahdavi et al. 2021).

Forced swim test

In this study, forced swim test (FST) was conducted to evaluate depressive-like behavior of rats during 5 minutes. FST uses a cylindrical transparent container that is filled with water (20-22°C) up to 2/3 of it. Each rat was float inside the cylindrical transparent container. During 5 minutes, immobility and climbing duration were measured. The duration of immobility was considered as depressed mood (Kordestani-Moghadam et al. 2020). Of note, climbing is defined as active vertical movement of the forepaws directed towards the sides of the chamber and immobility is characterized by the lack of movement except that which is necessary to keep the subject's nose above the water level (Carr and Lucki 2010). Both behaviors are important to evaluate the mood state of the rats.

Shuttle box apparatus

Shuttle box apparatus is used to assess passive avoidance memory in rats (Khakpoor et al. 2021; Torabi et al. 2022). Shuttle box apparatus consisted of two equal-sized compartments (25×25×25 cm), including a light and a dark compartment with a grid floor and Plexiglas walls that were separated by a guillotine door. Passive avoidance memory evaluation had two phases: training and test. In the training session, each rat was placed into the light compartment for a 60-second period. After opening the guillotine door and a complete entrance of the rat into the dark compartment, the door was closed and a 0.6 mA foot electric shock was delivered for 2 seconds through the grid floor. Twenty seconds later, the rat was transferred to its cage. The test session was performed 24h after training. In the test session, each rat was placed into the light compartment. The step-through latency to enter the dark compartment was measured as a positive index of memory function. The cut-off time was 300 seconds (Rezaie et al. 2020).

Experimental groups

The present study consisted of 12 groups (each group consisted of 6 female rats):

Group 1: control group (with no intervention).
Group 2: lithium 10 mg/kg group (only received i.p. injection of lithium, 10 mg/kg for 14 days).
Group 3: lithium 50 mg/kg group (only received i.p. injection of lithium, 50 mg/kg for 14 days).
Group 4: lithium 100 mg/kg group (only received i.p. injection of lithium, 100 mg/kg for 14 days).
Group 5: sham group (placed in the REM SD apparatus with large platforms, 6h/d for 14 days).
Group 6: sham + lithium 10 mg/kg group (placed in the REM SD apparatus with large platforms, 6h/d for 14 days, and received i.p. injection of lithium, 10 mg/kg for 14 days).
Group 7: sham + lithium 50 mg/kg group (placed in the REM SD apparatus with large platforms, 6h/d for 14 days, and received i.p. injection of lithium, 50 mg/kg for 14 days).
Group 8: sham + lithium 100 mg/kg group (placed in the REM SD apparatus with large platforms, 6h/d for 14 days, and received i.p. injection of lithium, 100 mg/kg for 14 days).
Group 9: REM SD group (placed in the REM SD apparatus and deprived from REM phase, 6h/d for 14 days).
Group 10: REM SD group + lithium 10 mg/kg group (placed in the REM SD apparatus and deprived from REM phase for 6h/d for 14 days, and received i.p. injection of lithium, 10 mg/kg for 14 days).

Group 11: REM SD group + lithium 50 mg/kg group (placed in the REM SD apparatus and deprived from REM phase for 6h/d for 14 days, and received i.p. injection of lithium, 50 mg/kg for 14 days).
Group 12: REM SD group + lithium 100 mg/kg group (placed in the REM SD apparatus and deprived from REM phase for 6h/d for 14 days, and received i.p. injection of lithium, 100 mg/kg for 14 days).

REM SD was done every day: 9:00 a.m. to 3:00 p.m. (on the last day, REM SD was performed from 9:00 a.m. to 1 p.m., due to the behavioral tests). Behavioral tests were performed as follows (30 min after REM SD):

Open field test, hot plate test, marble burying test, forced swim test, and shuttle box (training). 24h later, test session of the shuttle box was done. The hippocampus extraction was done 1h after the last behavioral test.

Real-time PCR

Total RNA extraction and preparation of cDNA

Total RNA was extracted from 100 mg of the hippocampus by Qiazol (Qiazol lysis reagent, USA) in a sterilized RNase-free tube. NanoDrop ND-100 spectrophotometer (Thermo Scientific, Waltham, MA, USA) evaluated the concentration and purity of RNA by the ratio of the absorbance at 260 nm and 280 nm (A 260 /A 280). RNA was converted into complementary DNA (cDNA) by DNase I first strand synthesis system for RT-PCR (Fermentase, Germany), according to the manufacturer's recommendations.

Real-time PCR reactions were done using Takara SYBR Premix Ex Taq II (Tli RNaseH Plus) (2X conc.) in a final volume of 20 µl on StepOnePlus Real-Time PCR System (Applied Biosystems). 2 µl of the synthesized cDNA was used in all reactions. The annealing temperature optimized for primers pairs was 64 °C. For quantification of target gene, standard curve method was applied. All the samples were loaded in duplicate and the mean data were used for further analysis. The specificity of PCR products was verified by observing a single peak in melting curve analysis. For complementary length verification, PCR products were visualized on 2.5% agarose gel (Malboosi et al. 2020).

Oligonucleotide set design

GAPDH was used as the housekeeping gene to normalize target gene expression. The primers that were used for the real-time PCR was BDNF. In order to measure the quantity of the target gene in each sample, first we had to identify the cycle at the fluorescence sample which was reached to a preset threshold that was appreciably above the background. Then, the cycle number was referred to a standard curve presents in each run of amplification. The data obtained from all the studied groups were normalized against the housekeeping gene (GAPDH). GenX (version 2.0.0) software ("MultiD Analyses AB" was the first company with focus on multidimensional data analyses.) was used to analyze data and detect significant differences in relative expression levels between samples and the control group. In order to use the software, the amount of RT PCR efficiencies (E) and the mean crossing point (CP) deviation between two groups are needed. Normalizing the target gene expression against the reference gene is done according to the following equation (Table 1):

$$\text{Ratio} = \left(E_{\text{target}}\right)^{\Delta CP \text{ target (Mean control}-\text{Mean sample)}} / \left(E_{\text{reference}}\right)^{\Delta CP \text{ reference (Mean control}-\text{Mean sample)}}$$

Statistical analyses

SPSS software (V.26) was used to analyze data. One-way ANOVA, two-way ANOVA, and post hoc Tukey's were used to compare groups. Data were expressed as mean ± SD and $P<0.05$ was considered as the level of statistical significance. One-way ANOVA was used to assess significant differences between control groups. Two-way ANOVA was used to assess significant difference between four groups of control and sham REM SD, or between four groups of sham REM SD and REM SD. This type of analysis leads to more correct and accurate comparisons, because REM SD group is compared with its most similar group (sham REM SD), not with controls (Rezaie et al. 2020; Torabi et al. 2022). Post hoc Tukey's was used to measure the exact differences between groups.

Results

Locomotor activity

The results of one-way ANOVA showed that there is no significant difference between control groups ($F_{3,23} = 0.84$, $P>0.05$). The results of two-way ANOVA showed that

Table 1 The primers used for the Real-time PCR

Primer	Sequence (5´→3´)
BDNF	F: 5'-GGACATATCCATGACCAGAAAGA-3' R: 5'-GGCAACAAACCACAACATTATCG-3'
GAPDH	F: 5'-CATTCTTCCACCTTTGATGCTG-3' R: 5'-TGGTCCAGGGTTTCTTACTCC-3'

there is no significant difference between control and sham groups [the effect of sleep ($F_{1,40} = 0.04$, $P>0.05$); the effect of lithium ($F_{3,40} = 2.25$, $P>0.05$); the effect of sleep*lithium ($F_{3,40} = 0.01$, $P>0.05$)]. The results of two-way ANOVA showed that there is a significant difference between sham and REM SD groups [the effect of sleep ($F_{1,40} = 164.24$, $P<0.001$); the effect of lithium ($F_{3,40} = 29.22$, $P<0.001$); the effect of sleep*lithium ($F_{3,40} = 18.83$, $P<0.001$)]. Post hoc Tukey test also showed that traveled distance in the open field was increased in REM SD group in comparison with sham group ($P<0.001$), and in REM SD + lithium 10 mg/kg group in comparison with sham group + lithium 10 mg/kg ($P<0.001$), and in REM SD + lithium 50 mg/kg group in comparison with sham group + lithium 50 mg/kg ($P<0.01$), indicating that locomotor activity was increased in all these groups (hyperlocomotion). However, traveled distance in the open field was decreased in both REM SD + lithium 50 mg/kg and REM SD + lithium 100 mg/kg groups in comparison with REM SD group ($P<0.001$), indicating that locomotor activity was decreased in all these groups (hypolocomotion) (Fig. 1).

Anxiety

The results of one-way ANOVA showed that there is a significant difference between control groups ($F_{3,23} = 10.85$, $P<0.001$). Post hoc Tukey test showed that time spent in middle squares was decreased in rats received lithium 100 mg/kg in comparison with control ($P<0.001$) and lithium 10 mg/kg groups ($P<0.01$), indicating anxiety-like behavior. The results of two-way ANOVA showed that there is a significant difference between control and sham groups only for the effect of lithium [the effect of sleep ($F_{1,40} = 0.90$, $P>0.05$); the effect of lithium ($F_{3,40} = 24.19$, $P<0.001$); the effect of sleep*lithium ($F_{3,40} = 0.50$, $P>0.05$)]. Post hoc Tukey test also showed that time spent in middle squares was decreased in sham + lithium 50 mg/kg ($P<0.05$) and sham + lithium 100 mg/kg ($P<0.001$) in comparison with sham group, indicating anxiety-like behavior. Anxiety level was also increased (reduced time spent in middle squares) in sham + lithium 100 mg/kg group in comparison with sham + lithium 10 mg/kg ($P<0.001$). The results of two-way ANOVA showed that there is a significant difference between sham and REM SD groups for the effect of sleep and the effect of lithium [the effect of sleep ($F_{1,40} = 58.05$, $P<0.001$); the effect of lithium ($F_{3,40} = 12.93$, $P<0.001$); the effect of sleep*lithium ($F_{3,40} = 2.56$, $P>0.05$)]. Post hoc Tukey test also showed that time spent in middle squares was increased in REM SD group in comparison with sham group ($P<0.001$), and in REM SD + lithium 10 mg/kg group in comparison with sham group + lithium 10 mg/kg ($P<0.001$), and in REM SD + lithium 50 mg/kg group in

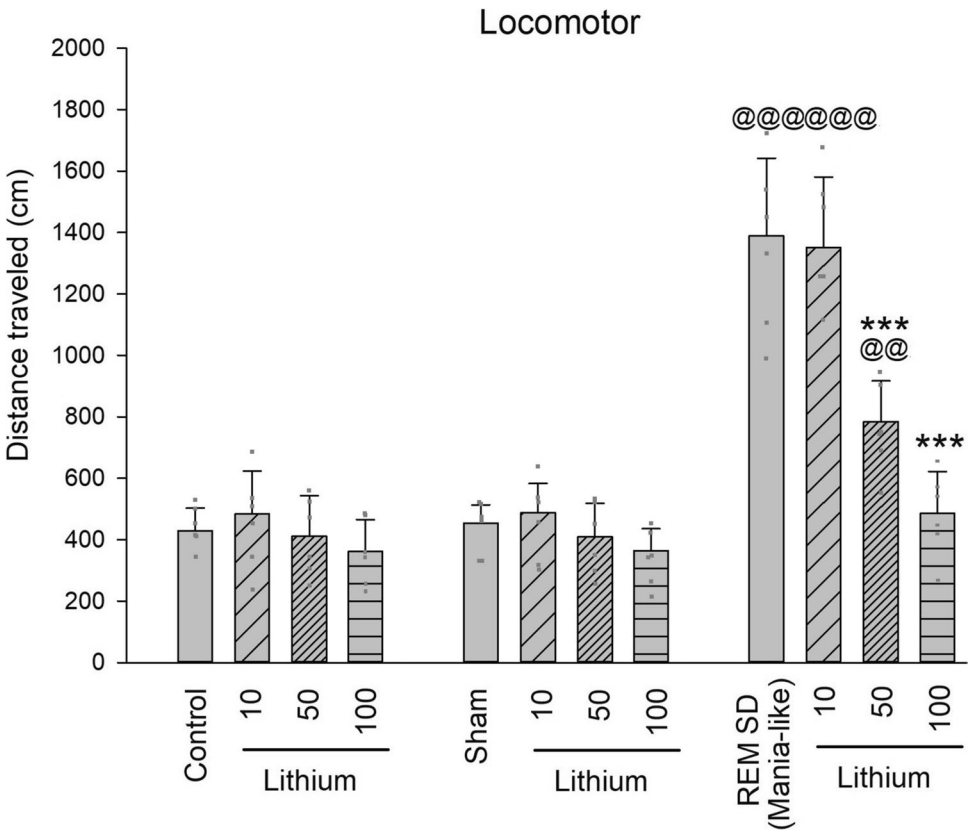

Fig. 1 Locomotor activity in the rats of control groups, sham groups, and REM SD (mania) groups. ***$P<0.001$ in comparison with its' control group (mania group); @@@$P<0.001$ and @@$P<0.01$ in comparison with respective group in sham groups ($n=6$) [grey dots: individual data points]

comparison with sham group + lithium 50 mg/kg ($P<0.01$), and in REM SD + lithium 100 mg/kg group in comparison with sham group + lithium 100 mg/kg ($P<0.05$), indicating decreased anxiety-like behavior. Also, time spent in middle squares was decreased in REM SD + lithium 50 mg/kg in comparison with REM SD group and with REM SD + lithium 10 mg/kg group ($P<0.01$), and in REM SD + lithium 100 mg/kg groups in comparison with REM SD group and with REM SD + lithium 10 mg/kg group ($P<0.001$), indicating anxiety-like behavior (Fig. 2).

