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Research report

Behavioural sensitization to repeated sleep deprivation in a mice model of mania

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Abstract

Sensitization to the effect of stress has been hypothesized as a mechanism to explain episode recurrence and cycle acceleration in bipolar disorder. Naturalistic observations and experimental work in human patients suggested that sleep deprivation can trigger manic episodes of illness. In rats sleep deprivation (SD) with the platform method caused mania-like behaviours thus providing an animal model of mania with face, construct, and predictive validity.

In the present study we administered SD or control stress to male CD1 mice following a dose–response protocol based on time of exposure to the experimental conditions (6, 12 or 24 h) and repetition of treatment (three times). SD, but not stress-control conditions, increased motor activity and aggressive behaviours. The behavioural activation followed a dose–response curve based on length of treatment, with non-significant trends after 6 h, significant effects after 12 h, and maximal effects after 24 h. Moreover, the behavioural activation followed a time–response curve, with progressive sensitization to the effects of SD, but not of control stress, upon its repetition.

This is the first animal model of behavioural sensitization to the effects of a specific stress (sleep deprivation) known to trigger mania in bipolar patients. We expect it to be useful to test the efficacy of antimanic and mood-stabilizer drugs, and to study the neurobiological correlates of manic reactions in order to gain new insight into the pathophysiology of bipolar illness and to identify new targets for treatment.

Keywords: Primary affective disorder; Bipolar disorder; Circadian regulation

1. Introduction

In humans bipolar disorder is defined by a pattern of recurrent depressive and manic episodes of illness, with interspersed periods of normal life in euthymic conditions. The occurrence of manic episodes is the distinctive feature of the disorder, while recurrence of depressive episode is common to primary affective disorder, and genetic studies showed that approximately 71% of the genetic influence on liability to mania is distinct from the genetic liability to depression [38].

Etiological research on bipolar disorder currently supports a role for the interaction of life stress and biological susceptibility, and aims at the dissection and investigation of the components of genomic and environmental factors, as well of their interaction [11]. The precise role of potential mediators or moderators of the relationship between childhood adversity, recent stressful life events, and depression recurrence has not yet been fully elucidated [27], but recent experimental work allowed to gain informations about the role of specific external stressors [18,27] and of their interaction with some biological substrates [12] in shaping the onset of illness and the recurrence of new episodes.

In the case of manic episodes of illness, naturalistic observations and experimental work in human patients [50,34,2,47,13] suggested a triggering role for sleep deprivation and schedule-disrupting life events, thus leading to the development of

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therapeutic programs aimed at controlling interpersonal and social rhythms in order to prevent recurrences [20]. The role of sleep deprivation as a triggering factor seemed independent from its causes [51], a summary of available findings showed manic episodes to be triggered by sleep–wake schedule-disrupting factors, and not by other stressors [30], and the mood-elevating properties of sleep deprivation have been confirmed also in the clinical treatment of bipolar depression [8].

A better awareness of the role of external stressors could help to implement animal models of bipolar disorder by modelling specific behavioural dimensions [23], thus possibly overcoming the problems that hamper validity and usefulness of available models for drug development, and for insight into the neuropathology underlying the disease [33,16] by providing animal models that mirror the situation seen in patients [24]. Following this line of reasoning, the behavioural dimensions of the manic syndrome could be modelled in animals using a trigger of proven clinical relevance in humans, such as sleep deprivation.

The behavioural effects of sleep disruption in rodents have been studied by administering sleep deprivation (SD) with the platform method [31]. Similar to human bipolar patients at the onset of mania, after sleep deprivation rats showed insomnia, hyperactivity, irritability, aggressiveness, hypersexuality, and stereotypy [22,26], and these behavioural changes were improved by haloperidol and prevented by lithium [25,26]. The behavioural effects of SD in rodents provided then an animal model of mania with face, construct, and predictive validity [36,33].

Several questions remained however unanswered.

