Sleep Medicine Reviews 84 (2025) 102179

Contents lists available at ScienceDirect

Sleep Medicine Reviews

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

Sleep abnormalities in mouse models of depression: a systematic review

Alberto Potenzieri [a,b,c], Andrea Escelsior [a,c], Gianluca Serafini [a,c], Antonio Uccelli [a,c], Antoine Adamantidis [d,1], Lino Nobili [a,e,*,1]

[a] Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, and Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy
[b] Brain Development and Disease Laboratory, Istituto Italiano di Tecnologia, Genoa, Italy
[c] IRCCS Ospedale Policlinico San Martino, Genova, Italy
[d] Zentrum für Experimentelle Neurologie, Department of Neurology, Inselspital University Hospital Bern, Bern, Switzerland
[e] Child Neuropsychiatry Unit, IRCCS Istituto Giannina Gaslini, Genoa, Italy

ARTICLE INFO

Handling Editor: Monica Andersen

Keywords:
Depression
Animal model
Stress
Rapid eye movement
Sleep fragmentation

ABSTRACT

Sleep disturbances are highly prevalent in people with major depressive disorder (MDD) and contribute to a vicious cycle that exacerbates both conditions. Electroencephalographic (EEG)-based sleep features of people with MDD are well described in systematic reviews and meta-analyses. However, sleep abnormalities in mouse models of MDD remain poorly characterized. We conducted a systematic review to evaluate the face validity of mouse models of MDD in relation to sleep alterations. Among the 22 articles we identified, the most consistently represented features of sleep disturbances in mouse models were increased rapid eye movement (REM) sleep and non-REM (NREM) sleep fragmentation. A blunted response to sleep deprivation was reported but only in a few studies and requires further investigation. Data regarding delta and theta power were limited and showed heterogeneous results. By providing a comprehensive summary of all mouse models in the field, our study serves as a resource to confirm the utility of animal models and guide researchers in studying sleep alterations in MDD.

1. Introduction

Major Depressive Disorder (MDD) is, along with anxiety disorders, the most common psychiatric disorder, affecting approximately 6 % of the population. It increases the risk of mortality by 60–80 % and significantly contributes to the global disease burden, ranking as one of the leading brain disorders causing disability-adjusted life years (DALYs) [1]. It is projected to become the leading global disease burden by 2030 [2].

Sleep and MDD are intricately linked. Sleep disturbances are highly prevalent among MDD patients, and independently, sleep alterations can predispose individuals to developing MDD [3]. Sleep disturbances are one of the nine diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) [4] and fall under the so-called "somatic" symptoms of MDD, alongside changes in body weight/-appetite, psychomotor agitation/retardation, and daily fatigue or loss of energy [5].

Numerous sleep alterations are described in MDD patients, including reduced total sleep time, non-rapid eye movement (NREM) sleep fragmentation, shortened latency to REM sleep, increased REM sleep density and alterations in power spectral density (PSD) [6–8], such as altered distribution and reduced delta power (also called slow wave activity, SWA), especially during the firsts NREM episodes. This finding supports the "S deficient hypothesis" of depression [9], which suggests that people with depression have impaired sleep pressure homeostatic mechanism (increased sleep need following increased time spent awake). This theory is also supposed to explain alteration in REM sleep, such as reduced REM sleep latency (due to REM disinhibition), and the therapeutic effect of sleep deprivation (SD).

Furthermore, insomnia is a predictive factor for depressive episodes and often represents an early sign of developing psychopathology [10,11]. The link between sleep disturbances and MDD is further supported at etiological levels. Indeed, both environmental [12] (e.g., stressors that contribute to both sleep disruption and low mood) and genetic factors [13–15], indicate a high degree of overlap between these conditions and suggest a common origin.

However, while sleep disturbances in MDD have been recognized for decades and are associated with suicidal ideation [10,11] and treatment resistance [3], this knowledge has led to limited clinical applications,

* Corresponding author. Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, and Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy.
E-mail address: lino.nobili@unige.it (L. Nobili).
[1] Contributed equally.

https://doi.org/10.1016/j.smrv.2025.102179
Received 17 March 2025; Received in revised form 16 September 2025; Accepted 18 September 2025
Available online 27 September 2025

Abbreviations

Chronic unpredictable mild stress CUMS
Corticosterone CORT
Designer receptors exclusively activated by designer drugs DREADD
Diagnostic and Statistical Manual of Mental Disorders DSM
Disability-adjusted life year DALY
Electroencephalography EEG
Electromyography EMG
Major depressive disorder MDD
Non-rapid eye movement NREM
Power spectral density PSD
Preferred reporting items for systematic reviews and meta-analyses PRISMA
Rapid eye movement REM
Restraint stress RS
Sleep deprivation SD
Slow-wave activity SWA
Social defeat stress SDS
Zeitgeber time: ZT

and none of the identified sleep features have proven robust enough to serve as biomarkers for improving MDD diagnosis and treatment.

At the mechanistic level, basic preclinical research can be instrumental in disentangling this complex relationship. Despite their limitations, animal models remain the gold standard for investigating molecular and circuit mechanisms in brain disorders, including MDD [16–18]. Although rat models of depression conceptually overlap with those in mice, here we chose to focus only on the mouse species due to its prevalent use in neuroscience research in the last decade, mainly because of lower costs and greater genetic accessibility [19]. Importantly, mouse models of depression exhibit phenotypes consistent with sleep disorders [20]. However, a comprehensive evaluation of their face validity in replicating the sleep disturbances observed in MDD is lacking in the literature.

In this context, we summarize the sleep alterations observed in validated mouse models of MDD, focusing on original research articles employing electroencephalography-electromyography (EEG-EMG) based methods. Although clinical evidence indicates that chronic stress is more relevant to the development of MDD [12,21], we also included studies involving acute stress paradigms, as they may offer relevant mechanistic insights into the early phases of the disorder and reliably induce anxiety-like behaviour in mice [22], a common comorbidity in people with MDD [23]. Our aim is to assess their face validity in modelling this aspect of human depression and to provide guidance for future research aimed at a deeper understanding of the neural circuit and molecular correlates of sleep disturbances in mouse model of MDD, ultimately paving the way for improved therapeutic approaches.

2. Methods

2.1. Search strategy

This systematic review was conducted in accordance with the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) [24] guidelines. It includes articles published up to and including August 2024 in PubMed/MEDLINE and Scopus databases combining the keyword “sleep” with the terms related to mouse models of depression, using the following logic:

1) “sleep” AND “mouse model” AND “depression” OR “depressive"
2) “sleep” AND “chronic social defeat stress” OR “chronic mild stress” OR “corticosterone” AND “mouse model” OR “chronic restraint stress” OR “chronic social stress” OR “unpredictable chronic mild stress” OR “social defeat stress” OR “learned helplessness")

2.2. Inclusion and exclusion criteria

Literature search and abstract screening were performed by the first reviewer (AP) while data eligibility, inclusion and extraction from the first two reviewers (AP and AE) independently.

During the initial screening, titles and abstracts were reviewed and research articles were excluded as wrong publication type (e.g., reviews, commentaries, editorials, book chapters), wrong population (e.g., studies conducted in species other than mice, or mouse models not related to MDD), wrong outcome (e.g., studies that did not assess sleep-related parameters; n = 322), wrong study design (e.g. lack of appropriate control groups), or were in a foreign language (i.e., not in English).

Then, full length articles were assessed for eligibility according to the following specific criteria.

Studies were included if they met the following criteria: published in full in peer-reviewed journals; *in vivo* studies performed in adult mice using EEG-EMG based sleep measure; preclinical studies using proper control mice; preclinical studies using either biological, genetic, pharmacological or behavioural model-related to depression.

Studies were excluded if they were: clinical studies; in species other than mouse; in mouse models of neurodevelopmental or neurodegenerative disorders; articles not differentiated between REM (or paradoxical) and NREM sleep; articles reporting no original data (e.g., reviews, meta-analyses, commentaries, or book chapters).

2.3. Quality assessment

The Syrcle of bias tool [25] was used to assess the quality of individual articles. Each study was first evaluated by a primary reviewer evaluating their risk of bias across 10 items and then cross-checked by a second reviewer. Discrepancies were resolved through discussion. Each item could be scored as low, high, or unclear risk of bias. A higher final total score indicates a lower risk of bias.

2.4. Data extraction

The following data based on EEG-EMG recording were extracted: time spent in each sleep stage (irrespective of whether it was expressed as percentages, total time, or relative values), sleep bout (or episode) number and duration, delta and theta power, sleep transition stage-specific transition, REM latency. To ensure uniformity between studies, only data of the 24-h or 12-h light or dark phase were used to analyse time spent in sleep stages, bout number and duration. As more relevant to MDD pathophysiology, throughout the manuscript we refer to articles involving chronic stress mouse models (i.e. at least one week of stress exposure). The effects of acute stress are described in a dedicated paragraph, in which we report sleep data for a maximum of 6 h after stress. When performed, we also described sleep deprivation (SD) or pharmacological, chemogenetic and optogenetic manipulation aimed at improving sleep in the depression mouse models. It should be noted that we referred to the phenotype of susceptible mice when referring to articles using the social defeat stress (SDS) paradigm.