OCD-like behavior

The results of one-way ANOVA showed that there is no significant difference between control groups ($F_{3,23} = 0.74$, $P>0.05$). The results of two-way ANOVA showed that there is no significant difference between control and sham groups [the effect of sleep ($F_{1,40} = 0.16$, $P>0.05$); the effect of lithium ($F_{3,40} = 0.43$, $P>0.05$); the effect of sleep*lithium ($F_{3,40} = 0.16$, $P>0.05$)]. The results of two-way ANOVA showed that there is a significant difference between sham and REM SD groups [the effect of sleep ($F_{1,40} = 70.94$, $P<0.001$); the effect of lithium ($F_{3,40} = 13.18$, $P<0.001$); the effect of sleep*lithium ($F_{3,40} = 12.48$, $P<0.001$)]. Post hoc Tukey test also showed that marbles buried was increased in REM SD group in comparison with sham group ($P<0.001$), and in REM SD + lithium 10 mg/kg group in comparison with sham group + lithium 10 mg/kg ($P<0.001$), and in REM SD + lithium 50 mg/kg group in comparison with sham group + lithium 50 mg/kg ($P<0.01$), indicating OCD-like behavior. However, marbles buried was decreased in both REM SD + lithium 50 mg/kg and REM SD + lithium 100 mg/kg groups in comparison with REM SD group ($P<0.001$), indicating decreased OCD-like behavior. Also, OCD-like behavior was decreased in both REM SD + lithium 50 mg/kg ($P<0.01$) and REM SD + lithium 100 mg/kg ($P<0.001$) groups in comparison with REM SD + lithium 10 mg/kg group (Fig. 3).

Immobility (depressive-like behavior)

The results of one-way ANOVA showed that there is no significant difference between control groups ($F_{3,23} = 0.55$, $P>0.05$). The results of two-way ANOVA showed that there is no significant difference between control and sham groups [the effect of sleep ($F_{1,40} = 2.95$, $P>0.05$); the effect of lithium ($F_{3,40} = 0.40$, $P>0.05$); the effect of sleep*lithium ($F_{3,40} = 0.38$, $P>0.05$)]. The results of two-way ANOVA showed that there is a significant difference between sham and REM SD groups [the effect of sleep ($F_{1,40} = 20.09$, $P<0.001$); the effect of lithium ($F_{3,40} = 11.79$, $P<0.001$); the effect of sleep*lithium ($F_{3,40} = 11.07$, $P<0.001$)]. Post

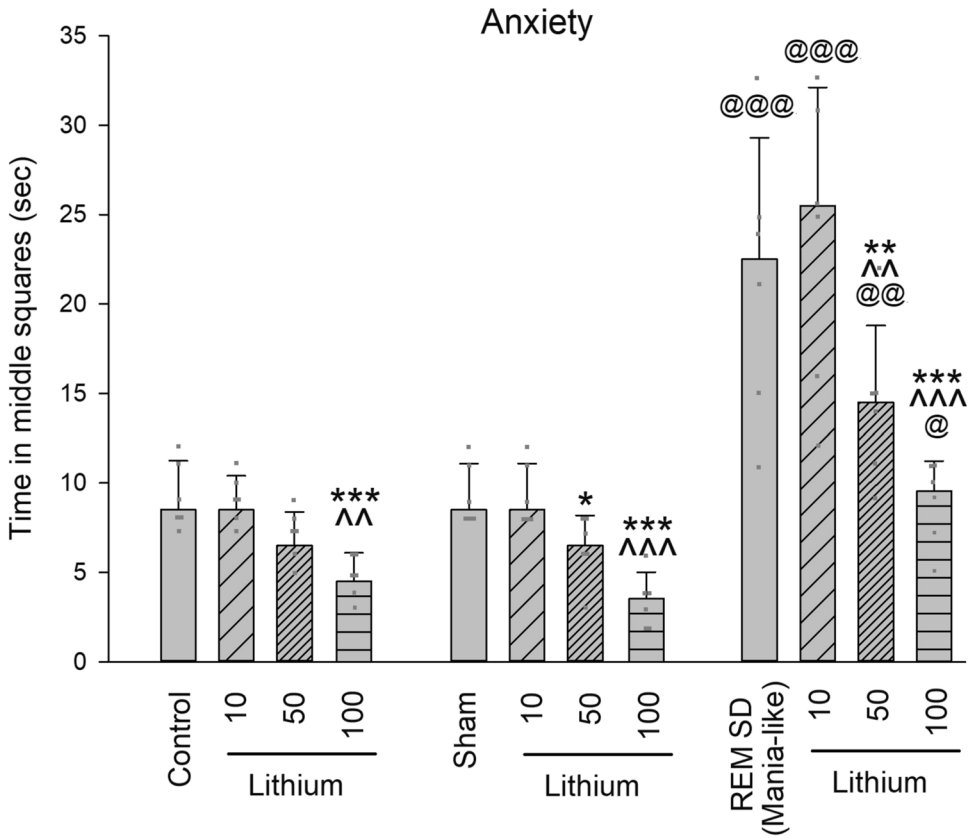

Fig. 2 Anxiety level in the rats of control groups, sham groups, and REM SD (mania) groups. ***$P<0.001$, **$P<0.01$, and *$P<0.05$ in comparison with its' control group (control or sham or mania group); ^^^$P<0.001$ and ^^$P<0.01$ in comparison with related group received lithium 10 mg/kg (control + lithium 10 mg/kg or sham + lithium 10 mg/kg or mania + lithium 10 mg/kg); @@@$P<0.001$, @@$P<0.01$, and @$P<0.05$ in comparison with respective group in sham groups ($n=6$) [grey dots: individual data points]

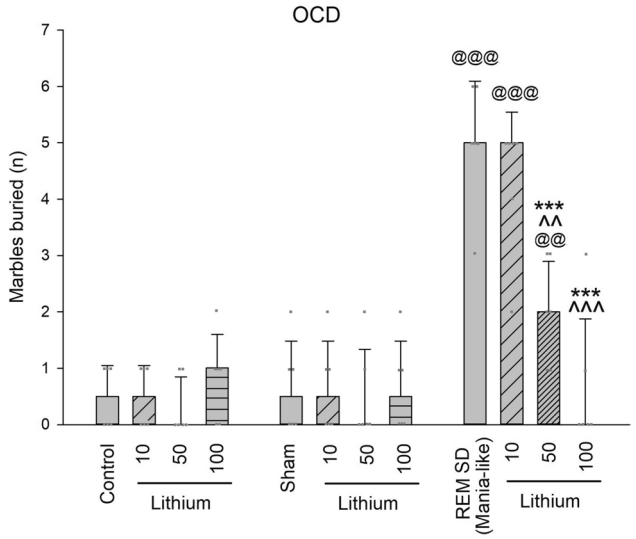

Fig. 3 OCD-like behavior in the rats of control groups, sham groups, and REM SD (mania) groups. ***$P<0.001$ in comparison with its' control group (mania group); ^^^$P<0.001$ and ^^$P<0.01$ in comparison with related group received lithium 10 mg/kg (mania + lithium 10 mg/kg); @@@$P<0.001$ and @@$P<0.01$ in comparison with respective group in sham groups ($n=6$) [grey dots: individual data points]

hoc Tukey test also showed that immobility was decreased in REM SD group in comparison with sham group ($P<0.001$), and in REM SD + lithium 10 mg/kg group in comparison with sham group + lithium 10 mg/kg ($P<0.001$), indicating antidepressant effect. Also, immobility was increased in both REM SD + lithium 50 mg/kg and REM SD + lithium 100 mg/kg groups in comparison with both REM SD and REM SD + lithium 10 mg/kg groups ($P<0.001$), indicating depressive-like behavior. However, it cannot be interpreted as a state of depression because lithium treatment only restored REM SD effects on immobility, while showed no significant difference compared with controls or sham REM SD rats. Therefore, it seems that lithium reversed the effect of REM SD on immobility rate in FST, but not the induction of depressive behavior (Fig. 4).

Climbing

The results of one-way ANOVA showed that there is a significant difference between control groups ($F_{3,23} = 6.90$, $P<0.01$). Post hoc Tukey test showed that climbing was increased in lithium 100 mg/kg group in comparison with control ($P<0.01$) and with lithium 10 and 50 mg/kg ($P<0.05$). The results of two-way ANOVA showed that there is a significant difference between control and sham groups for the effect of sleep and the effect of lithium

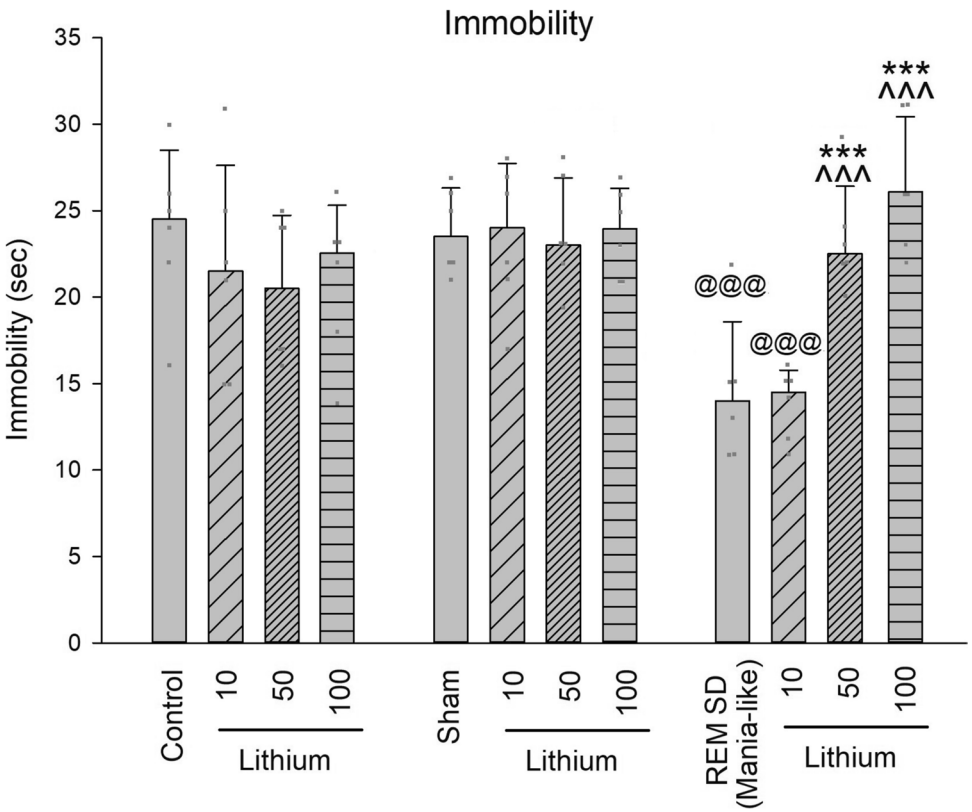

Fig. 4 Immobility (depressive-like behavior) in the rats of control groups, sham groups, and REM SD (mania) groups. ***$P<0.001$ in comparison with its' control group (mania group); ^^^$P<0.001$ in comparison with related group received lithium 10 mg/kg (mania + lithium 10 mg/kg); @@@$P<0.001$ in comparison with respective group in sham groups ($n=6$) [grey dots: individual data points]

[the effect of sleep ($F_{1,40}$ = 5.10, P<0.05); the effect of lithium ($F_{3,40}$ = 7.03, P<0.01); the effect of sleep*lithium ($F_{3,40}$ = 2.72, P>0.05)]. Post hoc Tukey test showed that climbing was decreased in sham + lithium 100 mg/kg in comparison with lithium 100 mg/kg group (P<0.05). The results of two-way ANOVA showed that there is a significant difference between sham and REM SD groups [the effect of sleep ($F_{1,40}$ = 8.80, P<0.01); the effect of lithium ($F_{3,40}$ = 5.13, P<0.01); the effect of sleep*lithium ($F_{3,40}$ = 9.27, P<0.001)]. Post hoc Tukey test also showed that climbing was increased in REM SD + lithium 10 mg/kg group in comparison with sham + lithium 10 mg/kg group, and with REM SD group (P<0.01). Furthermore, climbing was decreased in REM SD + lithium 50 mg/kg group (P<0.05), and in REM SD + lithium 100 mg/kg group (P<0.01), in comparison with REM SD + lithium 10 mg/kg group (Fig. 5).