The length of SD is usually 72 h, and it is unclear if the manic-like behaviours can be elicited by shorter amounts of sleep restriction, more similar to those observed in human patients. A dose–response effect of sleep restriction has never been defined. Current models of bipolar disorder suggest a role for stress sensitization and kindling phenomena in the progressive worsening of cyclicity that is often observed in human subjects [45,41,29,18], but no study addressed a possible sensitization to the effects of sleep deprivation, which is a known trigger of mania in bipolar patients [50,34,2,49,13]. On the other hand, no data about this specific issues are available in animals and no animal model of this peculiar characteristic of bipolar illness is available. In this respect it should also be noted that the platform method involves the administration of several stressors, such as isolation, immobilization, falling into water, which activate the hypothalamic-pituitary-adrenal axis [47] and could cause behavioural arousal independent of sleep deprivation [10], and the possible sensitization to sleep deprivation should then be separated from possible aspecific sensitization to stress [1].

This is important both because a model of progressive sensitization to the specific manic-inducing effects of sleep deprivation would be suitable for researches aimed at gaining insight on the pathophysiology of bipolar illness progression, and because in humans the study of sleep deprivation in the treatment of the depressive episodes of bipolar disorder suggested that repeating the treatment will lead to progressive benefits [3,4,8,14].

Finally, it is unknown if sleep deprivation would trigger manic reactions in other rodents, such as mice, which have become an invaluable research tool in the investigation of changes in brain functions over the lifespan in other areas of biomedical research [40].

The purpose of the present study is to provide a first answer to this questions.

2. Materials and methods

2.1. Animals

Male CD1 mice (Charles River, Calco, LC, Italy; $N = 72$; weight 33.0 ± 0.20 g) were housed 20 for a standard plastic cage with wood chip bedding under a 12 h artificial light-dark cycle (light on at 8:00 a.m.) at a constant temperature of $22 \pm 2\,^{\circ}C$ and relative humidity of approximately 60%. Tap water and standard laboratory rodent chow (muccedola, Settimo Milanese, MI, Italy) were provided ad libitum. The experimental procedures employed in the present study were in accordance with the European Communities Council Directive (86/609/EEC) and the subsequent Italian Law on the "Protection of animals used for experimental and other scientific reasons".

2.2. REM sleep deprivation procedure

Animals were placed into the flower-pot, a Plexi glass square based parallelepiped with a $41 \times 53 \times 41$ size, open on top, and subdivided into four sections of the same size ($20.5 \times 53 \times 20.5$) containing each a Plexi glass cylinder 10 cm tall and three large (small-platform). The upper surface of the cylinder is the only support point for the animal when each section is filled with warm water kept at a constant temperature (28 °C) and at the level of the cylinder's upper surface. In case of muscle relaxation (associated with paradoxical sleep), the animal would fall into the water and wake up. Previous research in mice showed that staying on a 3 cm platform for 24 h leads to a 78% decrease of slow wave sleep and to a 96% decrease of paradoxical sleep [46].

The control procedure was the same, except that a larger platform was used (diameter of 6 cm) thus allowing the animals to present all the phases of the wake–sleep cycle [45].

Food and water were made available through a grid placed on top of the water tank.

In order to assess possible relationships between the amount of exposure to sleep deprivation and behavioural changes (dose–response effects), timing of SD included three conditions: 24 h (from 8:00 p.m. to 8:00 p.m. of the day after), 12 h (8:00 a.m. to 8:00 p.m.), and 6 h (2:00 p.m. to 8:00 p.m.), which were followed by a behavioural assessment period and then by a free period (replacement in the cages). Animals were sleep deprived during their rest period (day) and their behaviours were evaluated during their activity period (night). The procedure was repeated three times (Fig. 1).

2.3. Behavioural assessment

Main outcomes were changes in motor activity and aggressive behaviour.

The measure of motor activity was the number of counts during 720 min in an open-field arena (480 mm × 480 mm; ActiMot, TSE system) equipped with two pairs of light-beam strips, spaced of 100 mm, one determining horizontal motor activity and the other determining vertical motor activity. Each pair of light-beam strip consisted of one transmitter strip and one receiver strip, both made up of 16 infrared sensors spaced of 28 mm. The open-field arenas, located in a quiet dark room, were interfaced with a personal computer and operated by the ActiMot software. The arenas were cleaned up with 70% alcohol after 720 min (from 8:00 p.m. to 8:00 a.m.). The number of counts was averaged over 180 min, thus leading to four time points for each animal (Fig. 2).