3. Results

3.1. Study selection and characteristics

In total, 4546 articles were found in electronic databases. After duplicate removal and screening of the title/abstract, 60 studies were assessed for eligibility, and 22 met our inclusion and exclusion criteria

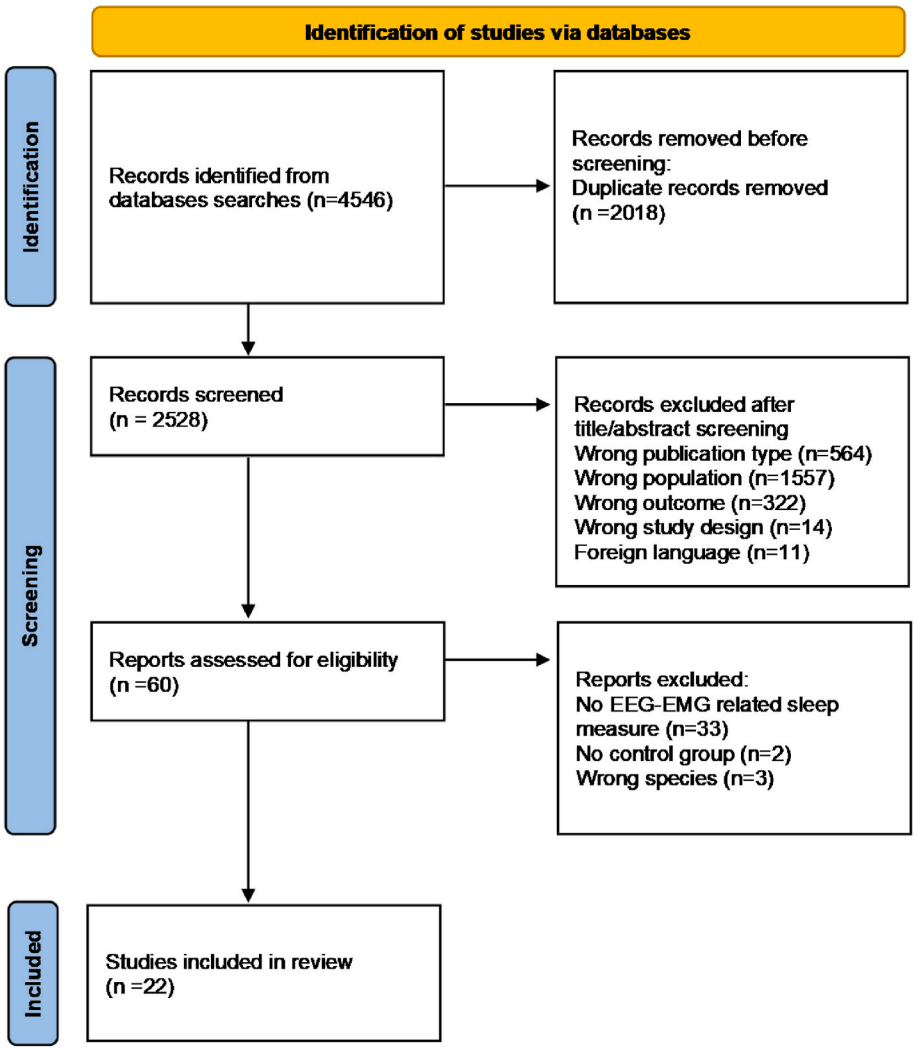

Fig. 1. Flowchart of the identification, screening and inclusion strategy for the articles selection. EEG-EMG: Electroencephalography- Electromyography.

(Fig. 1and Supplementary File 1).

In this systematic review, the following mouse models were considered to describe their sleep alterations (Table 1). Two studies used the acute restraint stress (RS) model [26,27], two used chronic RS [28, 29], and one study employed a variant that also included a water immersion procedure [30]. RS is widely used and assumes that prolonged, predictable, unpleasant situations (likely mimicking abuse, loss of control, or domination) induce depression-like behaviours. RS is implemented by placing a mouse in a cylindrical tube for at least 1–2 h per day for 2–3 weeks. The most striking feature of this model is the development of anxiety, although anhedonia-like behaviour (measured by sucrose preference test) and passive coping behaviour are also reported [31].

Two studies used the chronic unpredictable mild stress (CUMS) model of MDD [32,33]. The CUMS paradigm assumes that prolonged, varied (and unpredictable) stressors can induce MDD in human subjects. The CUMS model is implemented by exposing mice to different types of stressors (e.g., cage tilt, water/food deprivation, SD) in a randomized manner for variable durations, depending on the protocol [34]. It induces a chronic stress phenotype characterized by anhedonia-like behaviour (its most prominent feature), passive coping behaviour, and anxiety.

Six studies [35–40] used acute SDS, and five studies[38,41–44] used chronic SDS models. The chronic SDS model assumes that depression can be triggered by continuous, intense social conflict (e.g., bullying or abuse). Although there are some minor variations between protocols, it involves repeated exposure to an aggressive mouse for 10 consecutive days. Each defeat session lasts 5–10 min, followed by 24 h of sensory contact through a perforated divider [45]. This model induces strong social avoidance, anhedonia-like behaviour, and anxiety.

Two studies [46,47] used helpless mice, also known as H/Rouen mice, developed at Rouen University. This mouse model was created through selective breeding of mice that showed extreme responses in the tail suspension test, a measurement of passive coping behaviour. Helpless mice were bred from individuals exhibiting very high immobility scores in this test, while non-helpless mice were bred from those with exceptionally low immobility scores. This model is based on the genetic heritability of depression, in contrast to other models. Helpless mice exhibit strong passive coping behaviour also in the force swim test, anhedonia-like behaviour, and anxiety.

One study used corticosterone [48] (CORT) supplementation as a mouse model of depression. CORT models exhibit both anxiety and depression [18] and are useful for studying stress responses independently of specific stressors.

One study [49] used olfactory bulbectomy as a mouse model of depression. This model is based on the observation that depressive patients sometimes lose their sense of smell. Bulbectomy replicates core symptoms of depression, including passive coping behaviour, and heightened anxiety [50].

Table 1
Summary of the mouse model and sleep variables analysed in the articles included in the review. *sleep stage not specified in the manuscript.

Study	Mouse Model	Sleep variables
El Yacoubi et al. 2003 [46]	Helpless	Time spent in sleep stages; REM latency
El Yacoubi et al. 2012[47]	Helpless	Time spent in sleep stages
Feng et al. 2020 [35]	Acute social defeat stress	Time spent in sleep stages
Fuji et al. 2019 [36]	Acute social defeat stress	Time spent in sleep stages
Henderson et al. 2017 [38]	Acute/Chronic social defeat stress	Time spent in sleep stages; bouts number and duration; power spectral density
Henderson et al. 2024 [37]	Acute social defeat stress	Time spent in sleep stages
Le Dantec et al. 2014 [48]	Chronic corticosterone administration	Time spent in sleep stages; bouts number and duration; stage transition; power spectral density; REM latency
McCullough et al. 2021 [43]	Chronic social defeat stress	Time spent in sleep stages
Meerlo et al 2001 [27]	Acute restraint stress	Time spent in sleep stages
Nollet et al. 2019 [33]	Chronic unpredictable mild stress	Time spent in sleep stages; bouts number and duration; power spectral density
Olini et al. 2017 [51]	Chronic social defeat stress	Time spent in sleep stages; power spectral density; sleep deprivation
Radwan et al. 2021(a) [41]	Chronic social defeat stress	Time spent in sleep stages; bouts number and duration; stage transition; sleep deprivation;power spectral density
Radwan et al. 2021(b) [44]	Chronic social stress defeat	Time spent in sleep stages; bouts number and duration; stage transition; sleep deprivation;power spectral density
Smith et al. 2023 [39]	Acute social defeat stress	Time spent in sleep stages
Wells. et al. 2017 [42]	Chronic social defeat stress	Time spent in sleep stages; bouts number;power spectral density;REM latency
Xia et al. 2023 [29]	Chronic restraint stress	Time spent in sleep stages; bouts number and duration; REM latency
Xu et al. 2023 [26]	Acute restraint stress	Time spent in sleep stages
Yao et al. 2023 [32]	Chronic unpredictable mild stress	Time spent in sleep stages; bouts number and duration; stage transition;power spectral density*
Yasugaki et al. 2019 [30]	Water immersion and chronic restraint stress	Time spent in sleep stages; bouts number and duration; REM latency; power spectral density
Yu et al. 2022 [40]	Acute social defeat stress	Time spent in sleep stages
Yuan et al. 2020 [49]	Olfactory bulb ablation	Time spent in sleep stages
Zhang et al., 2024 [28]	Chronic restraint stress	Time spent in sleep stages; bouts number and duration; power spectral density

3.2. Time spent in wake, NREM, and REM

We first reviewed the total time spent in wakefulness, NREM sleep and REM sleep during the light phase, dark phase, or over a 24-h period in all models relative to the controls (Fig. 2, Table 2).

Across a 24-h recording period, nine studies analysed the time spent awake or asleep in mouse models of depression. Among them, five studies (56 %) reported a decrease in wakefulness [30,42,43,46,48]. Two studies found no significant differences in wakefulness [28,29], while the remaining two focused on total sleep time and similarly reported no changes compared to controls [32,33] (for a total of 44 %, grouped with the other two in Fig. 2). No study found an increase in time spent awake across 24 h. Eight studies analysed NREM sleep across 24 h: four studies (50 %) observed an increase in time spent in NREM sleep [30,42,43,46], while another three studies (38 %) found no significant differences [28,32,33]. One study (12 %) reported a decrease in NREM sleep [29]. Finally, when examining REM sleep, seven studies (88 %) reported an increase in time spent in REM sleep[28–30,33,42,43,46] , while one study (12 %) found no significant differences [32]. Notably, no studies observed a decrease in REM sleep during the 24-h period. Altogether, these results indicate that across 24 h, mouse models of MDD exhibit increased time spent in REM and, to a lesser extent, in NREM sleep.

During the light phase, which represents the resting period for rodents, eight studies analysed time spent awake. Five studies (62 %) found no significant differences in wakefulness compared to controls [28,30,41,44,51]. However, the study using the bulbectomy model of depression (13 %) reported a decrease in wakefulness [49], and two studies (one using RS and one using CUMS, 25 %) observed an increase in wakefulness [29,32]. For NREM sleep, five studies (63 %) reported no significant changes [28,30,44,49,51], while three studies (37 %) observed a reduction in time spent in this stage [29,32,41]. No study found an increase in time spent in NREM during the light phase. REM sleep was evaluated in eight studies, with six studies (75 %) finding no significant differences between groups [29,30,32,41,44,51] and two studies (25 %) reporting an increase in REM sleep during the light phase [28,49]. No study found decreased time spent in REM during the light phase. Altogether, these studies fail to consistently indicate specific changes in sleep macrostructure during the light phase in mouse models of MDD.