Pain subthreshold

The results of one-way ANOVA showed that there is a significant difference between control groups ($F_{3,23}$ = 3.89, P<0.05). Post hoc Tukey test showed that pain subthreshold was increased in lithium 100 mg/kg group in comparison with control and with lithium 10 mg/kg (P<0.05). The results of two-way ANOVA showed that there is a significant difference between control and sham groups for the effect of lithium [the effect of sleep ($F_{1,40}$ = 0.62, P>0.05); the effect of lithium ($F_{3,40}$ = 8.37, P<0.001); the effect of sleep*lithium ($F_{3,40}$ = 0.17, P>0.05)]. Post hoc Tukey test showed that pain subthreshold was increased in sham + lithium 100 mg/kg in comparison with lithium 100 mg/kg group and with sham group (P<0.05), indicating analgesic effect. The results of two-way ANOVA showed that there is a significant difference between sham and REM SD groups for the effect of sleep and the effect of lithium [the effect of sleep ($F_{1,40}$ = 90.59, P<0.001); the effect of lithium ($F_{3,40}$ = 17.80, P<0.001); the effect of sleep*lithium ($F_{3,40}$ = 1.11, P>0.05)]. Post hoc Tukey test also showed that pain subthreshold was decreased in REM SD group in comparison with sham group (P<0.001), and in REM SD (mania-like) + lithium 10 mg/kg group in comparison with sham + lithium 10 mg/kg group (P<0.01), and in REM SD + lithium 50 mg/kg group in comparison with sham + lithium 50 mg/kg group (P<0.01), and in REM SD + lithium 100 mg/kg group in comparison with sham + lithium 100 mg/kg group (P<0.05), indicating hyperalgesia. Furthermore, pain subthreshold was increased in REM SD + lithium 50 mg/kg group (P<0.01), and in REM SD + lithium 100 mg/kg group (P<0.001), in comparison with REM SD group. Also, pain subthreshold was increased in REM SD + lithium 50 mg/kg group (P<0.05), and in REM

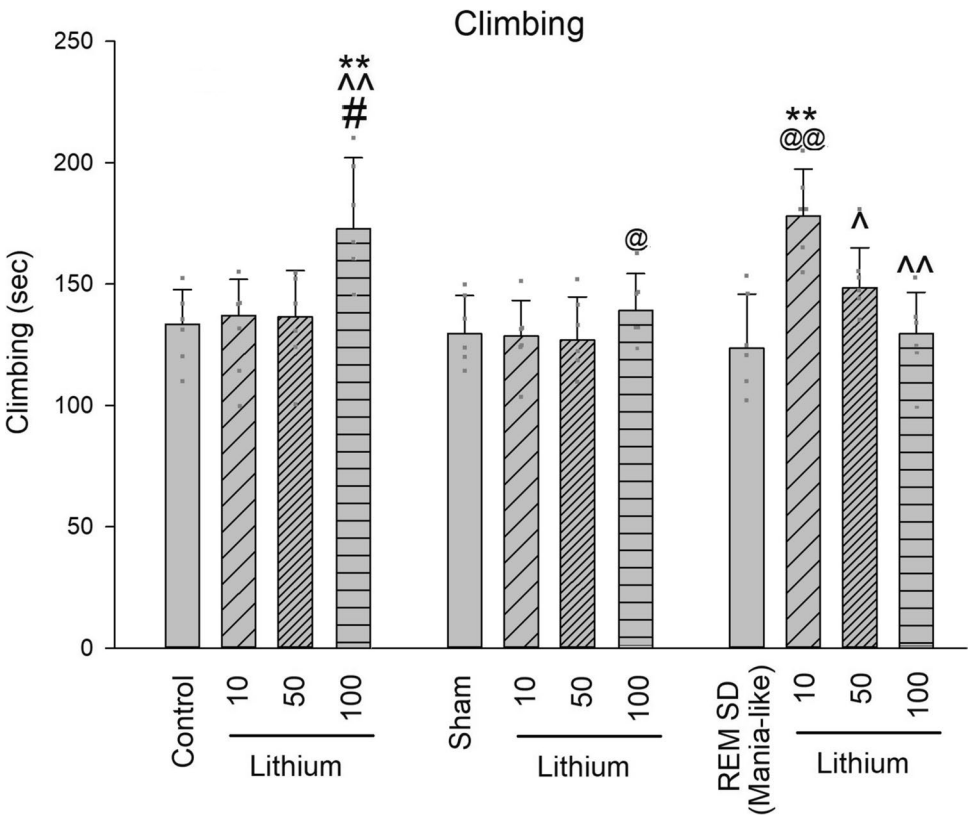

Fig. 5 Climbing in the rats of control groups, sham groups, and REM SD (mania) groups. $^{**}P<0.01$ in comparison with its' control group (control or mania group); $^{\wedge\wedge}P<0.01$ and $^{\wedge}P<0.05$ in comparison with related group received lithium 10 mg/kg (control + lithium 10 mg/kg or mania + lithium 10 mg/kg); $@@P<0.01$ and $@P<0.05$ in comparison with respective group in control or sham groups; $\#P<0.05$ in comparison with related group received lithium 50 mg/kg (control + lithium 50 mg/kg) (n = 6) [grey dots: individual data points]

SD + lithium 100 mg/kg group ($P<0.001$), in comparison with REM SD + lithium 10 mg/kg group, indicating an analgesic effect (Fig. 6).

Passive avoidance memory

The results of one-way ANOVA showed that there is no significant difference between control groups ($F_{3,23} = 0.08$, $P>0.05$). The results of two-way ANOVA showed that there is no significant difference between control and sham groups [the effect of sleep ($F_{1,40} = 0.08$, $P>0.05$); the effect of lithium ($F_{3,40} = 0.19$, $P>0.05$); the effect of sleep*lithium ($F_{3,40} = 0.55$, $P>0.05$)]. The results of two-way ANOVA showed that there is a significant difference between sham and REM SD groups for the effect of sleep and the effect of lithium [the effect of sleep ($F_{1,40} = 12.51$, $P<0.001$); the effect of lithium ($F_{3,40} = 3.19$, $P<0.05$); the effect of sleep*lithium ($F_{3,40} = 1.43$, $P>0.05$)]. Post hoc Tukey test also showed that passive avoidance memory was impaired in REM SD group in comparison with sham group ($P<0.001$), and in REM SD + lithium 10 mg/kg group in comparison with sham group + lithium 10 mg/kg ($P<0.001$). However, passive avoidance memory was restored in both REM SD + lithium 50 mg/kg and REM SD + lithium 100 mg/kg groups in comparison with both REM SD group and REM SD + lithium 10 mg/kg group ($P<0.001$) (Fig. 7).

Hippocampal BDNF level

The results of one-way ANOVA showed that there is a significant difference between control groups ($F_{3,23} = 62.35$, $P<0.001$). Post hoc Tukey test also showed that BDNF level was increased following administration of lithium (100 mg/kg) ($P<0.001$). The results of two-way ANOVA showed that only the effect of lithium was significant ($F_{3,40} = 178.96$, $P<0.001$), while the effect of sleep ($F_{1,40} = 2.57$, $P>0.05$) and the effect of sleep*lithium ($F_{3,40} = 2.45$, $P>0.05$) was not significant. Post hoc Tukey test also showed that BDNF was increased in sham group received lithium 100 mg/kg compared to controls received lithium 100 mg/kg ($P<0.05$). The results of two-way ANOVA showed that there is a significant difference between sham and REM SD groups for the effect of lithium ($F_{3,40} = 442.89$, $P<0.001$) and the effect of lithium*sleep ($F_{3,40} = 11.29$, $P<0.001$), while the effect of sleep ($F_{1,40} = 2.99$, $P>0.05$)] was not significant. Post hoc Tukey test also showed that BDNF was decreased in REM SD group in comparison with sham group ($P<0.001$), and in REM SD

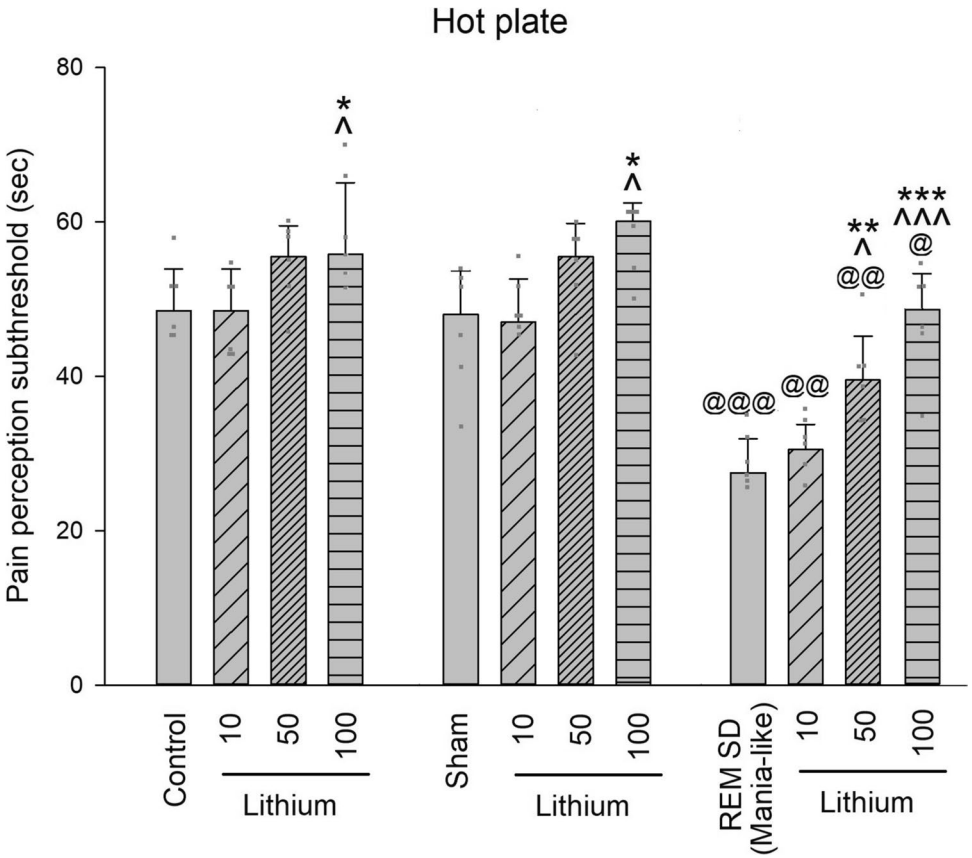

Fig. 6 Pain perception subthreshold in the rats of control groups, sham groups, and REM SD (mania) groups. ***$P<0.001$, **$P<0.01$, and *$P<0.05$ in comparison with its' control group (control or sham or mania group); ^^^$P<0.00$, ^^$P<0.01$, and ^$P<0.05$ in comparison with related group received lithium 10 mg/kg (control + lithium 10 mg/kg or sham + lithium 10 mg/kg or mania + lithium 10 mg/kg); @@@$P<0.001$, @@$P<0.01$, and @$P<0.05$ in comparison with respective group in sham groups ($n=6$) [grey dots: individual data points]