The measure of aggressive behaviour was the total time during which animals showed aggressive behaviours (attack bouts or flurries, rapid vibrations of the tail, bites) [39] when put in couples into an arena cage (40 cm × 40 cm) for 10 min soon after the SD procedure, and before the assessment of motor activity.

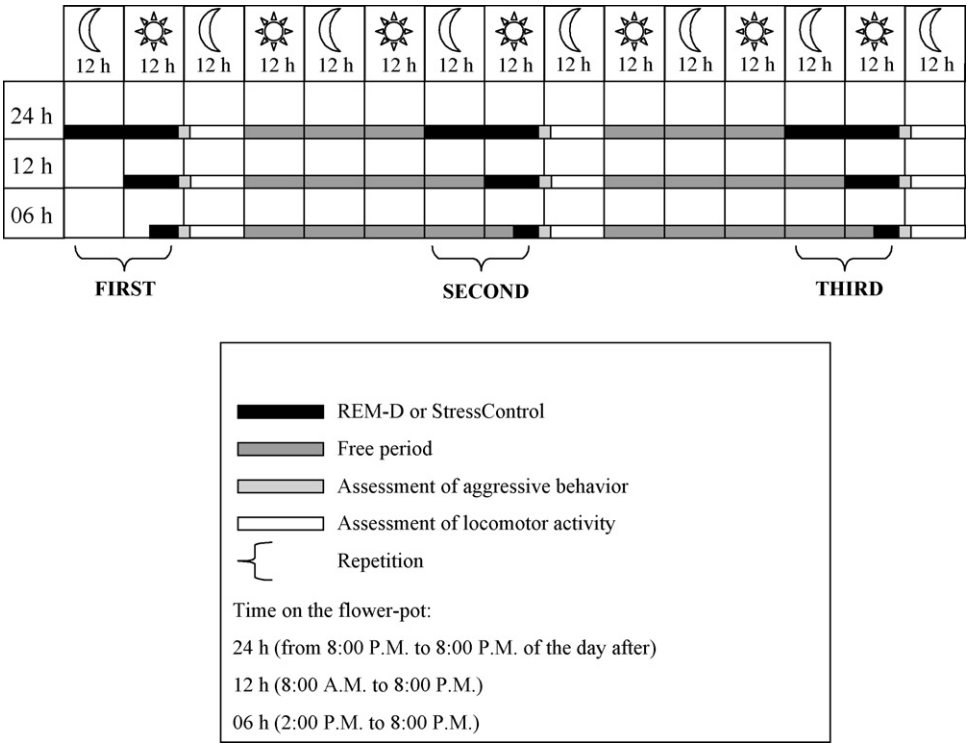

Fig. 1. Experimental procedure.

2.4. Statistical analysis

In the present study we had two dependent variables (motor activity and aggressive behaviour) and four independent factors: treatment (SD versus control condition), length of treatment (6, 12, or 24 h), repetition of treatment (first, second, third) and (only for the study of motor activity) time in the ActiMot. In order to assess the significance of the effects of the single factors as well as those of their interaction, data were analyzed with repeated measures multivariate ANOVAs.

3. Results

3.1. Motor activity

Data were analyzed with a 4-way repeated measures ANOVA with number of counts as dependent variable, and treatment (SD versus control condition), length of treatment (6, 12, or 24 h), repetition of treatment (first, second, third) and time in the ActiMot as independent factors (Fig. 2).

All animals in all conditions showed a higher motor activity at the beginning of the ActiMot observation, and a progressive decline over time (effect of time in the ActiMot: $F = 278.78$, d.f. 3,594; $p < 0.0001$). Both the treatment and its duration influenced motor activity, which was higher in SD animals ($F = 15.17$; d.f. 1,198; $p = 0.0001$) and increased with duration of treatment ($F = 41.34$; d.f. 2,198; $p < 0.0001$).

The pattern of change of motor activity over time did not follow parallel slopes in SD and control animals, with sleep deprived animals showing higher activity soon after treatment (time × treatment interaction: $F = 15.97$; d.f. 3,594; $p < 0.0001$). Length of SD influenced data following a dose–response curve, with no effect after 6-h SD, maximal effects after 24-h SD, and intermediate values after 12-h SD ($F = 8.20$; d.f. 6,594; $p < 0.0001$).