In the dark phase, which corresponds to the active period for mice, wakefulness was evaluated in 10 studies. Three studies (30 %) observed a decrease in wakefulness [30,38,48], while seven studies (70 %%) found no significant differences compared to controls [28,29,32,41,44,49,51]. NREM sleep was analysed in 10 studies, with three (30 %) reporting an increase [30,38,48]. The remaining seven studies (70 %) found no significant differences in NREM sleep [28,29,32,41,44,49,51]. Finally, in 10 studies evaluating REM sleep during the dark phase, four studies (40 %) reported an increase in time spent in REM sleep [28–30,38], five studies (50 %) found no differences [32,41,44,49,51], and one study (10 %) observed a decrease [48]. Overall, these results suggest increased REM sleep and NREM sleep in mouse models of MDD during the dark phase.

Eight articles [26,27,35,37,39,40,47] cannot be included in this analysis because they used acute mouse model of stress (described below) or they did not report statistical analysis for the cumulative or total % time spent across 24-h, for 12-h light or 12-h dark phase

3.3. Bouts number and duration

To gain insight into the mechanisms driving changes in sleep stages in mouse models of depression, we reviewed studies characterizing number (Fig. 3 and Table 3) and duration (Fig. 4 and Table 4) of stage-specific bouts (episodes).

3.4. Bouts number

Four studies analysed bouts number over a 24-h period. None of the studies found any differences in both wake or NREM bouts numbers compared to controls [28–30,42]. Conversely, all of them reported increase REM bouts number (Table 3).

Six studies (Nollet et al. measured only NREM and REM bouts [33]) analysed bouts number during the 12-h light phase. Regarding wake bout numbers, three studies (60 %) reported an increase [28,29,41], while two (40 %) found no changes [30,44]. For NREM bouts, four

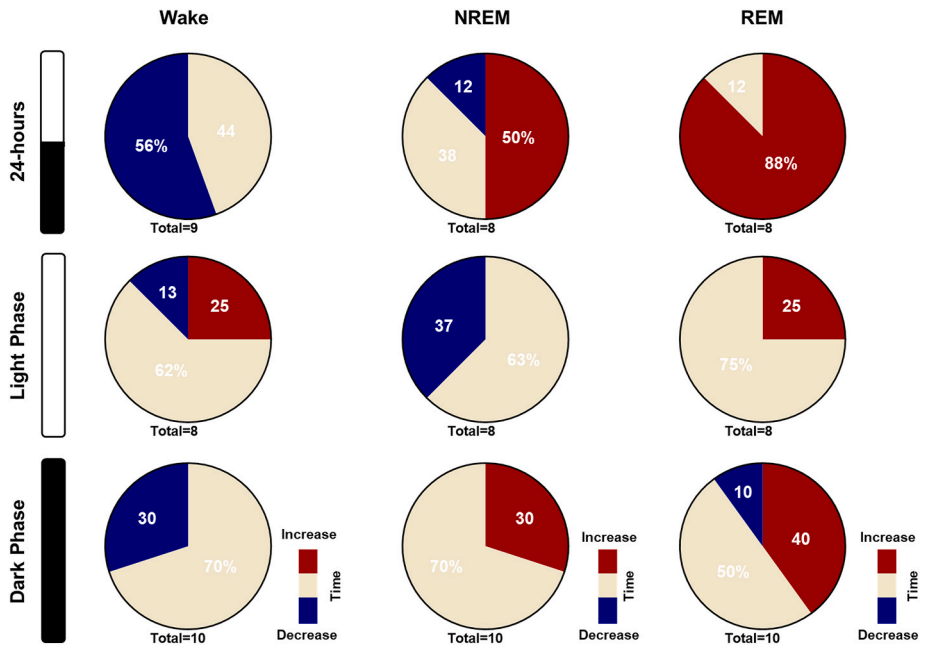

Fig. 2. Pie chart showing significant changes described in the articles included in the review for time spent in wake, NREM and REM sleep during 24-h, 12-h light phase or 12-h dark phase. The total number of the study used for creating the graph is typed under the figure, while the % is written inside. Note that both absolute and relative measure of time were used for the analysis. NREM: Non-rapid eye movement; REM: rapid eye movement.

Table 2
Study used for creating Fig. 2. Symbol was used to indicate higher, lower or same amount of time spent in that specific sleep stages in comparison to control. NA: Not available; NREM: Non-rapid eye movement; REM: rapid eye movement.

Study	Mouse Model	Wake			NREM			REM		
		24-h	Light phase	Dark phase	24-h	Light phase	Dark phase	24-h	Light phase	Dark phase
El Yacoubi et al., 2003[46]	Helplesss	↓	NA	NA	↑	NA	NA	↑	NA	NA
Henderson et al., 2017[38]	Chronic social defeat stress	NA	NA	↓	NA	NA	↑	NA	NA	↑
Le Dantec et al., 2014[48]	Chronic corticosterone	↓	NA	↓	NA	NA	↑	NA	NA	↓
McCullough et al., 2021[43]	Chronic social defeat stress	↓	NA	NA	↑	NA	NA	↑	NA	NA
Nollet et al., 2019[33]	Chronic unpredictable mild stress	=	NA	NA	=	NA	NA	↑	NA	NA
Olini et al., 2017[51]	Chronic social defeat stress	NA	=	=	NA	=	=	NA	=	=
Radwan et al., 2021 (a)[41]	Chronic social defeat stress	NA	=	=	NA	↓	=	NA	=	=
Radwan et al., 2021 (b)[44]	Chronic social defeat stress	NA	=	=	NA	=	=	NA	=	=
Wells. et al. 2017[42]	Chronic social defeat stress	↓	NA	NA	↑	NA	NA	↑	NA	NA
Xia et al., 2023[29]	Chronic restraint stress	=	↑	=	↓	↓	=	↑	=	↑
Yao et al., 2023[32]	Chronic unpredictable mild stress	=	↑	=	=	↓	=	=	=	=
Yasugaki et al., 2019[30]	Water immersion and chronic restraint stress	↓	=	↓	↑	=	↑	↑	=	↑
Yuan et al., 2020[49]	Olfactory bulb ablation	NA	↓	=	NA	=	=	NA	↑	=
Zhang et al. 2024[28]	Chronic restraint stress	=	=	=	=	=	=	↑	↑	↑

studies (67 %) observed an increase in bout numbers [28,29,33,41], while two (33 %) reported no changes [30,44]. For REM bouts, three studies [28,29,33] reported an increase in the number of bouts (50 %), while the other three found no differences [30,41,44].

Seven studies (Nollet et al. measured only NREM and REM bouts [33]) analysed bouts number during the 12-h dark phase. Two studies (33 %) reported an increase in wake bout numbers [38,48], while four others found no differences [28,30,41,44]. For NREM bouts, three studies (43 %) [33,37,48] reported an increase in the number of bouts, while four studies found no differences [28,30,41,44]. For REM bouts, four studies (57 %) [28,30,33,37] reported an increase in the number of bouts, while the other three [41,44,48] found no differences.

3.5. Bouts duration

Zhang et al. [28] analysed bout duration over a 24-h period and found no significant difference between wake and REM bout duration, but a decrease in NREM bout duration in chronic RS mice (Table 4).

Five studies (Nollet et al. measured only NREM and REM bouts [33]) analysed bouts duration during 12-h light phase. One study (25 %)

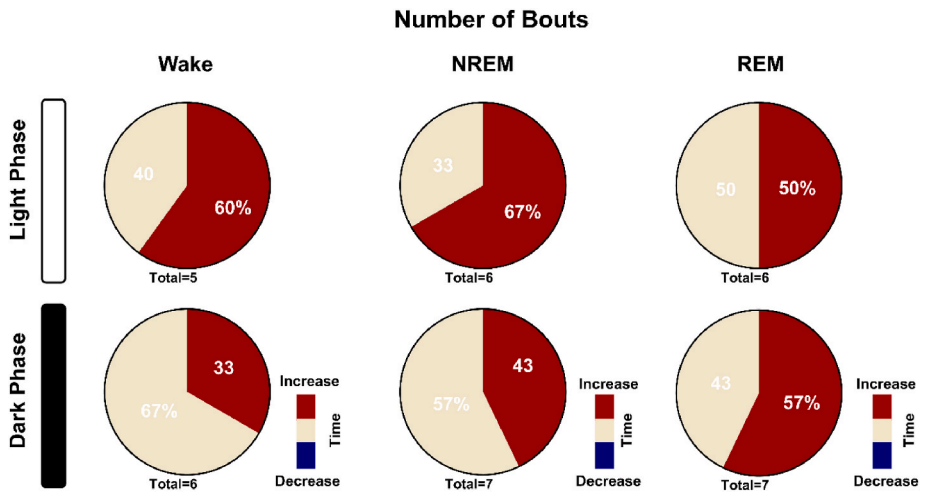

Fig. 3. Pie chart showing significant changes described in the articles included in the review for number of bouts during wake, NREM and REM sleep during 12-h light phase or 12-h dark phase. The total number of the study used for creating the graph is typed under the figure, while the % is written inside. Note that both absolute and relative measure of bouts number were used for the analysis. NREM: Non-rapid eye movement; REM: rapid eye movement.

Table 3
Study used for creating Fig. 3. Symbol was used to indicate higher, lower or same number of bouts in that specific sleep stages in comparison to control. NREM: Non-rapid eye movement; REM: rapid eye movement.

Study	Mouse Model	Wake			NREM			REM		
		24-h	Light phase	Dark phase	24-h	Light phase	Dark phase	24-h	Light phase	Dark phase
Henderson et al. 2017 [38]**	**Chronic social defeat stress**	**NA**	**NA**	↑	**NA**	**NA**	↑	**NA**	**NA**	↑
Le Dantec et al. 2014 [48]***	**Chronic corticosterone**	**NA**	**NA**	↑	**NA**	**NA**	↑	**NA**	**NA**	=
Nollet et al. 2019 33* **	**Chronic unpredictable mild stress**	**NA**	**NA**	**NA**	**NA**	↑	↑	**NA**	↑	↑
Radwan et al. 2021(a) [41]**	**Chronic social defeat stress**	**NA**	↑	=	**NA**	↑	=	**NA**	=	=
Radwan et al. 2021(b) [44]***	**Chronic social defeat stress**	**NA**	=	=	**NA**	=	=	**NA**	=	=
Wells. et al. 2017[42]***	**Chronic social defeat stress**	=	**NA**	**NA**	=	**NA**	**NA**	↑	**NA**	**NA**
Xia et al. 2023 [29]***	**Chronic restraint stress**	=	↑	**NA**	=	↑	**NA**	↑	↑	**NA**
Yasugaki et al. 2019 [30]*	**Water immersion and chronic restraint stress**	=	=	=	=	=	=	↑	=	↑
Zhang et al. 2024 [28]*	**Chronic restraint stress**	=	↑	=	=	↑	=	↑	↑	↑

*4 s epoch scoring; **5 s epoch scoring; ***10 s epoch scoring.