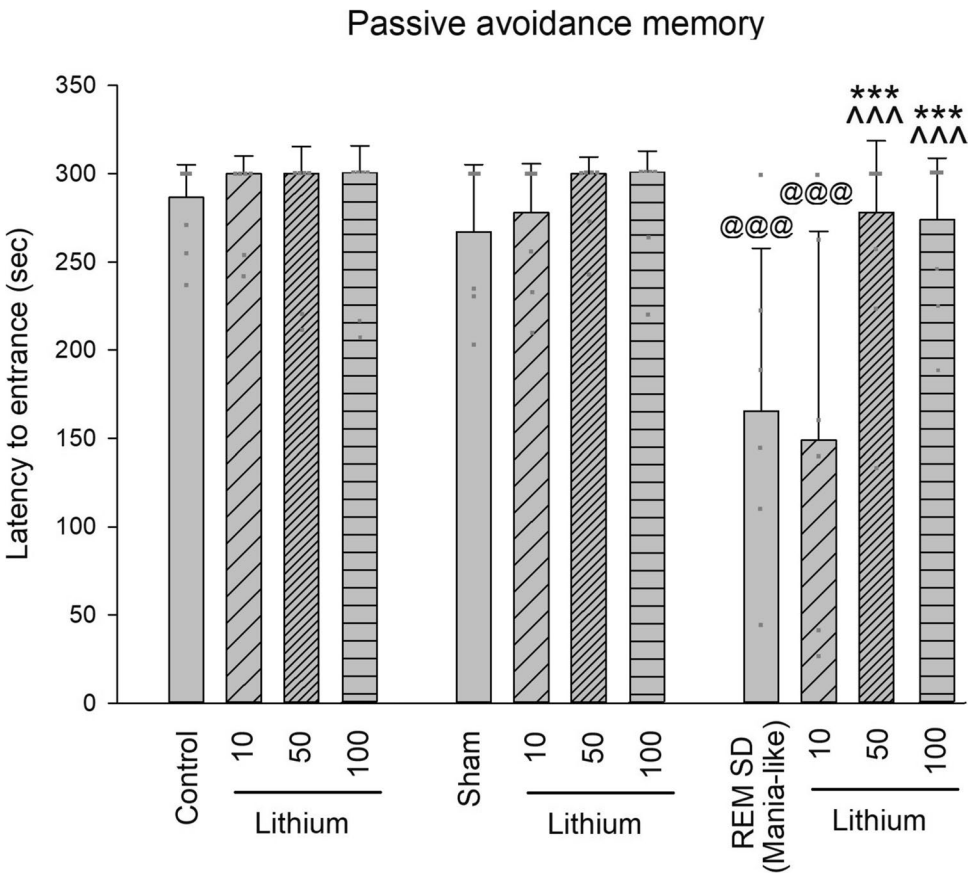

Fig. 7 Passive avoidance memory performance in the rats of control groups, sham groups, and REM SD (mania) groups. ***$P<0.001$ in comparison with its' control group (mania group); ^^^$P<0.001$ in comparison with related group received lithium 10 mg/kg (mania + lithium 10 mg/kg); @@@$P<0.001$ in comparison with respective group in sham groups ($n=6$) [grey dots: individual data points]

+ lithium 10 mg/kg group in comparison with sham group + lithium 10 mg/kg ($P<0.05$). However, lithium 50 mg/kg ($P<0.01$) and 100 mg/kg ($P<0.001$) increased BDNF level. Of note, BDNF level in REM SD rats received lithium 50 mg/kg was as much as sham rats, while in REM SD rats received lithium 100 mg/kg was much increased ($P<0.001$) (Fig. 8).

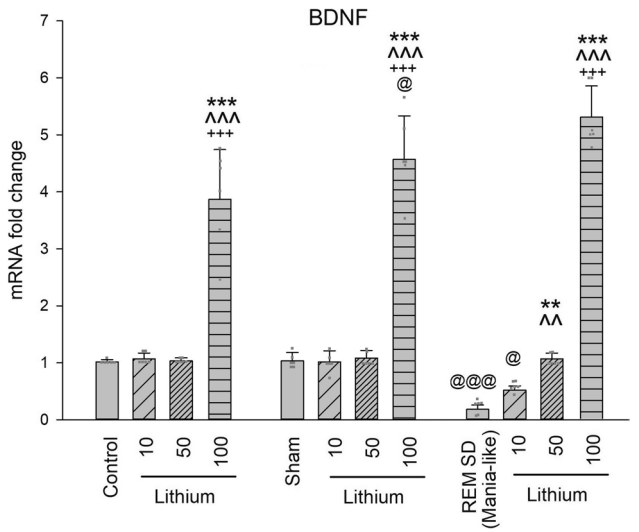

Fig. 8 Hippocampal BDNF level in the rats of control groups, sham groups, and REM SD (mania) groups. ***$P<0.001$ and **$P<0.01$ in comparison with its' control group (control or sham or mania group); ^^^$P<0.001$ and ^^$P<0.01$ in comparison with related group received lithium 10 mg/kg (control + lithium 10 mg/kg or sham + lithium 10 mg/kg or mania + lithium 10 mg/kg); + + +$P<0.001$ in comparison with related group received lithium 50 mg/kg (control + lithium 10 mg/kg or sham + lithium 10 mg/kg); @@@$P<0.001$ and @$P<0.05$ in comparison with respective group in control or in sham groups ($n=6$) [grey dots: individual data points]

Discussion

Overview

As the results showed, 6h/d REM SD for 14 days induced manic-like behaviors in female rats including hyperactivity, decreased anxiety level in the open field test, and decreased immobility (depressive-like behavior). Also, REM SD dramatically decreased pain subthreshold, suggesting an increased irritability. However, REM SD rats showed OCD-like behavior by burying more marbles than other rats. In addition, REM SD impaired passive avoidance memory. BDNF expression level in the hippocampus was also decreased in REM SD rats, while administration of lithium (50 mg/kg) restored BDNF level (reached BDNF levels in control rats). Also, administration of

lithium (100 mg/kg) increased BDNF expression level to a greater extent.

Lithium effects in non-REM SD rats

Our data showed that lithium (100 mg/kg) increased anxiety-like behavior, climbing, pain subthreshold, and BDNF expression level in control and sham REM SD rats. There are some studies showing that lithium may lead to anxiety-like behaviors in rats. Previous study has shown that prenatal exposure of lithium (30 mg/kg) induces anxiety-like behavior in rats (Kakhki et al. 2023). Lithium at high doses (toxic doses) may lead to hypolocomotion and anxiety-like behavior in rats (Hanak et al. 2017). Furthermore, it has been shown that lithium can induce long-lasting increases in anxiety-like behavior in pre-adolescent rats (Youngs et al. 2006). However, some studies have shown the anxiolytic effects of lithium (Samad et al. 2019; Torabi et al. 2022; Wang et al. 2023). Also, previous research has shown that lithium has no effect on freezing (anxiety-like) behavior in a rat model of conditioned fear stress (Muraki et al. 1999). Therefore, there seems to be inconsistency regarding the role of lithium in mediating anxiety-like behavior. In the present study, we showed that lithium dose-dependently normalized anxiety-like behavior changes in REM SD rats. However, we did not assess REM SD effects on lithium efficacy. We only showed that REM SD induced a possible manic-like state; while, lithium at the doses of 50 and 100 mg/kg abolished it. Of note, there is not enough evidence in this field. Previous research has shown that three sessions of 48h REM SD in male rats increase locomotor activity and decrease anxiety-like behavior (manic-like state), while lithium treatment does not affect anxiety changes, although it prevents REM SD-induced hyperlocomotion (Andrabi et al. 2020). We suggest that future studies should investigate the interaction effect of REM SD (especially in different durations) and lithium on anxiety and other behavioral parameters in both sexes. On the other hand, lithium can be used for the treatment of some aspects of neuropathic pain (Banafshe et al. 2012). It has been shown that lithium may induce a long-lasting analgesia in neuropathic mice via increasing beta-endorphin in the brain (Weinsanto et al. 2018). Also, early studies have reported the analgesic effects of lithium (Quinn and Marsden 1986; Tosca et al. 1981). We also showed that BDNF level was increased following lithium (100 mg/kg) administration in control and sham REM SD rats. As mentioned, lithium may increase the expression level of BDNF. A past study has shown that chronic lithium increases BDNF expression level in the brain of rats (Fukumoto et al. 2001). It has been revealed that lithium increases BDNF level in the hippocampus of a rat model of mania (induced by D-amphetamine) (Frey et al. 2006a). Other study has also reported that the neuroprotective effect of lithium may be related to the increased level of BDNF (Omata et al. 2008). Our data also showed that lithium at the highest dose increased BDNF expression level in all rats.

REM SD and mania

Both total SD and REM SD have deleterious effects on a wide-range of cognitive and behavioral functions. There are numerous preclinical and clinical studies showing the impairment effects of SD on cognitive performance and the mood state (Klumpers et al. 2015; Li et al. 2021; Looti Bashiyan et al. 2021; Torabi et al. 2022). It has been shown that 24h SD increases anxiety and depression, and decreases BDNF level in healthy volunteers (Li et al. 2021). Previous study has shown that chronic 4-week SD in rats leads to anxiety- and depressive-like behaviors, and cognitive decline (Li et al. 2023). Furthermore, SD induces depressive- and anxiety-like behaviors in forced swim test (FST), tail suspension test (TST), and elevated plus maze test (EPMT) in rats (Kang et al. 2021). It has also been revealed that SD impairs spatial learning and memory in rats (Zheng et al. 2024). In addition, 24h but not 4h SD impairs spatial memory performance in male rats (Kholghi et al. 2023). REM SD also affects cognitive and behavioral functions. It has been shown REM SD for 24h significantly attenuates memory acquisition in male Wistar rats (Javad-Moosavi et al. 2020). Furthermore, 24h REM SD impairs spatial and passive avoidance memory in rats (Mahdavi et al. 2021). Of note, the effects of total SD and REM SD on cognitive and behavioral functions are inconsistent and many studies have shown the improvement effects of both in some conditions (Maturana et al. 2015; Sikkens et al. 2019; Trautmann et al. 2018; Vaseghi et al. 2021).

On the other hand, REM SD may lead to manic-like state. REM SD is a non-pharmacological method that induces manic-like model in rodents. Previous studies have shown that REM SD induces manic-like behaviors in rats (Andrabi et al. 2020; Valvassori et al. 2017b). For example, it has been revealed that REM SD may lead to manic-like behaviors in rats via induction of mitochondrial dysfunction (Kim et al. 2022). Other study has shown that REM SD induces hyperactivity, reduces anxiety-like behavior, and leads to abnormal dyadic social interaction in rats (Andrabi et al. 2020). Note that, a decrease in sleep duration is not only a core manifestation of mania, but also a trigger for a manic episode (Gold and Kinrys 2019; Melo et al. 2017). Previous research has shown REM density changes in manic patients with reduced sleep (Zangani et al. 2020). It has been revealed that disruptions in circadian rhythms are underlie the disorder course of bipolar disorder (Gold and Kinrys 2019). Furthermore, irregular circadian rhythms may be related to episodes of mania and depression (Gold and Kinrys 2019).

Our data also showed that REM SD decreased BDNF level. Several studies have shown that SD decreases BDNF level. For example, 7-day SD reduces the level of BDNF and TrkB in the hippocampus of mice (Hwang et al. 2019). 24h SD decreases the level of BDNF in the CA1 region of the hippocampus in rats, leading to the impairment of long-term memory (Zagaar et al. 2013). Previous study has also shown that 24h REM SD reduces BDNF level in the hippocampus and the prefrontal cortex (Mahboubi et al. 2019). However, several inconsistent results have been reported (Vaseghi et al. 2021). Although mania has a complex pathophysiology, decreased BDNF level has been implicated as a mechanism involved in manic/bipolar disorder (Jornada et al. 2010). Previous study has reported that BDNF plays a central role in the progression of bipolar disorder (Grande et al. 2010). BDNF serum level is decreased during manic and depressive episodes in both treated and drug-free subjects, suggesting that BDNF levels are negatively correlated with the severity of manic and depressive symptoms (Cunha et al. 2006; Fernandes et al. 2009). It has been shown that BDNF levels in manic patients are significantly lower than healthy controls, while this difference vanished after successful treatment (Tramontina et al. 2009). Therefore, decreased BDNF expression level may be involved in the induction of manic-like behaviors following REM SD.