This dose–response effect was observed in SD animals, and was absent in the stress-control condition (treatment × length interaction: $F = 8.55$; d.f. 2,198; $p = 0.0003$). Then, these two factors (treatment and length) significantly interacted with time in the ActiMot in influencing motor activity (time × treatment × length interaction: $F = 6.33$; d.f. 6,594; $p < 0.0001$).

Repetition of treatment lead to increasingly higher and more prolonged patterns of motor activity (time × repetition interaction: $F = 5.67$; d.f. 6,594; $p < 0.0001$). Thus, both dose (increasing length) and repetition interacted in shaping the pattern of change of motor activity of animals after treatment (time × length of treatment × repetition interaction: $F = 2.11$; d.f. 12,594; $p = 0.0150$). This progressive sensitization to the effect of treatment was observed only in SD animals, and not in controls (treatment × repetition interaction: $F = 6.92$; d.f. 2,198; $p = 0.0012$).

Results of post-hoc comparisons (Newman–Keuls critical ranges test) are shown in Fig. 1. No significant effects of repetition and length of treatment were detected in stress-control conditions.

3.2. Aggressive behaviour

Data were analyzed with a 3-way repeated measures ANOVA with total time during which animals showed aggressive behaviours as dependent variable, and treatment (SD versus con-

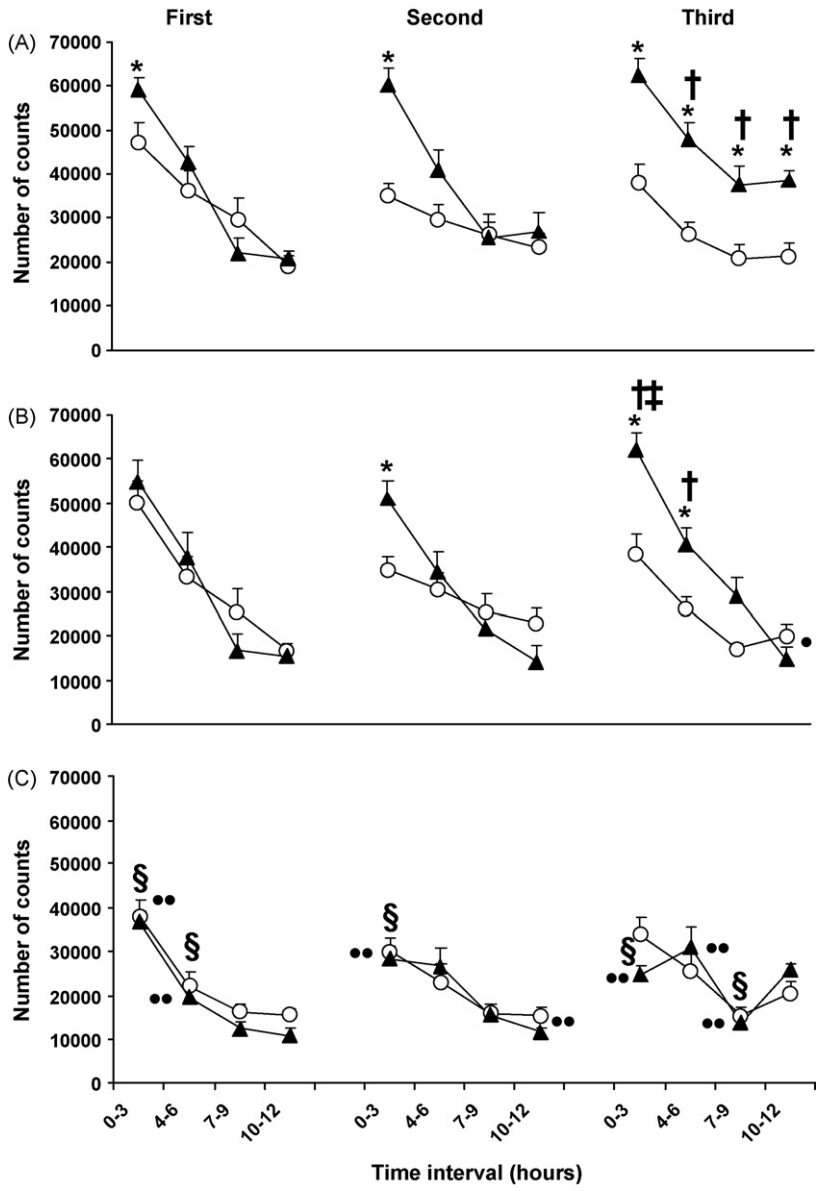

Fig. 2. Locomotor activity after repeated SD or stress-control condition (A = 24 h; B = 12 h; C = 6 h). Black triangles are for SD animals, white circles for controls. Each point is the group mean ($n = 12$) over 180 min; whiskers are standard error of means. Levels of significance of post-hoc comparisons (Newman–Keuls test) are shown as follows: $^{*}p < 0.001$, effect of treatment (SD vs. stress-control, same duration and repetition); $^{\dagger}p < 0.001$, effect of repetition (first