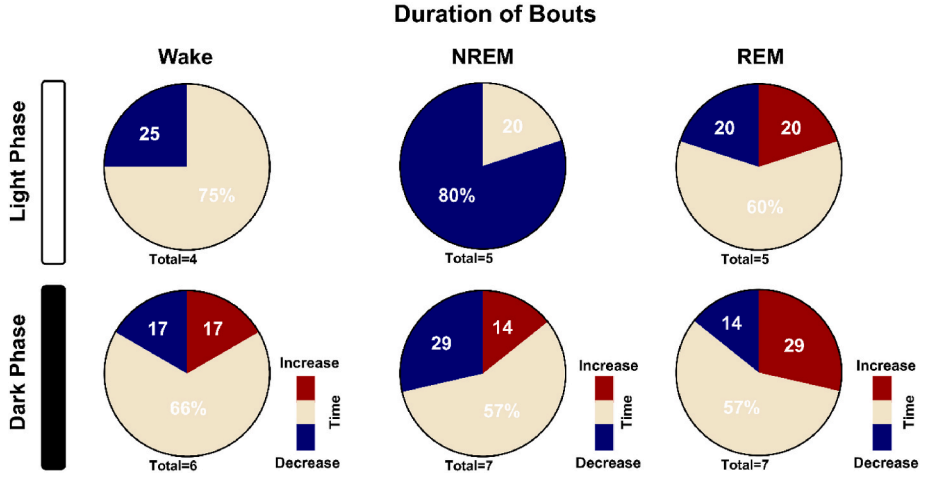

Fig. 4. Pie chart showing significant changes described in the articles included in the review for duration of bouts during wake, NREM and REM sleep during 12-h light phase or 12-h dark phase. The total number of the study used for creating the graph is typed under the figure, while the % is written inside. Note that both absolute and relative measure of bouts duration were used for the analysis. NREM: Non-rapid eye movement; REM: rapid eye movement.

Table 4
Study used for creating Fig. 4. Symbol was used to indicate higher, lower or same bouts duration in that specific sleep stages in comparison to control. NREM: Non-rapid eye movement; REM: rapid eye movement.

Study	Mouse Model	Wake			NREM			REM		
		24-h	Light phase	Dark phase	24-h	Light phase	Dark phase	24-h	Light phase	Dark phase
Henderson et al. 2017 [38]**	**Chronic social defeat stress**	**NA**	**NA**	↑	**NA**	**NA**	=	**NA**	**NA**	=
Le Dantec et al. 2014 [48]***	**Chronic corticosterone**	**NA**	**NA**	↓	**NA**	**NA**	↑	**NA**	**NA**	↓
Nollet et al. 2019 [33]***	**Chronic unpredictable mild stress**	**NA**	**NA**	**NA**	**NA**	↓	↓	**NA**	↑	↑
Radwan et al. 2021(a) [41]***	**Chronic social defeat stress**	**NA**	=	=	**NA**	↓	=	**NA**	=	=
Radwan et al. 2021(b) [44]***	**Chronic social defeat stress**	**NA**	=	=	**NA**	=	=	**NA**	=	=
Xia et al. 2023 [29]***	**Chronic restraint stress**	**NA**	=	=	**NA**	↓	=	**NA**	=	↑
Zhang et al. 2024 [28]*	**Chronic restraint stress**	=	↓	=	↓	↓	↓	=	↓	=

*4 s epoch scoring; **5 s epoch scoring; ***10 s epoch scoring.

found a reduction in wake bouts duration [28], while other three (75 %) reported no changes [29,41,44]. For NREM bouts, four studies (80 %) observed a decreased bout durations [28,29,33,41], while one (20 %) reported no change [44]. For REM sleep, one study (20 %) reported increased REM bout duration [33], one found decreased duration [28], and the other three (60 %) reported no changes [29,41,44].

Seven studies (Nollet et al. measured only NREM and REM bouts [33]) analysed bouts duration during the 12-h dark phase. Regarding wake bout duration, one study (17 %) reported a decrease [48]; one found an increase [38], and the other four (66 %) found no changes [28,29,41,44]. Two studies (29 %) observed decreased NREM bout duration [28,33], one reported an increased [48] while the other four (57 %) found no changes [29,38,41,44]. Regarding REM sleep bouts duration two studies [29,33] reported increased REM bout duration, one study [48] found a decrease, and the remaining four studies (57 %) found no changes [28,38,41,44].

Altogether, these results indicate an increased number of REM bouts with similar duration as well as increased number of NREM bouts with shorter duration (especially during light phase) in mouse model of MDD.

3.6. Sleep stages transitions

Only two studies evaluated sleep stage transitions in MDD mouse model during dark and light conditions [41,48]. During the dark phase, both articles observed an increased number of transitions from NREM sleep to wakefulness and vice versa, with no differences in transitions to and from REM sleep [41,48]. During the light phase, Radwan et al. found that mice exposed to chronic SDS exhibited an increased number of transitions between NREM to wake and vice versa [41]. Le Dantec et al. using corticosterone model also found an increased number of transitions from NREM to wake, but they reported a reduced number of transitions from NREM to REM and from REM to wake [48].

3.7. Power spectral density

PSD in specific frequency bands during brain states is known to reflect sleep quality. To evaluate this, we reviewed findings from studies analysing PSD during different brain states and activity phases, focusing on delta (Fig. 5 and Table 5) and theta (Fig. 6 and Table 6) waves due to their prominent roles in NREM and REM sleep, respectively.

3.8. Delta power

Across 24-h period, only Le Dantec et al. evaluate delta power and found no change during wake, NREM or REM sleep in chronic corticosterone treated mice [48] (Table 5).

During 12-h light phase, in wakefulness, two (67 %) studies found no differences in delta power while Yasugaki et al. [30] reported an increase. During NREM sleep, four studies (64 %) reported no changes in delta power compared to control conditions [33,41,44,48], one study found an increase [38], while one study [30] observed a decrease. During REM phase, two studies (67 %) found decrease delta power [28,

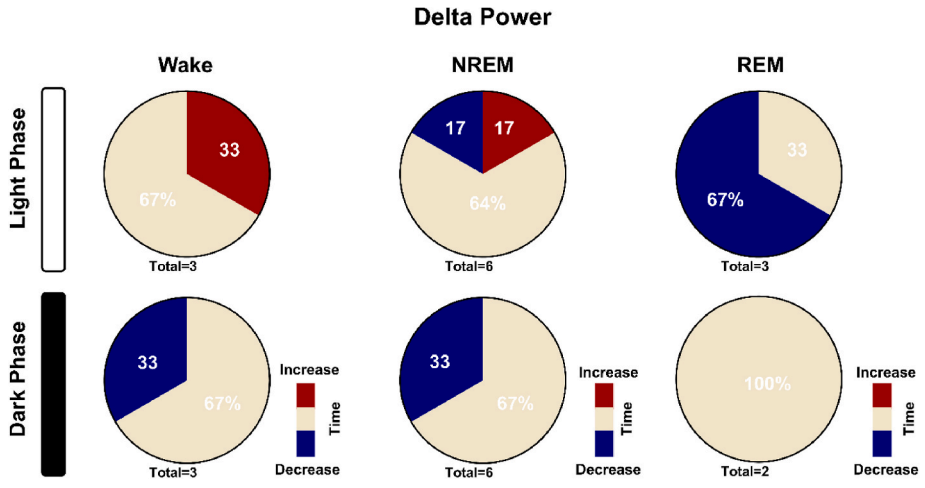

Fig. 5. Pie chart showing significant changes described in the articles included in the review for delta power during wake, NREM and REM sleep during 12-h light phase or 12-h dark phase. The total number of the study used for creating the graph is typed under the figure, while the % is written inside. Note that both absolute and relative measure of power were used for the analysis. NREM: Non-rapid eye movement; REM: rapid eye movement.

Table 5
Study used for creating Fig. 5. Symbol was used to indicate higher, lower or same delta power in that specific sleep stages in comparison to control. NA: Not available; NREM: Non-rapid eye movement; REM: rapid eye movement.