REM SD rats showed decreased anxiety and depressive-like behavior, while showed OCD-like behavior

Our data also showed that REM SD rats had decreased anxiety-like behavior that is not unexpected in manic phase. Patients with mania often show easy distractibility, lack of concentration, illogical condensations, hyperactivity or severe mobility, delusions of grandiosity, flight of ideas, irritability, and elevated or euphoric mood (Jain and Mitra 2022). Furthermore, it has been reported that the rate of anxiety disorders is the lowest among bipolar I patients (manic episodes that last for at least 7 days or manic symptoms that are so severe that the person needs immediate medical care), and the highest in the bipolar II patients (Rihmer et al. 2001). It has also been suggested that bipolar I patients have a relatively low rate of comorbid anxiety disorders (Rihmer et al. 2001). A previous meta-analysis study has reported that anxiety disorder comorbidity is lower in bipolar I than bipolar II (Yapici Eser et al. 2018). Furthermore, mood lability, anxiety, guilt, suicidality, and irritability are the only symptoms significantly more common in the mixed episodes; however, grandiosity and euphoric mood (but not anxiety) are more often observed in the pure manic group (Cassidy et al. 1998). On the contrary, previous study has shown the association of anxiety disorders with the manic phase of bipolar disorder in bipolar patients (Das 2013). It has also been shown that adults with manic episodes have an approximately equivalent relative risk of developing anxiety disorders (Olfson et al. 2017).

Our data also showed that depressive-like (immobility) was decreased, while climbing was not changed in REM SD rats. As mentioned, (see section "Forced swim test"), climbing is defined as active vertical movement of the forepaws directed towards the sides of the chamber. Both immobility and climbing may show the mood state of a rat. Although immobility (depressive-like behavior) was decreased in REM SD rats, climbing was not changed. We can suggest that hyperlocomotion induced by REM SD may affect the climbing data (although still the immobility was evident). Also, REM SD rats showed OCD-like behavior in the marble burying test. OCD has been classified as an anxiety disorder in DSM-III, DSM-III-R, and DSM-IV (Bartz and Hollander 2006). But although OCD has been previously considered as an anxiety disorder, many studies have suggested that this category can change (Bartz and Hollander 2006; Stein et al. 2010). In fact, anxiety disorders and OCD have a close relationship, and 90% of patients with OCD have coexisting psychiatric diagnoses, most commonly are anxiety disorders (Fenske and Petersen 2015). An association of anxiety symptoms with greater severity in acute mania has been demonstrated (Gonzalez-Pinto et al. 2012). In the present study, REM SD rats showed decreased anxiety level in the open field test in comparison with control, while they had also hyperlocomotion. We suggest that evaluating anxiety level in the open field test can be influenced by hyperlocomotion. Therefore, we cannot definitely conclude that REM SD rats had decreased anxiety, because hyperlocomotion can affect the rats' performance for evaluating anxiety. Of note, conducting other behavioral tests like elevated plus maze or light/dark transitions may be necessary for future accurate results. However, marble burying test showed a type of obsessive-compulsive-like behavior for REM SD rats. Previous study has reported a comorbidity of OCD and mania (Kalra et al. 2002). It has been revealed that some antidepressants including clomipramine, fluoxetine, and citalopram induce mania in OCD patients (Berk et al. 1996). Other study has declared that comorbidity of OCD in bipolar disorder is well documented (Zutshi et al. 2007). On the other hand, the potential effect of antidepressants on REM SD-induced OCD-like behavior has not been investigated. In the present study, lithium (as a mood stabilizing medicine) could restore OCD-like behavior induced by REM SD, but no article has been published in this field for antidepressants. This is the first study evaluating the effect of REM SD-induced mania on OCD-like behaviors in rats, and has shown a possible comorbidity of OCD and mania in female rats. However, a definitive interpretation of "manic" effects based on simple behavioral readouts in the present study may be not entirely reliable, because manic-like state in

rodents and humans may be different. Albeit more detailed studies are needed, as previous study declared, bipolar-OCD comorbidity needs further investigations in order to provide more solid evidences to give patients a more precise clinical diagnosis and a more targeted therapeutic approach (Mucci et al. 2018).

Decreased pain subthreshold in REM SD rats

Our data showed that REM SD rats had lower pain subthreshold than controls. Pain perception change in mania is a complicated issue. Previous research has shown that mania decreases perceived pain intensity in patients with chronic pain (Boggero and Cole 2016). It has been reported that >64% of chronic pain patients with bipolar disorder recall experiencing decreased pain intensity during manic or hypomanic states, characterized by elevated energy, reduced need for sleep, and positive affect (Travaglini et al. 2020). Note that, when the manic phase resolves, increases in pain have been usually observed, contributing to a cycle of overactivity and pain. Therefore, it's not unexpected that patients with bipolar pain often report higher pain intensity and interference than patients with pain with other mood disorders including major depressive disorder (Goldstein et al. 2009). On the other hand, previous research has shown that mania, characterized by positive affect, can dramatically decrease perceived pain intensity (Boggero and Cole 2016). It seems that this effect occurs via the affective (vs. the somatosensory) pathways of the pain system; however, this effect should be more investigate in further research (Boggero and Cole 2016). It has been shown that pain subthreshold in bipolar patients is lower than control or patients with schizophrenia (Atik et al. 2007).

Note that, REM SD often leads to hyperalgesia (Roehrs et al. 2006). Other study has shown that REM SD leads to a significant increase in the behavioral responses to noxious mechanical, thermal, and electrical stimuli in rats (Hakki Onen et al. 2001). Furthermore, it has been shown that REM SD increases pain-related behavior and malondialdehyde (MDA) level in the thalamus of rats (Anis Syahirah et al. 2022). Thus, decreased pain subthreshold in REM SD rats may be related to the effect of sleep deprivation. Overall, pain perception changes in manic or hypomanic phase have not been well investigated and the results are not sufficient.

Impaired memory in REM SD rats

As the results showed, REM SD rats had impaired memory performance. There is a large number of studies showing impairment effect of REM SD or SD on memory function (Lahimgarzadeh et al. 2022; Looti Bashiyan et al. 2021; Mahdavi et al. 2021; Sur and Lee 2022; Torabi et al. 2022; Yan et al. 2022). However, we used REM SD to induce a manic model, not to investigate its' effect on memory function. Evidence has shown that mania impairs memory and other cognitive functions. Previous research has reported that bipolar patients show cognitive impairments regardless of the phase of disorder (Vrabie et al. 2015). Also, during a manic episode, they showed higher impairments in verbal and working memory, executive function/reasoning, and problem solving (Vrabie et al. 2015). Other study has shown that executive function and verbal memory are impaired in bipolar patients (Martinez-Aran et al. 2004). Importantly, it has been revealed that verbal retrieval impairments can be considered as stable vulnerability indicators in bipolar disorder, while verbal encoding impairments are manic state indicators (Fleck et al. 2003). Furthermore, disrupted episodic memory for events encoded during mania has been reported in bipolar patients (King et al. 2013). Therefore, manic state can attenuate memory performance. On the other hand, REM SD by itself, significantly impairs memory function via suggested mechanisms including attenuating neurogenesis (Khodaverdiloo et al. 2021), decreasing the level of molecular factors such as BDNF and cAMP response element-binding (CREB) protein (Guo et al. 2016), increasing neuroinflammation (Ugalde-Muniz et al. 2022), and increasing oxidative stress (Alzoubi et al. 2017). In the present study, REM SD decreased BDNF expression level in the hippocampus. BDNF is significantly involved in memory function (Bekinschtein et al. 2008; Cefis et al. 2019). There are many studies shown the importance of BDNF function for memory performance (Fang et al. 2019; Mizoguchi et al. 2020; Zhang et al. 2015). Recovery of BDNF level is a critical mechanism for restoring memory function (Lee et al. 2020). Therefore, decreased BDNF level in REM SD rats may be involved in memory impairment.

Moderate and high doses of lithium restored REM SD effects with respect to BDNF level

The results showed that lithium at the doses of 50 and 100 mg/kg, partly and completely revered REM SD effects on behaviors and BDNF level, respectively. As we know, lithium is a potent mood stabilizer used for the treatment of bipolar disorder and for the decrease of mood swing (Sampogna et al. 2022). Although lithium has been used for many decades, its' mechanism of action has not been well understood. Lithium is mostly prescribed for the treatment of mania (Cade 1949). Also, lithium is useful for the treatment of major depression, particularly for augmentation of antidepressants (Crossley and Bauer 2007), aggressive behaviour (Sheard et al. 1976), and for preventing suicide risk (Grof and Grof 1990). Early studies have suggested that lithium normalizes the increased residual sodium during episodes of depression and mania in bipolar disorder (Coppen 1967). Importantly, lithium can decrease the resting membrane

potential and reduce neuronal excitability (Schou 1957). Other study has reported that lithium depolarizes the resting membrane potential back to the normal level, while in bipolar disorder, the resting membrane potential seems to be hyperpolarized (Thiruvengadam 2001). On the other hand, studies have found that bipolar patients treated with lithium have larger cortical and hippocampal volumes (Hajek et al. 2012; Moore et al. 2000). It should be noted that lithium is neuroprotective both *in vivo* and *in vitro* (Alda 2015). With respect to structural changes of brain in bipolar patients, it has been suggested that neuroprotective effect of lithium may be responsible for its mood stabilizing properties (Alda 2015). Furthermore, one of the most important neuroprotective effects of lithium is the suppression of stress effects on the brain (Gray and McEwen 2013). Lithium can also significantly restore brain neuroplasticity in bipolar disorder (Alda 2015). All these effects can be involved in attenuating manic state symptoms.

As mentioned, lithium restored the effect of REM SD on BDNF level. BDNF is associated with the mechanism of action of antidepressants and mood stabilizers (Castren and Rantamaki 2010). It has been reported that BDNF expression is significantly increased in the cerebral cortex and hippocampus after chronic antidepressant treatment (Schmidt et al. 2008). Chronic but not acute lithium treatment also increases intracellular BDNF protein levels in neuronal culture (Emamghoreishi et al. 2015). It has been shown that 5-day (but not 3 or 7-day) lithium treatment (1mM) increases intracellular BDNF protein levels in rat cortical neuronal culture (Yasuda et al. 2009). Lithium administration increases the expression of BDNF in the rodent brain (Fukumoto et al. 2001), especially in the hippocampus (Frey et al. 2006b) and the frontal cortex (Jacobsen and Mork 2004). Importantly, the neurotrophic effect of lithium in cortical neurons requires BDNF expression (Hashimoto et al. 2002). It has been declared that lithium increases TrkB activation and expression of BDNF (Pedersen et al. 2009), which supports the role of BDNF in bipolar disorder and/or mania. It has also been suggested that BDNF, as a protein involved in neuronal survival, dendritic branching, and synaptic plasticity (Huang and Reichardt 2001), is lower in the brain and serum of bipolar patients (Cunha et al. 2006; Monteleone et al. 2008). Previous study has shown that BDNF expression in the hippocampus and amygdala of manic-like rats is significantly decreased (Jornada et al. 2010). While, under both conditions, lithium normalizes the decreased level of BDNF (Jornada et al. 2010; Wu et al. 2014). Increased neuronal BDNF induced by lithium may be complementary to its ability to improve neuronal plasticity in glial cells. Impaired neuroplasticity has been indicated as an important feature of BD that is related to a deficiency in BDNF (Kapczinski et al. 2008); while, lithium induces a therapeutic effect, maybe via restoring BDNF level.