vs. third) in SD animals; $^{\ddagger}p < 0.001$, effect of repetition (second vs. third) in SD animals; $^{\bullet}p < 0.001$, effect of treatment length (24 h vs. 12 h) in SD animals; $^{\bullet\bullet}p < 0.001$, effect of treatment length (24 h vs. 06 h) in SD animals; $^{\S}p < 0.001$, effect of treatment length (12 h vs. 06 h) in SD animals.

trol condition), length of treatment (6, 12, or 24 h), and repetition of treatment (first, second, third) as independent factors (Fig. 3).

Both SD, duration of sleep deprivation, and repetition of treatment had clear-cut effects on aggressive behaviour: SD animals were more aggressive than controls ($\underline{F} = 46.20$; d.f. 1,66; $p < 0.0001$), length of sleep deprivation increased aggressive behaviour following a dose–response curve ($F = 9.93$; d.f. 2,66; $p = 0.0002$), and the effects increased upon repetition of treatment ($F = 23.15$; d.f. 2,132; $p < 0.0001$). The dose–response effect and the sensitization upon repetition were present after SD, but not in stress-control conditions (treatment × duration interaction: $F = 10.61$; d.f. 2,66; $p = 0.0001$; treatment × repetition interaction: $F = 12.92$; d.f. 2,132; $p < 0.0001$).

The dose–response effect (length of SD) significantly interacted with the time–response effect (repetition of treatment) in enhancing aggressive behaviour ($F = 12.46$; d.f. 4,132; $p < 0.0001$), with maximal effects after the third 24-h SD, no effect after the first 6-h SD, and intermediate values in the other conditions.

Thus, all the independent factors interacted in influencing the aggressive behaviour of the animals (treatment × length × time interaction: $F = 7.86$; d.f. 4,132; $p < 0.0001$).

Results of post-hoc comparisons (Newman–Keuls critical ranges test) are shown in Fig. 2. No significant effects of repetition and length of treatment were detected in stress-control conditions.