Study	Mouse Model	Wake			NREM			REM		
		24-h	Light phase	Dark phase	24-h	Light phase	Dark phase	24-h	Light phase	Dark phase
Henderson et al. 2017 [38]	**Chronic social defeat stress**	**NA**	**NA**	**NA**	**NA**	↑	=	**NA**	**NA**	**NA**
Le Dantec et al. 2014 [48]	**Chronic corticosterone**	=	=	=	=	=	=	=	=	=
Nollet et al. 2019 [33]	**Chronic unpredictable mild stress**	**NA**	**NA**	**NA**	**NA**	=	=	**NA**	**NA**	**NA**
Radwan et al. 2021(a) [41]	**Chronic social defeat stress**	**NA**	**NA**	**NA**	**NA**	=	=	**NA**	**NA**	**NA**
Radwan et al. 2021(b) [44]	**Chronic social defeat stress**	**NA**	=	=	**NA**	=	↓	**NA**	**NA**	**NA**
Yasugaki et al. 2019 [30]	**Water immersion and chronic restraint stress**	**NA**	↑	↓	**NA**	↓	↓	**NA**	↓	=
Zhang et al. 2024 [28]	**Chronic restraint stress**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	↓	**NA**

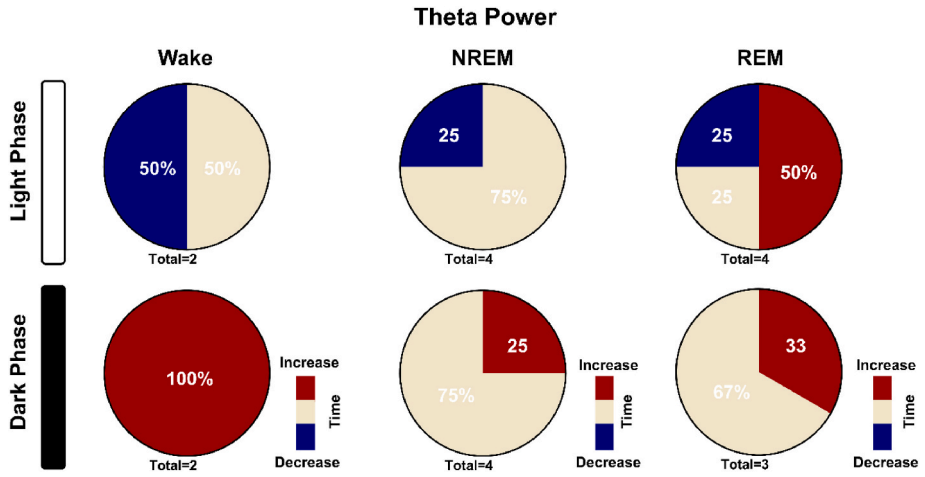

Fig. 6. Pie chart showing significant changes described in the articles included in the review for theta power during wake, NREM and REM sleep during 12-h light phase or 12-h dark phase. The total number of the study used for creating the graph is typed under the figure, while the % is written inside. Note that both absolute and relative measure of power were used for the analysis. NREM: Non-rapid eye movement; REM: rapid eye movement.

Table 6
Study used for creating Fig. 6. Symbol was used to indicate higher, lower or same theta power in that specific sleep stages in comparison to control. NA: Not available; NREM: Non-rapid eye movement; REM: rapid eye movement.

Study	Mouse Model	Wake			NREM			REM		
		24-h	Light phase	Dark phase	24-h	Light phase	Dark phase	24-h	Light phase	Dark phase
Henderson et al. 2017 [38]	**Chronic social defeat stress**	**NA**	**NA**	**NA**	**NA**	↓	=	**NA**	**NA**	**NA**
Le Dantec et al. 2014 [48]	**Chronic corticosterone**	=	=	=	↑	=	↑	=	=	=
Nollet et al. 2019 [33]	**Chronic unpredictable mild stress**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	↑	↑
Radwan et al. 2021(a) [41]	**Chronic social defeat stress**	**NA**	**NA**	**NA**	**NA**	=	=	**NA**	**NA**	**NA**
Yasugaki et al. 2019 [30]	**Water immersion and chronic restraint stress**	**NA**	↓	↑	**NA**	=	=	**NA**	↓	=
Zhang et al. 2024 [28]	**Chronic restraint stress**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**	↑	**NA**

30], while Le Dantec et al. reported no change [48].

During 12-h dark phase, two studies (67 %) found no change in delta power between control and mouse models during wakefulness [41,48], while Yasugaki et al. reported a decrease [30]. During NREM sleep, two studies [30,41] reported decrease delta power, while other 4 studies reported no significant changes [33,38,41,48]. Finally, only two studies assessed delta power during REM [30,48], without finding any significant changes compared to control conditions.

3.9. *Theta power*

Across 24-h period, only Le Dantec et al. evaluate theta power during wake, NREM or REM sleep. Although they found no difference during wake or REM sleep, they reported a significant increase in theta power during NREM [48] (Table 6).

During 12-h light phase, only two studies evaluated theta power during wake state. While Le Dantec [48] et al. reported no difference, Yasugaki et al. reported decreased theta power in mouse model [30].

During NREM, Henderson et al. [38] found decrease theta power after chronic SDS, while other three studies (75 %) reported no significant difference [30,41,48]. During REM, two studies (50 %) found increased theta power [28,33], one study decrease [30] and one study no change [48].

During 12-h dark phase, Le Dantec et al. reported similar theta power in mouse model of MDD, while only Yasugaki et al. found an increase in mouse model compared to control [30,48]. During NREM, three studies (75 %) reported no significant differences [30,38,41] while Le Dantec et al. [48] found again an increase. During REM, two studies (67 %) reported similar theta power [30,48] between mouse model of MDD and control, while Nollet et al. [33] found an increase in MDD.

3.10. REM latency

As a possible biomarker in MDD [52], five studies quantified REM sleep latency, defined as the time interval between the onset of sleep and the first occurrence of REM sleep.

Three studies found reduced REM sleep latency in mouse models of MDD [42,46,47], while two studies [30,48] found no difference in REM sleep latency compared to control.

3.11. Sleep deprivation

SD is of strong interest to the field of depression because it is well known to increase positive mood under acute administration [53] and could, therefore, have therapeutic applications. However, only three studies have examined the role of subsequent SD in mouse models of depression.

Radwan et al.[41,44] performed a 4-h SD using a platform that woke the mice through randomized electric pulses. They found that sleep-deprived chronic SDS mice exhibited impaired homeostatic responses and NREM sleep response post-SD. Indeed, the SWA, which reflects the intensity of NREM sleep, was not significantly increased by SD in chronic SDS mice compared to controls.

Olini et al. [51] investigated the effects of a 4-h SD paradigm induced by placing novel objects in the cage. Similarly to Radwan [44], they found that chronic SDS mice showed a blunted NREM response with decreased SWA during recovery sleep. However, these mice also exhibited an increase in REM sleep during recovery.

3.12. Interventions aimed at improving sleep

Two studies performed pharmacological interventions [32,42] and one study utilized chemogenetic [28] approaches to rescue sleep problems in mouse models of depression.

Yao et al. [32] found that chronic intraperitoneal melatonin treatment was able to rescue reduced NREM sleep, shortened total sleep time, as well as other parameters of sleep efficiency. For example, sleep latency, sleep bout duration, and a normalization in the increased alpha and beta power were observed in the CUMS mouse model after melatonin treatment. Importantly, melatonin also normalized depressive-like behaviours (evaluated with sucrose preference and tail suspension tests). This indicates that improving sleep paramaters in mouse models of depression alleviates their depressive-like symptoms.

Wells et al. [42] reported the use of the kappa-opioid receptor antagonist JDTic to mitigate sleep alterations in chronic SDS mice. They observed a rescue in the number of REM sleep bouts, but no significant improvement was noted in other EEG parameters.

Zhang et al. [28] used a chemogenetic approach to address sleep alterations in the chronic RS mouse model. They used an inhibitory DREADD (Designer receptors exclusively activated by designer drugs) targeting glutamatergic neurons in the lateral habenula, which are REM-active in this model. Acute treatment with intraperitoneal DREADD activator (clozapine-N-oxide) was shown to normalize the increased REM sleep time observed in the chronic RS mouse model as well as depressive-like behaviour (assessed by the sucrose preference and forced swim test).

3.13. Acute effect of stress

Eight articles reported sleep measures immediately after the stress procedure (e.g. maximum 6 h after the end of the stress procedure) (Table 7). Three articles reported increased time asleep [35,36,40], while another four articles found increased time spent awake at the expense of both REM and NREM sleep [26,37–39]. Intriguingly, in all four of these latter studies, the stress procedure (and subsequent recording) was performed during light phase (Table 7). Meerlo and colleagues [27] used acute RS during light phase and found a significant decrease in NREM sleep after 6 h (in C57BL6/J but not in BALB/CJ mice) without any significant difference in REM sleep.

4. Discussion

Several narrative reviews have described the intricate relationship between sleep and MDD in humans [3,6,7], and some systematic reviews have evaluated the possibilities of using EEG-related sleep measures as a biomarker of disease and/or for patient stratifications [52,54]. However, this systematic review is the first to investigate sleep-associated alterations in mouse models of MDD. A hypnogram reporting a summary of the macrostructural findings discussed is depicted in Fig. 7.

One key finding from this analysis was that across 24-h EEG recordings, mouse models of MDD spent less time in wakefulness and more time in both NREM and REM sleep. The latter is arguably the most striking feature of MDD mouse models and well replicate the finding in human. Notably, models with completely different aetiologies

Table 7
Acute effect of stress on sleep. Symbol was used to indicate higher, lower or same amount of time spent in that specific sleep stages in comparison to control. * Feng et al. reported time spent in sleep states during two time-points. On the left, data from 1 to 3 ZT, on the right data from 4 to 6. ** Henderson et al. reported time spent in sleep states during two time-points. On the left, data from 10 to 13 ZT, on the right data from 13 to 16. NREM: Non-rapid eye movement; REM: rapid eye movement. ZT: Zeitgeber time.