Limitations

(1) One of the limitations of the present research is related to control, sham, and REM SD groups. The rats of these groups did not receive any injection, while saline injection (rather than no injection) may be a more accurate control group to compare with lithium groups.
(2) Multiple platform apparatus for the induction of REM SD has a limitation. It has been reported that multiple platform apparatus may also decrease non-REM sleep (about 30%) (Eydipour et al. 2020; Machado et al. 2004). We did not use EEG (electroencephalogram) to assess the efficiency of the apparatus to induce REM SD (Mahdavi et al. 2021), but previous studies have shown that rats are deprived of the REM phase using this apparatus (Eydipour et al. 2020; Javad-Moosavi et al. 2020; Kang et al. 2013; Tripathi and Jha 2022).
(3) In addition, we showed that lithium (100 mg/kg) increased BDNF level in all rats (control, sham-REM SD, and REM SD). However, this effect did not induce a significant change in the rats' behavior. Although increased BDNF expression level in REM SD rats exposed to the high dose of lithium may be involved in the restoration of REM SD effects, but increased BDNF expression level in control and sham-REM SD rats exposed to the high dose of lithium with no significant behavioral changes may question the role of BDNF in modulating manic-like features induced by chronic REM SD. Also, we can focus on the possible role of other neurotrophins like nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), neurotrophin-3, or neurotrophin-4. The role of other molecular factors and neurotransmitters in the modulation of manic-like features may also be important. On the other hand, lithium can affect the expression level of these neurotrophins (Simoes et al. 2017; Varela et al. 2015), although other studies have shown no effect (Dal-Pont et al. 2019; Valvassori et al. 2017a). Therefore, conflicting reports on the effect of lithium on neurotrophins could reinforce this limitation.
(4) Finally, the level of gonadal hormones was not measured, whereas the phase of the estrous cycle can affect the performance of female rats in behavioral tests.

Conclusion

In conclusion, our data showed that 6h/d REM SD for 14 days induced hyperactivity and decreased anxiety, depressive-like behavior, and BDNF level. Also, REM SD significantly decreased pain subthreshold and induced OCD-like behavior. In addition, REM SD impaired memory performance. On the other

hand, moderate and high doses of lithium partly or completely reversed REM SD effects on behavioral functions and BDNF level. We can suggest that hyperlocomotion (as a manic-like feature in rodents) may affect the results of the FST (depressive-like behavior) and OFT (anxiety-like behavior). But on the other hand, it seems that chronic REM SD can induce a manic-like state in female rats, characterized by hyperlocomotion and reduced anxiety. However, we also showed OCD-like behavior in REM SD rats. Of note, previous studies have shown the comorbidity of OCD and mania (bipolar disorder) (Bertolin et al. 2021; Chen and Dilsaver 1995; Dilsaver et al. 1994). In the present study, we showed a possible manic-like model of rodents induced by chronic REM SD in female rats characterized by hyperlocomotion, OCD-like behavior, and decreased anxiety- and depressive-like behaviors. We suggest that future studies should investigate behavioral and mood changes following chronic REM SD in both sexes, and should focus on the type of mood disturbances induced by REM SD. The relationship between the manic-like feature of mood and chronic REM SD should also be investigated in future studies.

Authors' contributions N.A., Y.M., G.KH., and Z. E. conducted the behavioral tests, genetic experiments, and data analyses. H.K. participated in writing and drafting. S.V. designed the study, supervised the research process, wrote the manuscript. All the authors approved the final version.

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Data availability Will be available upon a reasonable request.

Declarations

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References

Alda M (2015) Lithium in the treatment of bipolar disorder: pharmacology and pharmacogenetics. Mol Psychiatry 20:661–670

Alex KD, Pehek EA (2007) Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. Pharmacol Ther 113:296–320

Alzoubi KH, Rababa'h AM, Owaisi A, Khabour OF (2017) L-carnitine prevents memory impairment induced by chronic REM-sleep deprivation. Brain Res Bull 131:176–182

Andrabi M, Andrabi MM, Kunjunni R, Sriwastva MK, Bose S, Sagar R, Srivastava AK, Mathur R, Jain S, Subbiah V (2020) Lithium acts to modulate abnormalities at behavioral, cellular, and molecular levels in sleep deprivation-induced mania-like behavior. Bipolar Disord 22:266–280

Anis Syahirah MS, Che Badariah AA, Idris L, Rosfaiizah S, Liza N (2022) Impact of rapid eye movement sleep deprivation on pain behaviour and oxidative stress in the thalamus: role of Tualang honey supplementation. Malays J Med Sci 29:69–79

Atik L, Konuk N, Akay O, Ozturk D, Erdogan A (2007) Pain perception in patients with bipolar disorder and schizophrenia. Acta Neuropsychiatr 19:284–290

Banafshe HR, Mesdaghinia A, Arani MN, Ramezani MH, Heydari A, Hamidi GA (2012) Lithium attenuates pain-related behavior in a rat model of neuropathic pain: possible involvement of opioid system. Pharmacol Biochem Behav 100:425–430

Bartz JA, Hollander E (2006) Is obsessive-compulsive disorder an anxiety disorder? Prog Neuropsychopharmacol Biol Psychiatry 30:338–352

Beaulieu JM, Sotnikova TD, Yao WD, Kockeritz L, Woodgett JR, Gainetdinov RR, Caron MG (2004) Lithium antagonizes dopamine-dependent behaviors mediated by an AKT/glycogen synthase kinase 3 signaling cascade. Proc Natl Acad Sci U S A 101:5099–5104

Bekinschtein P, Cammarota M, Katche C, Slipczuk L, Rossato JI, Goldin A, Izquierdo I, Medina JH (2008) BDNF is essential to promote persistence of long-term memory storage. Proc Natl Acad Sci U S A 105:2711–2716

Berk M, Koopowitz LF, Szabo CP (1996) Antidepressant induced mania in obsessive compulsive disorder. Eur Neuropsychopharmacol 6:9–11

Bertolin S, Alonso P, Segalas C, Real E, Alemany-Navarro M, Soria V, Jimenez-Murcia S, Crespo JM, Menchon JM (2021) First manic/hypomanic episode in obsessive-compulsive disorder patients treated with antidepressants: a systematic review. J Psychiatr Res 137:319–327

Boggero IA, Cole JD (2016) Mania reduces perceived pain intensity in patients with chronic pain: preliminary evidence from retrospective archival data. J Pain Res 9:147–152

Cade JF (1949) Lithium salts in the treatment of psychotic excitement. Med J Aust 2:349–352

Carr GV, Lucki I (2010) CHAPTER 4.2 - The role of serotonin in depression. In: Müller CP, Jacobs BL (eds) Handbook of behavioral neuroscience. Elsevier, pp 493–505

Cassidy F, Murry E, Forest K, Carroll BJ (1998) Signs and symptoms of mania in pure and mixed episodes. J Affect Disord 50:187–201

Castren E, Rantamaki T (2010) The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. Dev Neurobiol 70:289–297

Cefis M, Prigent-Tessier A, Quirie A, Pernet N, Marie C, Garnier P (2019) The effect of exercise on memory and BDNF signaling is dependent on intensity. Brain Struct Funct 224:1975–1985

Chen PH, Chung CC, Liu SH, Kao YH, Chen YJ (2022) Lithium treatment improves cardiac dysfunction in rats deprived of rapid eye movement sleep. Int J Mol Sci 23(19):11226

Chen YW, Dilsaver SC (1995) Comorbidity for obsessive-compulsive disorder in bipolar and unipolar disorders. Psychiatry Res 59:57–64

Coppen A (1967) The biochemistry of affective disorders. Br J Psychiatry 113:1237–1264

Crossley NA, Bauer M (2007) Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. J Clin Psychiatry 68:935–940

Cunha AB, Frey BN, Andreazza AC, Goi JD, Rosa AR, Goncalves CA, Santin A, Kapczinski F (2006) Serum brain-derived neurotrophic factor is decreased in bipolar disorder during depressive and manic episodes. Neurosci Lett 398:215–219

Dal-Pont GC, Jorio MTS, Resende WR, Gava FF, Aguiar-Geraldo JM, Possamai-Della T, Peper-Nascimento J, Quevedo J, Valvassori SS (2019) Effects of lithium and valproate on behavioral parameters and neurotrophic factor levels in an animal model of mania induced by paradoxical sleep deprivation. J Psychiatr Res 119:76–83

Das A (2013) Anxiety disorders in bipolar I mania: prevalence, effect on illness severity, and treatment implications. Indian J Psychol Med 35:53–59

de Brouwer G, Fick A, Harvey BH, Wolmarans W (2019) A critical inquiry into marble-burying as a preclinical screening paradigm of relevance for anxiety and obsessive-compulsive disorder: Mapping the way forward. Cogn Affect Behav Neurosci 19:1–39

de Sousa RT, van de Bilt MT, Diniz BS, Ladeira RB, Portela LV, Souza DO, Forlenza OV, Gattaz WF, Machado-Vieira R (2011) Lithium increases plasma brain-derived neurotrophic factor in acute bipolar mania: a preliminary 4-week study. Neurosci Lett 494:54–56

Dilsaver SC, Chen YW, Swann AC, Shoaib AM, Krajewski KJ (1994) Suicidality in patients with pure and depressive mania. Am J Psychiatry 151:1312–1315

Dubovsky SL (2015) Mania. Continuum (Minneap Minn) 21:737–755

Emamghoreishi M, Keshavarz M, Nekooeian AA (2015) Acute and chronic effects of lithium on BDNF and GDNF mRNA and protein levels in rat primary neuronal, astroglial and neuroastroglia cultures. Iran J Basic Med Sci 18:240–246

Ennaceur A (2014) Tests of unconditioned anxiety - pitfalls and disappointments. Physiol Behav 135:55–71

Ettenberg A, Ayala K, Krug JT, Collins L, Mayes MS, Fisher MPA (2020) Differential effects of lithium isotopes in a ketamine-induced hyperactivity model of mania. Pharmacol Biochem Behav 190:172875

Eydipour Z, Nasehi M, Vaseghi S, Jamaldini SH, Zarrindast MR (2020) The role of 5-HT4 serotonin receptors in the CA1 hippocampal region on memory acquisition impairment induced by total (TSD) and REM sleep deprivation (RSD). Physiol Behav 215:112788

Fang W, Liao W, Zheng Y, Huang X, Weng X, Fan S, Chen X, Zhang X, Chen J, Xiao S, Thea A, Luan P, Liu J (2019) Neurotropin reduces memory impairment and neuroinflammation via BDNF/NF-kappaB in a transgenic mouse model of Alzheimer's disease. Am J Transl Res 11:1541–1554

Fenske JN, Petersen K (2015) Obsessive-compulsive disorder: diagnosis and management. Am Fam Physician 92:896–903

Fernandes BS, Gama CS, Kauer-Sant'Anna M, Lobato MI, Belmonte-de-Abreu P, Kapczinski F (2009) Serum brain-derived neurotrophic factor in bipolar and unipolar depression: a potential adjunctive tool for differential diagnosis. J Psychiatr Res 43:1200–1204

Fernandes BS, Molendijk ML, Kohler CA, Soares JC, Leite CM, Machado-Vieira R, Ribeiro TL, Silva JC, Sales PM, Quevedo J, Oertel-Knochel V, Vieta E, Gonzalez-Pinto A, Berk M, Carvalho AF (2015) Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: a meta-analysis of 52 studies. BMC Med 13:289

Fleck DE, Shear PK, Zimmerman ME, Getz GE, Corey KB, Jak A, Lebowitz BK, Strakowski SM (2003) Verbal memory in mania: effects of clinical state and task requirements. Bipolar Disord 5:375–380

Frey BN, Andreazza AC, Cereser KM, Martins MR, Valvassori SS, Reus GZ, Quevedo J, Kapczinski F (2006a) Effects of mood stabilizers on hippocampus BDNF levels in an animal model of mania. Life Sci 79:281–286

Frey BN, Andreazza AC, Rosa AR, Martins MR, Valvassori SS, Reus GZ, Hatch JP, Quevedo J, Kapczinski F (2006b) Lithium increases nerve growth factor levels in the rat hippocampus in an animal model of mania. Behav Pharmacol 17:311–318

Fukumoto T, Morinobu S, Okamoto Y, Kagaya A, Yamawaki S (2001) Chronic lithium treatment increases the expression of brain-derived neurotrophic factor in the rat brain. Psychopharmacology 158:100–106

Gao TH, Ni RJ, Liu S, Tian Y, Wei J, Zhao L, Wang Q, Ni P, Ma X, Li T (2021) Chronic lithium exposure attenuates ketamine-induced mania-like behavior and c-Fos expression in the forebrain of mice. Pharmacol Biochem Behav 202:173108

Gideons ES, Lin PY, Mahgoub M, Kavalali ET, Monteggia LM (2017) Chronic lithium treatment elicits its antimanic effects via BDNF-TrkB dependent synaptic downscaling. eLife 6:e25480. https://doi.org/10.7554/eLife.25480

Gold AK, Kinrys G (2019) Treating circadian rhythm disruption in bipolar disorder. Curr Psychiatry Rep 21:14

Goldstein BI, Houck PR, Karp JF (2009) Factors associated with pain interference in an epidemiologic sample of adults with bipolar I disorder. J Affect Disord 117:151–156