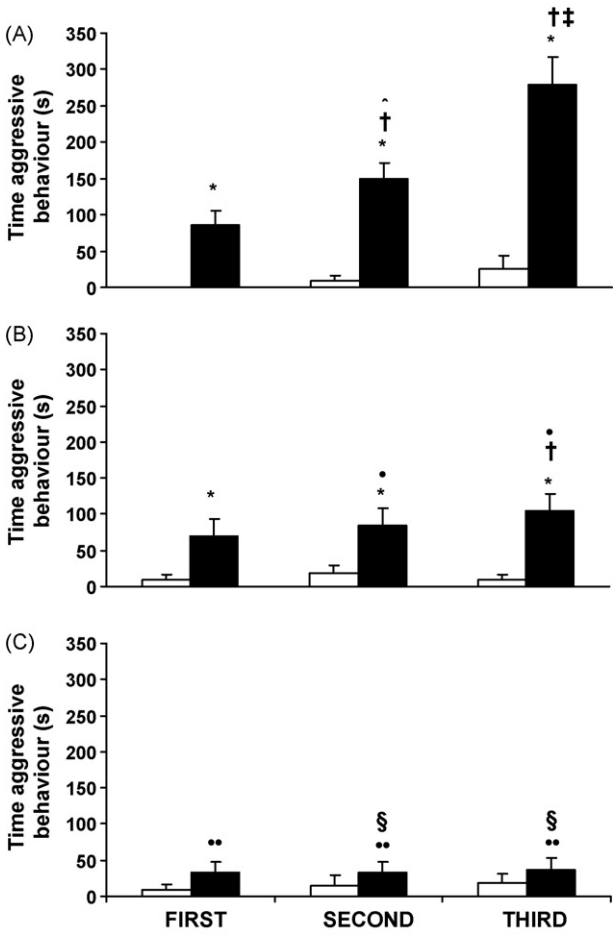

Fig. 3. Aggressive behaviour after repeated SD or stress-control condition (A = 24 h; B = 12 h; C = 6 h). Black bars are for SD animals, white bars for controls. Each bar is the group mean ($n = 12$), whiskers are standard error of means. Levels of significance of post-hoc comparisons (Newman–Keuls test) are shown as follows: $^{*}p < 0.001$, effect of treatment (SD vs. stress-control, same duration and repetition); $^{\wedge}p < 0.001$, effect of repetition (first vs. second) in SD animals; $^{\dagger}p < 0.001$, effect of repetition (first vs. third) in SD animals; $^{\ddagger}p < 0.001$, effect of repetition (second vs. third) in SD animals; $^{\bullet}p < 0.001$, effect of treatment length (24 h vs. 12 h) in SD animals; $^{\bullet\bullet}p < 0.001$, effect of treatment length (24 h vs. 06 h) in SD animals; $^{\S}p < 0.001$, effect of treatment length (12 h vs. 06 h) in SD animals.

3.3. Stress-control condition

Given the absence of an electrocorticographic evaluation of sleep we cannot exclude that the stress-control condition could have influenced the sleep–wake cycle in analogy to previous findings in rats [35]. To check for possible confounding effects of this limitation, following Silva et al. [46] we compared motor activity (12 h ActiMot observation) after 24 h of SD, of stress-control condition, and of home cage conditions (no stress) in three groups of 12 animals each. Results showed that SD significantly enhanced activity in respect to both stress-control and home cage conditions, which did not differ among themselves (Fig. 4).

A two-way ANOVA with motor activity as the dependent variable and time in the ActiMot and treatment (home cage, control stress, or sleep deprivation) as factors showed a significant effect of time ($F = 14.67$; d.f. 3,99; $p < 0.0001$) and a significant interaction of time and treatment ($F = 3.08$; d.f. 6,99; $p = 0.0083$). Post-hoc comparisons (Newman–Keuls test) confirmed that activity after SD was higher than activity both after control stress ($p = 0.0013$ at hours 0–3, $p = 0.057$ at hours 4–6) and in home cage conditions ($p = 0.0010$ at hours 0–3 and $p = 0.0009$ at hours 4–6). These two latter conditions did not significantly differ among themselves at any time point.

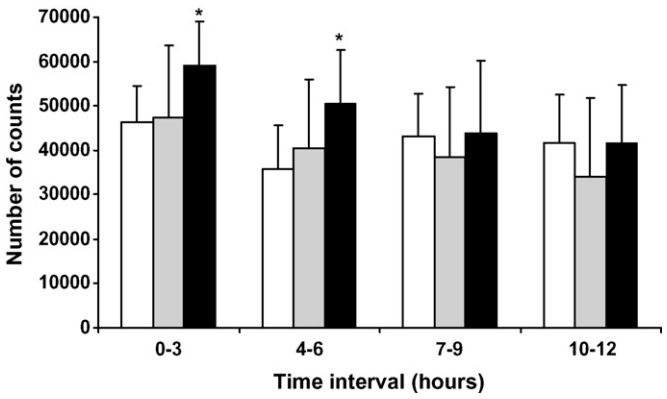

Fig. 4. Locomotor activity after 24 h of SD, stress-control, or in home cage conditions. Black bars are for SD animals, grey for stress-control, and white for home cage. Each bar is the group mean ($n = 12$) over 180 min; whiskers are standard deviations. Marked columns are significantly different from both stress-control and home cage groups (Newman–Keuls test, $^{*}p < 0.001$).

4. Discussion

SD, but not stress-control conditions, increased motor activity and aggressive behaviour in mice. These effects replicated in mice the model of mania after sleep deprivation which showed face, construct, and predictive validity in rats [36].