Study	Mouse Model	Wake	NREM	REM	Stress Time	Sleep Recording
Feng et al., 2020[35]*	Acute restraint stress	↓ =	↑ =	= ↑	ZT 0-1 Dark phase	1-3/4-6 Dark phase
Fuji et al. 2019 [36]	**Acute social defeat stress**	↓	↑	=	**ZT 11–12 Light phase**	**ZT 12–18 Dark phase**
Henderson et al. 2017 [38]**	**Acute social defeat stress**	↑ =	↓ =	↓ =	**ZT 9:30–10 Light phase**	**ZT 10–13/ 13–16 Light phase**
Henderson et al. 2024 [37]	**Acute social defeat stress**	↑	↓	↓	**ZT 9:30–10 Light phase**	**ZT 10–13 Light phase**
Meerlo et al. 2001 [27]	**Acute restraint stress**	**NA**	↓	=	**ZT 6–7 Light phase**	**ZT 7–12 Light phase**
Smith et al. 2019 [39]	**Acute social defeat stress**	↑	↓	↓	**ZT 3–5 Light phase**	**ZT 5–9 Light phase**
Xu et al. 2020 [26]	**Acute restraint stress**	↑	↓	↓	**ZT 1–3 Light phase**	**ZT 3–5 Light phase**
Yu et al. 2022 [40]	**Acute social defeat stress**	**NA**	↑	↑	**ZT 11–12 Dark phase**	**ZT 0–5 Light phase**

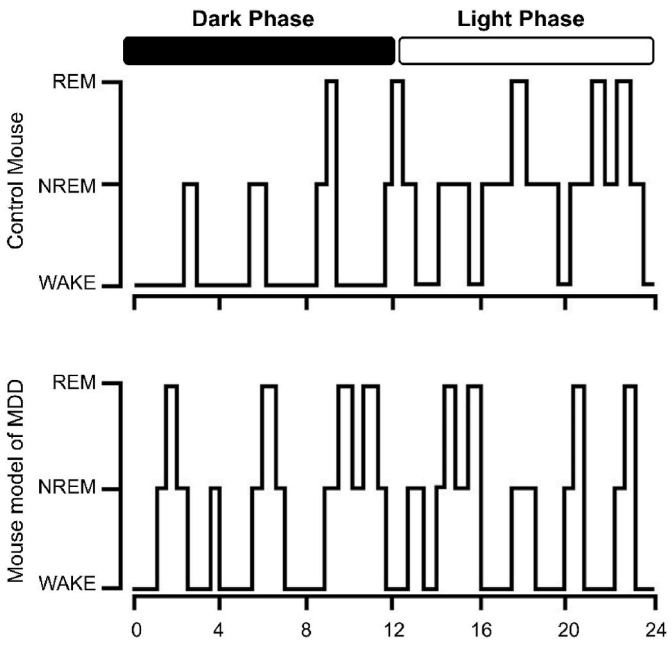

Fig. 7. Hypnogram showing the summary of the findings of the systematic review. It shows a hypnogram of a control mouse (top) that spend most of the time sleep during the light (inactive phase) and more time awake during the dark (active phase). In the hypnogram of mouse model of MDD, most of the author found an increase time spent asleep during the dark phase, sleep fragmentation as reflected by increased number of transitions during the light phase and an overall increase in REM sleep, particularly during the dark phase. MDD: major depressive disorder; NREM: Non-rapid eye movement; REM: rapid eye movement.

consistently reproduce this pattern. Interestingly, the increase in REM sleep is observed both during the light and dark phases but is most consistently reported in studies evaluating sleep over a 24-h period (approximately 90 % of the studies).

Another important feature of MDD mouse models is the tendency to spend more time in NREM, during the 24-h and during the dark phase, whereas during the light phase, they exhibit a trend toward less time spent in NREM sleep. Although this discrepancy between mouse models and their human counterparts could appear to be a major limitation of mouse models of MDD, sleep quantity doesn't always reflect in better sleep quality.

Indeed, another important feature frequently found in people with MDD is reduced sleep efficiency and impaired restorative properties of NREM sleep. Consistent with this, several authors observed that in mouse models of MDD, both the number of bouts in wake and NREM sleep are increased and their duration is reduced during both light and dark phase [28,29,33,41] indicating NREM sleep fragmentation, a feature that is further evidenced (although investigated in a limited number of studies) by an increased number of sleep-wake transitions [41,48].

These data suggest that mouse models of MDD replicate well both NREM sleep fragmentation and increased REM sleep observed in people with MDD. However, there are species-specific differences in sleep architecture that should be considered. The polyphasic nature of sleep and its more even distribution across the 24-h cycle in mice may lead to a less linear expression of the homeostatic drive, making these alterations more evident in 24-h recordings.

Conversely, an increased number of REM bouts [28,29,33,38] without always a corresponding increase in duration it has been reported in mouse models of MDD. Notably, several studies also found reduced REM latency in mouse models [42,46,47]. This suggests that circuits initiating REM sleep, rather than those maintaining it, are responsible for the increased REM sleep observed in mouse models of MDD. Although in humans with MDD, increased REM sleep is primarily driven by shortened REM latency, a longer first REM episode, and overall increased REM duration [55] (features often interpreted as signs of REM disinhibition [56]), we cannot exclude the involvement of similar underlying biological processes. In both species, increased activation of REM-initiating circuits, though still not fully characterized [57], may be responsible for earlier and more frequent REM onset.

The power of delta frequency during NREM sleep, instead, a putative measure of sleep pressure [58], shows mixed results [26,30,33,35,44] and need further investigation. However, three studies have investigated sleep recovery after SD in mouse models of MDD (and all using chronic SDS) [41,44,51], and they found that SD does not induce a significant increase in SWA, as commonly observed in control mice. This could be due to pre-existing sleep abnormalities in SDS models, such as NREM sleep fragmentation, which may imply impairments in the accumulation of sleep pressure and the disruption of homeostatic mechanisms. Interestingly, a recent preprint [59] reported a flattening of the typical sine wave curve of delta waves during the 24-h in a repetitive swim stress model, together with a blunted SD response, and showed how alterations of this mechanism are linked to synaptic downscaling [60,61], and related to the antidepressant effect of SD. Indeed, in line with clinical data, where delta power reduction is linked to altered process S and SD response [56,61], this is a good example of findings highlighting the need for systematic analysis of SD and recovery paradigms in mouse models, that integrate SWA measure together with molecular measures and behavioural readouts post SD. Conversely, findings on theta rhythm were discordant across studies, depending both on the phase and brain states. Although REM sleep is indeed increased in several mouse models, only two articles reported an increase in theta rhythm during REM [28,33]. This may suggest an alteration in the circuits responsible for generating theta activity during REM sleep [62]. Additionally, the increase in REM sleep without a corresponding rise in theta rhythm could indicate a compensatory mechanism for deficits in other sleep stages, such as NREM, but with limited functional restoration.

A critical question for preclinical researchers investigating sleep alterations in mouse models of MDD is: which model best replicates these disturbances? A definitive answer remains elusive, particularly because several models are represented by a single study in each case.

Nonetheless, while increased REM sleep is the most prominent finding observed across multiple models, NREM sleep disturbances, including fragmentation and a blunted response to SD, are better characterized in SDS models [41,44,51], highlighting their suitability for investigating these specific processes.

To further improve translational relevance, preclinical researchers working with mouse models should also aim to adopt measures more parallel to those used in humans, such as measuring the length of the first REM sleep episode and showing the full 24-h distribution of delta power, to allow better comparison with human patients.

We also included a small section on the effect of acute stress on sleep, a recent active area of investigation [22]. Intriguingly, we found that when the stress paradigm (and subsequent sleep recording) was applied during the light phase [26,37–39], mice spent more time awake at the expense of both NREM and REM sleep, while when it occurred during the dark phase [35], or at the transition between light–dark [36] or dark–light [40], acute stress induced a predominant increase in NREM sleep, and to a lesser extent REM sleep. We can speculate that the effects of acute stress may depend on the physiological variables linked to circadian phase, with dark-phase stress (active phase, higher arousal and corticosterone levels [63]) promoting rebound sleep, and light-phase stress (rest phase, lower arousal and corticosterone levels) leading to prolonged arousal and delayed recovery. However, this hypothesis requires more systematic investigation, also considering recent work [35,40] suggesting that acute stress increases total sleep time in mice as mechanism that helps reduce anxiety and provides restorative benefits.

Finally, several mechanistic and translational questions remain unresolved. In particular, none of the studies included in the review

evaluated the predictive validity of mouse models. Given that pharmacological treatments are the gold standard for MDD and both classical and new antidepressants are known to reverse depressive-like behaviors in mouse models [16], it is striking that almost none of the studies included in our review assess their effects on sleep phenotypes. This represents a critical gap in the literature of mouse models on MDD, especially considering that such interventions could clarify key biological mechanisms underlying the effects of antidepressants—such as REM sleep suppression by classical drugs [6] and the link between ketamine and sleep pressure [64]. These studies could elucidate fundamental questions, such as the role of hypercholinergic tone in increased REM sleep [65] and deficient process S in NREM disturbances [66].

5. Conclusion

Mouse models of MDD exhibit several sleep features observed in their human counterparts, such as increased REM sleep and NREM sleep fragmentation, suggesting good face validity. Due to species-specific differences in sleep architecture, these alterations often emerge more clearly over a full 24-h cycle, or during both light and dark phases. However, in contrast to what is typically observed in humans, these models generally show a decrease in time spent awake over 24 h. Further research is needed to elucidate the mechanisms underlying this complex phenomenon, as not all the studies included in this review reported bout numbers, stage-specific sleep transitions, or power spectral analysis during sleep. Moreover, the predictive validity of these models regarding sleep phenotypes remains unknown. A circuit dissection approach combined with pharmacology should be prioritized in future studies to shed light on key biological mechanisms driving increased REM sleep, NREM sleep fragmentation, and the effects of antidepressants observed in clinical patients. In conclusion, our work represents the first systematic review summarizing sleep alterations in mouse models of MDD, providing a valuable resource for both basic and clinical neuroscientists and highlighting research gaps that need to be addressed.

Limitations of the study

There are several limitations to our study. First, there is a relatively small number of studies included and a disparity in the types of mouse models described in the selected articles. Of the 22 publications reviewed, 10 articles used SDS and five used RS. Therefore, our results inevitably reflect more the findings of those specific stress procedures and models. Our study may be sensitive to both selection and publication biases. Selection bias may occur if, during the literature search or article selection process, some articles were favoured over others. However, none of the authors were involved in the publications reviewed here, and our literature search employed very broad search terms (see Methods). Publication bias may also be present in our review. For instance, it is possible that only data with high face validity for the mouse models or statistically significant results were published. Furthermore, our conclusions rely on the statistically significant results reported within the included studies that are based only on the use of internal controls, where effect size was not reported. The heterogeneity of experimental protocols and analysis protocols (such as different epoch scoring time) introduces another level of variability. Lastly, almost all studies included in the review (see Table 1) used only male mice. Future studies should address potential sex differences by including female mice.

Practice points

- Mouse models of MDD replicate several sleep alterations observed in humans, such as increased REM sleep and NREM sleep disturbances.
- Species-specific differences in sleep architecture must be considered when comparing mouse models to humans.
- The increase in REM sleep time across different mouse models suggests the potential use of animal models for developing circuit-level manipulations targeting REM as therapeutic interventions for MDD.
- NREM fragmentation, and blunted responses to SD suggest a process S deficiency in mouse models of MDD.
- Unlike humans with MDD, mouse models tend to spend more time asleep, particularly during the active (dark) phase, reflecting potential species-specific differences in circadian rhythms, sleep architecture and stress-adaptive responses.