Gonzalez-Pinto A, Galan J, Martin-Carrasco M, Ballesteros J, Maurino J, Vieta E (2012) Anxiety as a marker of severity in acute mania. Acta Psychiatr Scand 126:351–355

Grande I, Fries GR, Kunz M, Kapczinski F (2010) The role of BDNF as a mediator of neuroplasticity in bipolar disorder. Psychiatry Investig 7:243–250

Gray JD, McEwen BS (2013) Lithium's role in neural plasticity and its implications for mood disorders. Acta Psychiatr Scand 128:347–361

Grof P, Grof E (1990) Varieties of lithium benefit. Prog Neuropsychopharmacol Biol Psychiatry 14:689–696

Guo L, Guo Z, Luo X, Liang R, Yang S, Ren H, Wang G, Zhen X (2016) Phosphodiesterase 10A inhibition attenuates sleep deprivation-induced deficits in long-term fear memory. Neurosci Lett 635:44–50

Hajek T, Cullis J, Novak T, Kopecek M, Hoschl C, Blagdon R, O'Donovan C, Bauer M, Young LT, Macqueen G, Alda M (2012) Hippocampal volumes in bipolar disorders: opposing effects of illness burden and lithium treatment. Bipolar Disord 14:261–270

Hakki Onen S, Alloui A, Jourdan D, Eschalier A, Dubray C (2001) Effects of rapid eye movement (REM) sleep deprivation on pain sensitivity in the rat. Brain Res 900:261–267

Hanak AS, Chevillard L, Lebeau R, Risede P, Laplanche JL, Benturquia N, Megarbane B (2017) Neurobehavioral effects of lithium in the rat: investigation of the effect/concentration relationships and the contribution of the poisoning pattern. Prog Neuropsychopharmacol Biol Psychiatry 76:124–133

Hashimoto R, Takei N, Shimazu K, Christ L, Lu B, Chuang DM (2002) Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity. Neuropharmacology 43:1173–1179

Huang EJ, Reichardt LF (2001) Neurotrophins: roles in neuronal development and function. Annu Rev Neurosci 24:677–736

Hwang L, Ko IG, Jin JJ, Kim SH, Kim CJ, Chang B, Rho JH, Moon EJ, Yi JW (2019) Dexmedetomidine ameliorates memory impairment in sleep-deprived mice. Anim Cells Syst (Seoul) 23:371–379

Jacobsen JP, Mork A (2004) The effect of escitalopram, desipramine, electroconvulsive seizures and lithium on brain-derived neurotrophic factor mRNA and protein expression in the rat brain and the correlation to 5-HT and 5-HIAA levels. Brain Res 1024:183–192

Jain A, Paroma M (2020) Bipolar affective disorder. Harvard

Javad-Moosavi BZ, Nasehi M, Vaseghi S, Jamaldini SH, Zarrindast MR (2020) Activation and Inactivation of Nicotinic Receptnors in the Dorsal Hippocampal Region Restored Negative Effects of Total (TSD) and REM Sleep Deprivation (RSD) on Memory Acquisition, Locomotor Activity and Pain Perception. Neuroscience 433:200–211

Jornada LK, Moretti M, Valvassori SS, Ferreira CL, Padilha PT, Arent CO, Fries GR, Kapczinski F, Quevedo J (2010) Effects of mood stabilizers on hippocampus and amygdala BDNF levels in an animal model of mania induced by ouabain. J Psychiatr Res 44:506–510

Kakhki S, Goodarzi M, Abbaszade-Cheragheali A, Rajabi M, Masoumipour AH, Khatibi SR, Beheshti F (2023) Folic acid supplementation improved cognitive deficits associated with lithium administration during pregnancy in rat offspring. Int J Dev Neurosci 83:615–630

Kalra H, Tandon R, Saluja B, Mohan I (2002) Obsessive compulsive disorder:co-morbidity in manic phase of bipolar affective disorder. Indian J Psychiatry 44:377–379

Kang WS, Park HJ, Chung JH, Kim JW (2013) REM sleep deprivation increases the expression of interleukin genes in mice hypothalamus. Neurosci Lett 556:73–78

Kang X, Jiang L, Lan F, Tang YY, Zhang P, Zou W, Chen YJ, Tang XQ (2021) Hydrogen sulfide antagonizes sleep deprivation-induced depression- and anxiety-like behaviors by inhibiting neuroinflammation in a hippocampal Sirt1-dependent manner. Brain Res Bull 177:194–202

Kapczinski F, Frey BN, Kauer-Sant'Anna M, Grassi-Oliveira R (2008) Brain-derived neurotrophic factor and neuroplasticity in bipolar disorder. Expert Rev Neurother 8:1101–1113

Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE (2005) Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 62:617–627

Khakpoor M, Vaseghi S, Mohammadi-Mahdiabadi-Hasani MH, Nasehi M (2021) The effect of GABA-B receptors in the basolateral amygdala on passive avoidance memory impairment induced by MK-801 in rats. Behav Brain Res 409:113313

Khodaverdiloo A, Farhadi M, Jameie M, Jameie SB, Pirhajati V (2021) Neurogenesis in the rat neonate's hippocampus with maternal short-term REM sleep deprivation restores by royal jelly treatment. Brain Behav 11:e2423

Kholghi G, Alipour V, Rezaie M, Zarrindast MR, Vaseghi S (2023) The interaction effect of sleep deprivation and treadmill exercise in various durations on spatial memory with respect to the oxidative status of rats. Neurochem Res 48(7):2077–2092

Kim SA, Kim S, Park HJ (2022) REM-Sleep Deprivation Induces Mitochondrial Biogenesis in the Rat Hippocampus. In Vivo 36:1726–1733

King MJ, MacDougall AG, Ferris S, Herdman KA, Bielak T, Smith JR, Abid MA, McKinnon MC (2013) Impaired episodic memory for events encoded during mania in patients with bipolar disorder. Psychiatry Res 205:213–219

Klumpers UM, Veltman DJ, van Tol MJ, Kloet RW, Boellaard R, Lammertsma AA, Hoogendijk WJ (2015) Neurophysiological effects of sleep deprivation in healthy adults, a pilot study. PLoS ONE 10:e0116906

Kordestani-Moghadam P, Nasehi M, Vaseghi S, Khodagholi F, Zarrindast MR (2020) The role of sleep disturbances in depressive-like behavior with emphasis on alpha-ketoglutarate dehydrogenase activity in rats. Physiol Behav 224:113023

Kraepelin E (1913). Psychiatrie; ein Lehrbuch für Studierende und Ärzte, vol 3

Krug JT, Klein AK, Purvis EM, Ayala K, Mayes MS, Collins L, Fisher MPA, Ettenberg A (2019) Effects of chronic lithium exposure in a modified rodent ketamine-induced hyperactivity model of mania. Pharmacol Biochem Behav 179:150–155

Lahimgarzadeh R, Vaseghi S, Nasehi M, Rouhollah F (2022) Effect of multi-epitope derived from HIV-1 on REM sleep deprivation-induced spatial memory impairment with respect to the level of immune factors in mice. Iran J Basic Med Sci 25:164–172

Lee SS, Kim CJ, Shin MS, Lim BV (2020) Treadmill exercise ameliorates memory impairment through ERK-Akt-CREB-BDNF signaling pathway in cerebral ischemia gerbils. J Exerc Rehabil 16:49–57

Li B, Hsieh YR, Lai WD, Tung TH, Chen YX, Yang CH, Fang YC, Huang SY (2023) Melatonin ameliorates neuropsychiatric behaviors, gut microbiome, and microbiota-derived metabolites in rats with chronic sleep deprivation. Int J Mol Sci 24(23):16820

Li S, Zhou H, Yu Y, Lyu H, Mou T, Shi G, Hu S, Huang M, Hu J, Xu Y (2021) Effect of repetitive transcranial magnetic stimulation on the cognitive impairment induced by sleep deprivation: a randomized trial. Sleep Med 77:270–278

Liu RJ, Fuchikami M, Dwyer JM, Lepack AE, Duman RS, Aghajanian GK (2013) GSK-3 inhibition potentiates the synaptogenic and antidepressant-like effects of subthreshold doses of ketamine. Neuropsychopharmacology 38:2268–2277

Looti Bashiyan M, Nasehi M, Vaseghi S, Khalifeh S (2021) Investigating the effect of crocin on memory deficits induced by total sleep deprivation (TSD) with respect to the BDNF, TrkB and ERK levels in the hippocampus of male Wistar rats. J Psychopharmacol (Oxford, England) 35(6):744–754. https://doi.org/10.1177/02698811211000762

Machado RB, Hipolide DC, Benedito-Silva AA, Tufik S (2004) Sleep deprivation induced by the modified multiple platform technique: quantification of sleep loss and recovery. Brain Res 1004:45–51

Mahboubi S, Nasehi M, Imani A, Sadat-Shirazi MS, Zarrindast MR, Vousooghi N, Noroozian M (2019) Benefit effect of REM-sleep deprivation on memory impairment induced by intensive exercise in male wistar rats: with respect to hippocampal BDNF and TrkB. Nat Sci Sleep 11:179–188

Mahdavi MS, Nasehi M, Vaseghi S, Mousavi Z, Zarrindast MR (2021) The effect of alpha lipoic acid on passive avoidance and social interaction memory, pain perception, and locomotor activity in REM sleep-deprived rats. Pharmacol Rep 73:102–110

Malboosi N, Nasehi M, Hashemi M, Vaseghi S, Zarrindast MR (2020) The neuroprotective effect of NeuroAid on morphine-induced amnesia with respect to the expression of TFAM, PGC-1alpha, DeltafosB and CART genes in the hippocampus of male Wistar rats. Gene 742:144601

Martinez-Aran A, Vieta E, Reinares M, Colom F, Torrent C, Sanchez-Moreno J, Benabarre A, Goikolea JM, Comes M, Salamero M (2004) Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. Am J Psychiatry 161:262–270

Maturana MJ, Pudell C, Targa AD, Rodrigues LS, Noseda AC, Fortes MH, Dos Santos P, Da Cunha C, Zanata SM, Ferraz AC, Lima MM (2015) REM sleep deprivation reverses neurochemical and other depressive-like alterations induced by olfactory bulbectomy. Mol Neurobiol 51:349–360

McAllister AK, Katz LC, Lo DC (1999) Neurotrophins and synaptic plasticity. Annu Rev Neurosci 22:295–318

Melo MCA, Abreu RLC, Linhares Neto VB, de Bruin PFC, de Bruin VMS (2017) Chronotype and circadian rhythm in bipolar disorder: A systematic review. Sleep Med Rev 34:46–58

Miklowitz DJ, Johnson SL (2006) The psychopathology and treatment of bipolar disorder. Annu Rev Clin Psychol 2:199–235

Mizoguchi Y, Yao H, Imamura Y, Hashimoto M, Monji A (2020) Lower brain-derived neurotrophic factor levels are associated with age-related memory impairment in community-dwelling older adults: the Sefuri study. Sci Rep 10:16442

Monteleone P, Serritella C, Martiadis V, Maj M (2008) Decreased levels of serum brain-derived neurotrophic factor in both depressed and euthymic patients with unipolar depression and in euthymic patients with bipolar I and II disorders. Bipolar Disord 10:95–100

Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK (2000) Lithium-induced increase in human brain grey matter. Lancet 356:1241–1242

Mucci F, Toni C, Favaretto E, Vannucchi G, Marazziti D, Perugi G (2018) Obsessive-compulsive disorder with comorbid bipolar disorders: clinical features and treatment implications. Curr Med Chem 25:5722–5730

Muraki I, Inoue T, Hashimoto S, Izumi T, Ito K, Ohmori T, Koyama T (1999) Effect of subchronic lithium carbonate treatment on anxiolytic-like effect of citalopram and MKC-242 in conditioned fear stress in the rat. Eur J Pharmacol 383:223–229

National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals (2011) Guide for the Care and Use of Laboratory Animals, 8th edn. National Academies Press (US), Washington (DC). Available from: https://www.ncbi.nlm.nih.gov/books/NBK54050/. https://doi.org/10.17226/12910

Olfson M, Mojtabai R, Merikangas KR, Compton WM, Wang S, Grant BF, Blanco C (2017) Reexamining associations between mania, depression, anxiety and substance use disorders: results from a prospective national cohort. Mol Psychiatry 22:235–241