The behavioural activation followed a dose–response curve based on length of treatment (Figs. 2 and 3), with non-significant trends after 6 h, significant effects after 12 h, and maximal effects after 24 h. Moreover, the behavioural activation followed a time–response curve, with progressive sensitization to the effect of SD, but not of control stress, upon its repetition.

Sensitization to the effect of stress and kindling have been hypothesized as mechanisms to explain the phenomena of episode recurrence and regression, and cycle acceleration observed during the illness progression and worsening that characterizes bipolar disorder [43], and have been enriched up to now by clinical and preclinical observations of the effects of proximal and distal stressors [42].

The issue is of great clinical relevance, because the worsening of cyclicity is a key feature of bipolar illness, and can make it disabling, with significant associated comorbidity and suicide risk, impairment in functioning, and infringement of quality of life [15], and with prospective trials showing that patients affected by bipolar disorder are expected to spend, in the long term, roughly one-third of follow-up weeks with symptoms of varying degrees of severity despite medication-based psychiatric care [37,9].

To our best knowledge, here we provide the first animal model of sensitization to a stress (sleep deprivation) which

studies in human patients have consistently shown to be a major trigger of bipolar manic episodes, over the lifetime, in natural settings (see Section 1). The model has face validity, because the behavioural changes observed after treatment resemble symptoms of human mania (increased motor activity, increased aggressive behaviours). The model has construct validity, because it uses the same triggering factor (sleep deprivation) which has been consistently reported to trigger human mania [50,34,2,49,13]. Predictive validity (how the model responds to the same drugs utilized in humans) was not assessed here, but was high in rats, with haloperidol and lithium which antagonized the hyperactivity induced by sleep deprivation [26]. This model could then be useful to test the efficacy of antimanic and mood-stabilizer drugs, and to study the neurobiological correlates of manic reactions to sleep deprivation, in order to gain new insight into the pathophysiology of bipolar illness and to identify new targets for treatment.

Following this perspective, the first developments of the current model are expected from the study of the circadian clock. EEG power density during sleep is correlated with the neuronal activity in the suprachiasmatic nuclei (SCN), and both vigilance state transitions and sleep deprivation influenced SCN function [17] and gene expression in the whole brain: extended waking can affect basic cellular functions such as RNA and protein synthesis, neural plasticity, neurotransmission, and metabolism [48]. The homeostatic regulation of sleep need is under genetic control [21], and gene variants could then influence behaviours associated with sleep deprivation. Mice carrying a mutation in the CLOCK gene showed mania-like behavioural abnormalities, which were reverted by chronic lithium [44], and in human bipolar patients a mutation in the 3′ flanking region of CLOCK markedly influenced circadian rhythms of activity and sleep [5] and patterns of fMRI neural responses to emotional stimuli [6]. In mice pharmacological inhibition of glycogen synthase kinase 3 (GSK3) activity by lithium influenced the cyclical expression of core clock genes [32], and in human bipolar patients a polymorphism in the promoter gene for GSK 3-beta influenced response to lithium and core features of bipolar illness [7]. Moreover, in rodents SD markedly increased the activity of the brain monoamine systems targeted by psychotropic drugs active for bipolar disorder, i.e. serotonin [28] and dopamine [53]. These systems, in turn, talk back to the SCN and can potentiate circadian regulation by clock genes expression of the clock genes [19,52]. Further research is expected to improve insight into the pathophysiology of bipolar illness by clarifying these mechanisms.

An unresolved question is the possible specificity of the behavioural effects of REM versus slow wave sleep deprivation. According to the few data reported, the platform method reduces both stages of sleep in mice [46] and in rats [35], with an higher reduction of REM in all the available studies [35]. In our same SD conditions, however, slow wave sleep was decreased to 22% of baseline levels in mice [46]. Our study suggests then that sleep deprivation has a manic-inducing effect both in respect to control stress and in respect to home cage conditions, and that this effect is specific of sleep loss because control stress lacks it in respect to home cage (no stress) conditions, but further research is needed to disentangle the possible specific roles of REM and slow wave sleep deprivation.

Further research will also address the limitations of the present study, which include a length of the observation period into the ActiMot that was not sufficient to observe normalization of motor activity after the most powerful treatment (third sleep deprivation for 24 h, see Fig. 2 top right panel), the lack of assessment of predictive validity with drugs, and the lack of electroencephalographic measurements of sleep.

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