Research agenda

- Preclinical studies suggest that mouse models replicate some sleep features of MDD. However, our knowledge is primarily based on models of SDS and RS. Therefore, further research is needed to determine which mouse models best replicate the sleep disturbances observed in MDD.
- There is an urgent need to assess the predictive validity of mouse models of MDD with respect to sleep phenotype. Both classic and novel antidepressant rescue depressive-like behaviours in mouse models, but their effects on sleep remain to be elucidated.
- In humans, at least two subtypes of depression (atypical and melancholic) have been described, characterized by distinct hypothalamic-pituitary-adrenal axis alterations. A systematic analysis of hypothalamic-pituitary-adrenal axis-related sleep disturbances in MDD mouse models is warranted.
- The neural circuit alterations driving increased REM sleep and the effects of antidepressants in MDD mouse models remain open questions. Future studies should investigate the potential role of hypercholinergic tone and the activity of key neuronal regions regulating REM sleep.
- The role of process S in MDD mouse models needs to be elucidated, particularly its contribution to NREM sleep fragmentation and its involvement in the behavioural rescue effects of SD.
- There is a need to characterize sleep disturbances in female mouse models of MDD to address potential sex differences.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

The work was supported by #NEXTGENERATIONEU (NGEU) and funded by the Italian Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRPP), project MNESYS (PE0000006) - A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 October 11, 2022).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2025.102179.

References

[1] GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the global burden of disease study 2019. Lancet Psychiatry 2022;9:137–50. https://doi.org/10.1016/S2215-0366(21)00395-3.
[2] Malhi GS, Mann JJ. Depression. Lancet 2018;392:2299–312. https://doi.org/10.1016/S0140-6736(18)31948-2.
[3] Plante DT. The evolving nexus of sleep and depression. Am J Psychiatr 2021;178:896–902. https://doi.org/10.1176/appi.ajp.2021.21080821.
[4] Diagnostic and statistical manual of mental disorders: DSM-5™. 5th ed. Arlington, VA, US: American Psychiatric Publishing, Inc.; 2013. https://doi.org/10.1176/appi.books.9780890425596.

[5] Sharpley CF, Bitsika V. Differences in neurobiological pathways of four "clinical content" subtypes of depression. Behav Brain Res 2013;256:368–76. https://doi.org/10.1016/j.bbr.2013.08.030.

[6] Riemann D, Krone LB, Wulff K, Nissen C. Sleep, insomnia, and depression. Neuropsychopharmacology 2020;45:74–89. https://doi.org/10.1038/s41386-019-0411-y.

[7] Pandi-Perumal SR, Monti JM, Burman D, Karthikeyan R, BaHammam AS, Spence DW, Brown GM, Narashimhan M. Clarifying the role of sleep in depression: a narrative review. Psychiatry Res 2020;291:113239. https://doi.org/10.1016/j.psychres.2020.113239.

[8] Mayers AG, Baldwin DS. The relationship between sleep disturbance and depression. Int J Psychiatr Clin Pract 2006;10:2–16. https://doi.org/10.1080/13651500500328087.

[9] Borbély AA. The S-deficiency hypothesis of depression and the two-process model of sleep regulation. Pharmacopsychiatry 1987;20:23–9. https://doi.org/10.1055/s-2007-1017069.

[10] Pigeon WR, Pinquart M, Conner K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. J Clin Psychiatry 2012;73:e1160–7. https://doi.org/10.4088/JCP.11r07586.

[11] Malik S, Kanwar A, Sim LA, Prokop LJ, Wang Z, Benkhadra K, Murad MH. The association between sleep disturbances and suicidal behaviors in patients with psychiatric diagnoses: a systematic review and meta-analysis. Syst Rev 2014;3:18. https://doi.org/10.1186/2046-4053-3-18.

[12] Krishnan V, Nestler EJ. The molecular neurobiology of depression. Nature 2008;455:894–902. https://doi.org/10.1038/nature07455.

[13] Stein MB, McCarthy MJ, Chen C-Y, Jain S, Gelernter J, He F, Heeringa SG, Kessler RC, Nock MK, Ripke S, Sun X, Wynn GH, Smoller JW, Ursano RJ. Genome-wide analysis of insomnia disorder. Mol Psychiatr 2018;23:2238–50. https://doi.org/10.1038/s41380-018-0033-5.

[14] O'Connell KS, Frei O, Bahrami S, Smeland OB, Bettella F, Cheng W, Chu Y, Hindley G, Lin A, Shadrin A, Barrett EA, Lagerberg TV, Steen NE, Dale AM, Djurovic S, Andreassen OA. Characterizing the genetic overlap between psychiatric disorders and sleep-related phenotypes. Biol Psychiatry 2021;90:621–31. https://doi.org/10.1016/j.biopsych.2021.07.007.

[15] Jansen PR, Watanabe K, Stringer S, Skene N, Bryois J, Hammerschlag AR, de Leeuw CA, Benjamins JS, Muñoz-Manchado AB, Nagel M, Savage JE, Tiemeier H, White T, Tung JY, Hinds DA, Vacic V, Wang X, Sullivan PF, van der Sluis S, Polderman TJC, Smit AB, Hjerling-Leffler J, Van Someren EJW, Posthuma D. Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. Nat Genet 2019;51:394–403. https://doi.org/10.1038/s41588-018-0333-3.

[16] Tian X, Russo SJ, Li L. Behavioral animal models and neural-circuit framework of depressive disorder. Neurosci Bull 2024. https://doi.org/10.1007/s12264-024-01270-7.

[17] Wang Q, Timberlake MA, Prall K, Dwivedi Y. The recent progress in animal models of depression. Prog Neuropsychopharmacol Biol Psychiatry 2017;77:99–109. https://doi.org/10.1016/j.pnpbp.2017.04.008.

[18] Gururajan A, Reif A, Cryan JF, Slattery DA. The future of rodent models in depression research. Nat Rev Neurosci 2019;20:686–701. https://doi.org/10.1038/s41583-019-0221-6.

[19] Cryan JF, Holmes A. The ascent of mouse: advances in modelling human depression and anxiety. Nat Rev Drug Discov 2005;4:775–90. https://doi.org/10.1038/nrd1825.

[20] Yasugaki S, Okamura H, Kaneko A, Hayashi Y. Bidirectional relationship between sleep and depression. Neurosci Res 2023. https://doi.org/10.1016/j.neures.2023.04.006.

[21] Krishnan V, Nestler EJ. Animal models of depression: molecular perspectives. Curr Top Behav Neurosci 2011;7:121–47. https://doi.org/10.1007/7854_2010_108.

[22] Yu X, Nollet M, Franks NP, Wisden W. Sleep and the recovery from stress. Neuron 2025;S0896–6273(25). https://doi.org/10.1016/j.neuron.2025.04.028. 00311–3.

[23] Saha S, Lim CCW, Cannon DL, Burton L, Bremner M, Cosgrove P, Huo Y, J McGrath J. Co-morbidity between mood and anxiety disorders: a systematic review and meta-analysis. Depress Anxiety 2021;38:286–306. https://doi.org/10.1002/da.23113.

[24] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021;10:89. https://doi.org/10.1186/s13643-021-01626-4.

[25] Hooijmans CR, Rovers MM, de Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 2014;14:43. https://doi.org/10.1186/1471-2288-14-43.

[26] Xu Y-X, Liu G-Y, Ji Z-Z, Li Y-Y, Wang Y-L, Wu X-Y, Liu J-L, Ma D-X, Zhong M-K, Gao C-B, Xu Q. Restraint stress induced anxiety and sleep in mice. Front Psychiatr 2023;14:1090420. https://doi.org/10.3389/fpsyt.2023.1090420.

[27] Meerlo P, Easton A, Bergmann BM, Turek FW. Restraint increases prolactin and REM sleep in C57BL/6J mice but not in BALB/cJ mice. Am J Physiol Regul Integr Comp Physiol 2001;281:R846–54. https://doi.org/10.1152/ajpregu.2001.281.3.R846.

[28] Zhang Z, Zhang W, Fang Y, Wang N, Liu G, Zou N, Song Z, Liu H, Wang L, Xiao Q, Zhao J, Wang Y, Lei T, Zhang C, Liu X, Zhang B, Luo F, Xia J, He C, Hu Z, Ren S, Zhao H. A potentiation of REM sleep-active neurons in the lateral habenula may be responsible for the sleep disturbance in depression. Curr Biol 2024;34:3287–3300.e6. https://doi.org/10.1016/j.cub.2024.05.075.

[29] Xia T-J, Wang Z, Jin S-W, Liu X-M, Liu Y-G, Zhang S-S, Pan R-L, Jiang N, Liao Y-H, Yan M-Z, Du L-D, Chang Q. Melatonin-related dysfunction in chronic restraint stress triggers sleep disorders in mice. Front Pharmacol 2023;14:1210393. https://doi.org/10.3389/fphar.2023.1210393.

[30] Yasugaki S, Liu C-Y, Kashiwagi M, Kanuka M, Honda T, Miyata S, Yanagisawa M, Hayashi Y. Effects of 3 weeks of water immersion and restraint stress on sleep in mice. Front Neurosci 2019;13:1072. https://doi.org/10.3389/fnins.2019.01072.

[31] Codeluppi SA, Chatterjee D, Prevot TD, Bansal Y, Misquitta KA, Sibille E, Banasr M. Chronic stress alters astrocyte morphology in mouse prefrontal cortex. Int J Neuropsychopharmacol 2021;24:842–53. https://doi.org/10.1093/ijnp/pyab052.

[32] Yao D, Li R, Hao J, Huang H, Wang X, Ran L, Fang Y, He Y, Wang W, Liu X, Wang M. Melatonin alleviates depression-like behaviors and cognitive dysfunction in mice by regulating the circadian rhythm of AQP4 polarization. Transl Psychiatry 2023;13:310. https://doi.org/10.1038/s41398-023-02614-z.