Omata N, Murata T, Takamatsu S, Maruoka N, Mitsuya H, Yonekura Y, Fujibayashi Y, Wada Y (2008) Neuroprotective effect of chronic lithium treatment against hypoxia in specific brain regions with upregulation of cAMP response element binding protein and brain-derived neurotrophic factor but not nerve growth factor: comparison with acute lithium treatment. Bipolar Disord 10:360–368

Pedersen BK, Pedersen M, Krabbe KS, Bruunsgaard H, Matthews VB, Febbraio MA (2009) Role of exercise-induced brain-derived neurotrophic factor production in the regulation of energy homeostasis in mammals. Exp Physiol 94:1153–1160

Prickaerts J, Moechars D, Cryns K, Lenaerts I, van Craenendonck H, Goris I, Daneels G, Bouwknecht JA, Steckler T (2006) Transgenic mice overexpressing glycogen synthase kinase 3beta: a putative model of hyperactivity and mania. J Neurosci 26:9022–9029

Quinn N, Marsden CD (1986) Lithium for painful dystonia in Parkinson's disease. Lancet 1:1377

Rezaie M, Nasehi M, Vaseghi S, Mohammadi-Mahdiabadi-Hasani MH, Zarrindast MR, Nasiri Khalili MA (2020) The protective effect of alpha lipoic acid (ALA) on social interaction memory, but not passive avoidance in sleep-deprived rats. Naunyn Schmiedebergs Arch Pharmacol 393:2081–2091

Rihmer Z, Szadoczky E, Furedi J, Kiss K, Papp Z (2001) Anxiety disorders comorbidity in bipolar I, bipolar II and unipolar major depression: results from a population-based study in Hungary. J Affect Disord 67:175–179

Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T (2006) Sleep loss and REM sleep loss are hyperalgesic. Sleep 29:145–151

Rygula R, Golebiowska J, Kregiel J, Holuj M, Popik P (2015) Acute administration of lithium, but not valproate, modulates cognitive judgment bias in rats. Psychopharmacology 232:2149–2156

Samad N, Imran I, Zulfiqar I, Bilal K (2019) Ameliorative effect of lithium chloride against d-galactose induced behavioral and memory impairment, oxidative stress and alteration in serotonin function in rats. Pharmacol Rep 71:909–916

Sampogna G, Janiri D, Albert U, Caraci F, Martinotti G, Serafini G, Tortorella A, Zuddas A, Sani G, Fiorillo A (2022) Why lithium should be used in patients with bipolar disorder? A scoping review and an expert opinion paper. Expert Rev Neurother 22(11–12):923–934. https://doi.org/10.1080/14737175.2022.2161895

Schmidt HD, Banasr M, Duman RS (2008) Future antidepressant targets: neurotrophic factors and related signaling cascades. Drug Discov Today Ther Strateg 5:151–156

Schou M (1957) Biology and pharmacology of the lithium ion. Pharmacol Rev 9:17–58

Sheard MH, Marini JL, Bridges CI, Wagner E (1976) The effect of lithium on impulsive aggressive behavior in man. Am J Psychiatry 133:1409–1413

Sikkens D, Riemersma-Van der Lek RF, Meesters Y, Schoevers RA, Haarman BCM (2019) Combined sleep deprivation and light therapy: clinical treatment outcomes in patients with complex unipolar and bipolar depression. J Affect Disord 246:727–730

Simoes LR, Abreu R, Generoso JS, Goularte JA, Collodel A, Giridharan VV, Arumanayagam ACS, Valvassori SS, Quevedo J, Barichello T (2017) Prevention of memory impairment and neurotrophic factors increased by lithium in Wistar rats submitted to pneumococcal meningitis model. Mediators Inflamm 2017:6490652

Sofroniew MV, Howe CL, Mobley WC (2001) Nerve growth factor signaling, neuroprotection, and neural repair. Annu Rev Neurosci 24:1217–1281

Stein DJ, Fineberg NA, Bienvenu OJ, Denys D, Lochner C, Nestadt G, Leckman JF, Rauch SL, Phillips KA (2010) Should OCD be classified as an anxiety disorder in DSM-V? Depress Anxiety 27:495–506

Sur B, Lee B (2022) Myricetin prevents sleep deprivation-induced cognitive impairment and neuroinflammation in rat brain via regulation of brain-derived neurotropic factor. Korean J Physiol Pharmacol 26:415–425

Szabo ST, Blier P (2002) Effects of serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibition plus 5-HT(2A) receptor antagonism on the firing activity of norepinephrine neurons. J Pharmacol Exp Ther 302:983–991

Thase ME, Jindal R, Howland RH, Gotlib IH, Hammen C (2002) Handbook of depression. Harvard, pp 192–218

Thiruvengadam A (2001) Effect of lithium and sodium valproate ions on resting membrane potentials in neurons: an hypothesis. J Affect Disord 65:95–99

Torabi Z, Rezaie M, Aramvash A, Nasiri-Khalili MA, Nasehi M, Abedi B, Vaseghi S (2022) Interaction of lithium and sleep deprivation on memory performance and anxiety-like behavior in male Wistar rats. Behav Brain Res 428:113890

Tosca P, Bezzi G, Cecchi M, Zerbi F (1981) Effects of lithium salts on pain experience in depressed patients. Bibl Psychiatr 161:134–40. https://doi.org/10.1159/000395819

Tramontina JF, Andreazza AC, Kauer-Sant'anna M, Stertz L, Goi J, Chiarani F, Kapczinski F (2009) Brain-derived neurotrophic factor serum levels before and after treatment for acute mania. Neurosci Lett 452:111–113

Trautmann N, Foo JC, Frank J, Witt SH, Streit F, Treutlein J, von Heydendorff SC, Gilles M, Forstner AJ, Ebner-Priemer U, Nothen MM, Deuschle M, Rietschel M, Major Depressive Disorder Working Group of the Psychiatric Genomics C (2018) Response to therapeutic sleep deprivation: a naturalistic study of clinical and genetic factors and post-treatment depressive symptom trajectory. Neuropsychopharmacology 43:2572–2577

Travaglini LE, Kuykendall L, Bennett ME, Abel EA, Lucksted A (2020) Relationships between chronic pain and mood symptoms among veterans with bipolar disorder. J Affect Disord 277:765–771

Tripathi S, Jha SK (2022) REM sleep deprivation alters learning-induced cell proliferation and generation of newborn young neurons in the dentate gyrus of the dorsal hippocampus. ACS Chem Neurosci 13:194–206

Tunca Z, Ozerdem A, Ceylan D, Yalcin Y, Can G, Resmi H, Akan P, Ergor G, Aydemir O, Cengisiz C, Kerim D (2014) Alterations in BDNF (brain derived neurotrophic factor) and GDNF (glial cell line-derived neurotrophic factor) serum levels in bipolar disorder: The role of lithium. J Affect Disord 166:193–200

Ugalde-Muniz P, Hernandez-Luna MG, Garcia-Velasco S, Lugo-Huitron R, Murcia-Ramirez J, Martinez-Tapia RJ, Noriega-Navarro R, Navarro L (2022) Activation of dopamine D2 receptors attenuates neuroinflammation and ameliorates the memory impairment induced by rapid eye movement sleep deprivation in a murine model. Front Neurosci 16:988167

Valvassori SS, Borges CP, Varela RB, Bavaresco DV, Bianchini G, Mariot E, Arent CO, Resende WR, Budni J, Quevedo J (2017a) The different effects of lithium and tamoxifen on memory formation and the levels of neurotrophic factors in the brain of male and female rats. Brain Res Bull 134:228–235

Valvassori SS, Cararo JH, Marino CAP, Possamai-Della T, Ferreira CL, Aguiar-Geraldo JM, Dal-Pont GC, Quevedo J (2022) Imipramine induces hyperactivity in rats pretreated with ouabain: Implications to the mania switch induced by antidepressants. J Affect Disord 299:425–434

Valvassori SS, Resende WR, Dal-Pont G, Sangaletti-Pereira H, Gava FF, Peterle BR, Carvalho AF, Varela RB, Dal-Pizzol F, Quevedo J (2017b) Lithium ameliorates sleep deprivation-induced mania-like behavior, hypothalamic-pituitary-adrenal (HPA) axis alterations, oxidative stress and elevations of cytokine concentrations in the brain and serum of mice. Bipolar Disord 19:246–258

Varela RB, Valvassori SS, Lopes-Borges J, Mariot E, Dal-Pont GC, Amboni RT, Bianchini G, Quevedo J (2015) Sodium butyrate and mood stabilizers block ouabain-induced hyperlocomotion and increase BDNF, NGF and GDNF levels in brain of Wistar rats. J Psychiatr Res 61:114–121

Vaseghi S, Arjmandi-Rad S, Kholghi G, Nasehi M (2021) Inconsistent effects of sleep deprivation on memory function. EXCLI J 20:1011–1027

Vrabie M, Marinescu V, Talasman A, Tautu O, Drima E, Miclutia I (2015) Cognitive impairment in manic bipolar patients: important, understated, significant aspects. Ann Gen Psychiatry 14:41

Wang J, Xu C, Liu C, Zhou Q, Chao G, Jin Y (2023) Effects of different doses of lithium on the central nervous system in the rat valproic acid model of autism. Chem Biol Interact 370:110314

Weinsanto I, Mouheiche J, Laux-Biehlmann A, Aouad M, Maduna T, Petit-Demouliere N, Chavant V, Poisbeau P, Darbon P, Charlet A, Giersch A, Parat MO, Goumon Y (2018) Lithium reverses mechanical allodynia through a mu opioid-dependent mechanism. Mol Pain 14:1744806917754142

Wohr M (2022) Measuring mania-like elevated mood through amphetamine-induced 50-kHz ultrasonic vocalizations in rats. Br J Pharmacol 179:4201–4219

Wu R, Fan J, Zhao J, Calabrese JR, Gao K (2014) The relationship between neurotrophins and bipolar disorder. Expert Rev Neurother 14:51–65

Yamada K, Nabeshima T (2003) Brain-derived neurotrophic factor/TrkB signaling in memory processes. J Pharmacol Sci 91:267–270

Yan YN, Williams JP, Niu K, Zhang WH, Zhang JF, Shi L, An JX (2022) Intraperitoneal ozone injection prevents REM sleep deprivation - induced spatial learning and memory deficits by suppressing the expression of Sema3A in the hippocampus in rats. Iran J Basic Med Sci 25:980–988

Yapici Eser H, Kacar AS, Kilciksiz CM, Yalcinay-Inan M, Ongur D (2018) Prevalence and associated features of anxiety disorder comorbidity in bipolar disorder: a meta-analysis and meta-regression study. Front Psychiatry 9:229

Yasuda S, Liang MH, Marinova Z, Yahyavi A, Chuang DM (2009) The mood stabilizers lithium and valproate selectively activate the promoter IV of brain-derived neurotrophic factor in neurons. Mol Psychiatry 14:51–59

Youngs RM, Chu MS, Meloni EG, Naydenov A, Carlezon WA Jr, Konradi C (2006) Lithium administration to preadolescent rats causes long-lasting increases in anxiety-like behavior and has molecular consequences. J Neurosci 26:6031–6039

Zagaar M, Dao A, Levine A, Alhaider I, Alkadhi K (2013) Regular exercise prevents sleep deprivation associated impairment of long-term memory and synaptic plasticity in the CA1 area of the hippocampus. Sleep 36:751–761

Zangani C, Casetta C, Saunders AS, Donati F, Maggioni E, D'Agostino A (2020) Sleep abnormalities across different clinical stages of bipolar disorder: a review of EEG studies. Neurosci Biobehav Rev 118:247–257

Zhang L, Fang Y, Lian Y, Chen Y, Wu T, Zheng Y, Zong H, Sun L, Zhang R, Wang Z, Xu Y (2015) Brain-derived neurotrophic factor ameliorates learning deficits in a rat model of Alzheimer's disease induced by abeta1-42. PLoS ONE 10:e0122415

Zheng X, Wang R, Ma B, Zhang J, Qian X, Fang Q, An J (2024) rTMS reduces spatial learning and memory deficits induced by sleep deprivation possibly via suppressing the expression of kynurenine 3-monooxygenase in rats. Behav Brain Res 456:114704

Zutshi A, Kamath P, Reddy YC (2007) Bipolar and nonbipolar obsessive-compulsive disorder: a clinical exploration. Compr Psychiatry 48:245–251