[33] Nollet M, Hicks H, McCarthy AP, Wu H, Möller-Levet CS, Laing EE, Malki K, Lawless N, Wafford KA, Dijk D-J, Winsky-Sommerer R. REM sleep's unique associations with corticosterone regulation, apoptotic pathways, and behavior in chronic stress in mice. Proc Natl Acad Sci U S A 2019;116:2733–42. https://doi.org/10.1073/pnas.1816456116.

[34] Antoniuk S, Bijata M, Ponimaskin E, Wlodarczyk J. Chronic unpredictable mild stress for modeling depression in rodents: meta-Analysis of model reliability. Neurosci Biobehav Rev 2019;99:101–16. https://doi.org/10.1016/j.neubiorev.2018.12.002.

[35] Feng X, Zhao H-Y, Shao Y-J, Lou H-F, Zhu L-Y, Duan S, Yu Y-Q. Anxiolytic effect of increased NREM sleep after acute social defeat stress in mice. Neurosci Bull 2020;36:1137–46. https://doi.org/10.1007/s12264-020-00473-y.

[36] Fujii S, Kaushik MK, Zhou X, Korkutata M, Lazarus M. Acute social defeat stress increases sleep in mice. Front Neurosci 2019;13:322. https://doi.org/10.3389/fnins.2019.00322.

[37] Henderson F, Dumas S, Gangarossa G, Bernard V, Pujol M, Poirel O, Pietrancosta N, El Mestikawy S, Daumas S, Fabre V. Regulation of stress-induced sleep perturbations by dorsal raphe VGLUT3 neurons in male mice. Cell Rep 2024;43:114411. https://doi.org/10.1016/j.celrep.2024.114411.

[38] Henderson F, Vialou V, El Mestikawy S, Fabre V. Effects of social defeat stress on sleep in mice. Front Behav Neurosci 2017;11:227. https://doi.org/10.3389/fnbeh.2017.00227.

[39] Smith J, Honig-Frand A, Antila H, Choi A, Kim H, Beier KT, Weber F, Chung S. Regulation of stress-induced sleep fragmentation by preoptic glutamatergic neurons. Curr Biol 2024;34:12–23.e5. https://doi.org/10.1016/j.cub.2023.11.035.

[40] Yu X, Zhao G, Wang D, Wang S, Li R, Li A, Wang H, Nollet M, Chun YY, Zhao T, Yustos R, Li H, Zhao J, Li J, Cai M, Vyssotski AL, Li Y, Dong H, Franks NP, Wisden W. A specific circuit in the midbrain detects stress and induces restorative sleep. Science 2022;377:63–72. https://doi.org/10.1126/science.abn0853.

[41] Radwan B, Jansen G, Chaudhury D. Abnormal sleep signals vulnerability to chronic social defeat stress. Front Neurosci 2020;14:610655. https://doi.org/10.3389/fnins.2020.610655.

[42] Wells AM, Ridener E, Bourbonais CA, Kim W, Pantazopoulos H, Carroll FI, Kim K-S, Cohen BM, Carlezon WA. Effects of chronic social defeat stress on sleep and circadian rhythms are mitigated by kappa-opioid receptor antagonism. J Neurosci 2017;37:7656–68. https://doi.org/10.1523/JNEUROSCI.0885-17.2017.

[43] McCullough KM, Missig G, Robble MA, Foilb AR, Wells AM, Hartmann J, Anderson KJ, Neve RL, Nestler EJ, Ressler KJ, Carlezon WA. Nucleus accumbens medium spiny neuron subtypes differentially regulate stress-associated alterations in sleep architecture. Biol Psychiatry 2021;89:1138–49. https://doi.org/10.1016/j.biopsych.2020.12.030.

[44] Radwan B, Yanez Touzet A, Hammami S, Chaudhury D. Prolonged exposure to social stress impairs homeostatic sleep regulation. Front Neurosci 2021;15:633955. https://doi.org/10.3389/fnins.2021.633955.

[45] Golden SA, Covington HE, Berton O, Russo SJ. A standardized protocol for repeated social defeat stress in mice. Nat Protoc 2011;6:1183–91. https://doi.org/10.1038/nprot.2011.361.

[46] El Yacoubi M, Bouali S, Popa D, Naudon L, Leroux-Nicollet I, Hamon M, Costentin J, Adrien J, Vaugeois J-M. Behavioral, neurochemical, and electrophysiological characterization of a genetic mouse model of depression. Proc Natl Acad Sci U S A 2003;100:6227–32. https://doi.org/10.1073/pnas.1034823100.

[47] El Yacoubi M, Popa D, Martin B, Zimmer L, Hamon M, Adrien J, Vaugeois J-M. Genetic association between helpless trait and depression-related phenotypes: evidence from crossbreeding studies with H/Rouen and NH/Rouen mice. Int J Neuropsychopharmacol 2012;15:363–74. https://doi.org/10.1017/S1461145711000605.

[48] Le Dantec Y, Hache G, Guilloux JP, Guiard BP, David DJ, Adrien J, Escourrou P. NREM sleep hypersomnia and reduced sleep/wake continuity in a neuroendocrine mouse model of anxiety/depression based on chronic corticosterone administration. Neuroscience 2014;274:357–68. https://doi.org/10.1016/j.neuroscience.2014.05.050.

[49] Yuan M-Y, Chen Z-K, Ni J, Wang T-X, Jiang S-Y, Dong H, Qu W-M, Huang Z-L, Li R-X. Ablation of olfactory bulb glutamatergic neurons induces depressive-like behaviors and sleep disturbances in mice. Psychopharmacology (Berl) 2020;237:2517–30. https://doi.org/10.1007/s00213-020-05552-6.

[50] Hendriksen H, Korte SM, Olivier B, Oosting RS. The olfactory bulbectomy model in mice and rat: one story or two tails? Eur J Pharmacol 2015;753:105–13. https://doi.org/10.1016/j.ejphar.2014.10.033.

[51] Olini N, Rothfuchs I, Azzinnari D, Pryce CR, Kurth S, Huber R. Chronic social stress leads to altered sleep homeostasis in mice. Behav Brain Res 2017;327:167–73. https://doi.org/10.1016/j.bbr.2017.03.022.

[52] Pillai V, Kalmbach DA, Ciesla JA. A meta-analysis of electroencephalographic sleep in depression: evidence for genetic biomarkers. Biol Psychiatry 2011;70:912–9. https://doi.org/10.1016/j.biopsych.2011.07.016.
[53] Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: review and hypothesis. Am J Psychiatr 1990;147:14–21. https://doi.org/10.1176/ajp.147.1.14.
[54] Leitner C, Dalle Piagge F, Tomic T, Nozza F, Fasiello E, Castronovo V, De Gennaro L, Baglioni C, Ferini-Strambi L, Galbiati A. Sleep alterations in major depressive disorder and insomnia disorder: a network meta-analysis of polysomnographic studies. Sleep Med Rev 2025;80:102048. https://doi.org/10.1016/j.smrv.2025.102048.
[55] Baglioni C, Nanovska S, Regen W, Spiegelhalder K, Feige B, Nissen C, Reynolds CF, Riemann D. Sleep and mental disorders: a meta-analysis of polysomnographic research. Psychol Bull 2016;142:969–90. https://doi.org/10.1037/bul0000053.
[56] Borbély AA, Wirz-Justice A. Sleep, sleep deprivation and depression. A hypothesis derived from a model of sleep regulation. Hum Neurobiol 1982;1:205–10.
[57] Luppi P-H, Chancel A, Malcey J, Cabrera S, Fort P, Maciel RM. Which structure generates paradoxical (REM) sleep: the brainstem, the hypothalamus, the amygdala or the cortex? Sleep Med Rev 2024;74:101907. https://doi.org/10.1016/j.smrv.2024.101907.
[58] Borbély AA. A two process model of sleep regulation. Hum Neurobiol 1982;1:195–204.
[59] Gardner W, Sarrazin DH, Balzinger M, Marchese C, Ragno A, Ramanathan C, Veleanu M, Vestring S, Normann C, Bourgin P, Serchov T. The mPFC molecular clock mediates the effects of sleep deprivation on depression-like behavior and regulates sleep consolidation and homeostasis. 2025.06.09.658701, https://doi.org/10.1101/2025.06.09.658701; 2025.
[60] Wolf E, Kuhn M, Normann C, Mainberger F, Maier JG, Maywald S, Bredl A, Klöppel S, Biber K, van Calker D, Riemann D, Sterr A, Nissen C. Synaptic plasticity model of therapeutic sleep deprivation in major depression. Sleep Med Rev 2016;30:53–62. https://doi.org/10.1016/j.smrv.2015.11.003.
[61] Tononi G, Cirelli C. Sleep function and synaptic homeostasis. Sleep Med Rev 2006;10:49–62. https://doi.org/10.1016/j.smrv.2005.05.002.
[62] Boyce R, Williams S, Adamantidis A. REM sleep and memory. Curr Opin Neurobiol 2017;44:167–77. https://doi.org/10.1016/j.conb.2017.05.001.
[63] Haller J, Millar S, van de Schraaf J, de Kloet RE, Kruk MR. The active phase-related increase in corticosterone and aggression are linked. J Neuroendocrinol 2000;12:431–6. https://doi.org/10.1046/j.1365-2826.2000.00470.x.
[64] Duncan WC, Selter J, Brutsche N, Sarasso S, Zarate CA. Baseline Delta sleep ratio predicts acute ketamine mood response in major depressive disorder. J Affect Disord 2013;145:115–9. https://doi.org/10.1016/j.jad.2012.05.042.
[65] Palagini L, Baglioni C, Ciapparelli A, Gemignani A, Riemann D. REM sleep dysregulation in depression: state of the art. Sleep Med Rev 2013;17:377–90. https://doi.org/10.1016/j.smrv.2012.11.001.
[66] Wirz-Justice A, den Hoofdakker RHV. Sleep deprivation in depression: what do we know, where do we go? Biol Psychiatry 1999;46:445–53. https://doi.org/10.1016/S0006-3223(99)00125-0.