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REVIEW ARTICLE

Crosstalk between the subiculum and sleep–wake regulation: A review

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Summary

The circuitry underlying the initiation, maintenance, and coordination of wakefulness, rapid eye movement sleep, and non-rapid eye movement sleep is not thoroughly understood. Sleep is thought to arise due to decreased activity in the ascending reticular arousal system, which originates in the brainstem and awakens the thalamus and cortex during wakefulness. Despite the conventional association of sleep–wake states with hippocampal rhythms, the mutual influence of the hippocampal formation in regulating vigilance states has been largely neglected. Here, we focus on the subiculum, the main output region of the hippocampal formation. The subiculum, particulary the ventral part, sends extensive monosynaptic projections to crucial regions implicated in sleep–wake regulation, including the thalamus, lateral hypothalamus, tuberomammillary nucleus, basal forebrain, ventrolateral preoptic nucleus, ventrolateral tegmental area, and suprachiasmatic nucleus. Additionally, second-order projections from the subiculum are received by the laterodorsal tegmental nucleus, locus coeruleus, and median raphe nucleus, suggesting the potential involvement of the subiculum in the regulation of the sleep–wake cycle. We also discuss alterations in the subiculum observed in individuals with sleep disorders and in sleep-deprived mice, underscoring the significance of investigating neuronal communication between the subiculum and pathways promoting both sleep and wakefulness.

KEYWORDS
NREM sleep, REM sleep, sleep, subiculum, vigilance state, wake

1 | INTRODUCTION

Natural sleep, a phenomenon observed in all animals, particularly mammals, continues to be a scientific enigma. Sleep disorders affect a significant portion of the population (Baranowski & Jabkowski, 2023), impacting both physical and mental well-being (Smith & Lee, 2022). Investigating the neuronal circuits that underlie sleep–wake regulation offers potential for deeper insights into the functions of sleep and the development of improved treatments for sleep disorders.

In humans, non-human primates, and rodents, vigilance states are typically characterised through the use of electroencephalogram (EEG) and electromyogram (EMG) recordings (Ishikawa et al., 2017; Joyce et al., 2023; Rahimi et al., 2015), which measure global cortical and muscular activities, respectively. This classification delineates vigilance states into three main phases: wakefulness, non-rapid eye movement sleep (NREMS), and rapid eye movement sleep (REMS). The wakeful state displays heterogeneity characterised by unsynchronised EEG oscillations of low amplitude and mixed frequencies, along with variable muscle activity (Rahimi et al., 2023b; Sulaman

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et al., 2023). NREMS is defined by high-amplitude, low-frequency delta oscillations (0.1–5 Hz) and spindles (bursts of 7–15 Hz oscillations) in the EEG, accompanied by reduced postural muscle tone (Bandarabadi et al., 2020). During REMS, the EEG predominantly exhibits theta (5–10 Hz) and gamma oscillations (30–80 Hz), while the axial posture muscles experience a complete loss of muscle tone (Rahimi et al., 2023b; Sulaman et al., 2023) (Figure 1).

Recent studies utilising techniques such as cell- and region-specific pharmacological manipulations have led to transformative advancements in our understanding of sleep regulation, unveiling numerous brain nuclei that selectively modulate our arousal states. These nuclei responsible for controlling sleep–wake states are typically heterogeneous, housing mixed neuronal populations that can maintain various vigilance states (Sulaman et al., 2023). It is generally believed that sleep arises from reduced activity in the ascending reticular arousal system (Sulaman et al., 2023), which originates in the brainstem and awakens the thalamus and cortex during wakefulness through a well-known ‘bottom-up’ pathway (Krone et al., 2017). However, while sleep–wake states are typically associated with neocortical and hippocampal rhythms, the potential role of neocortical

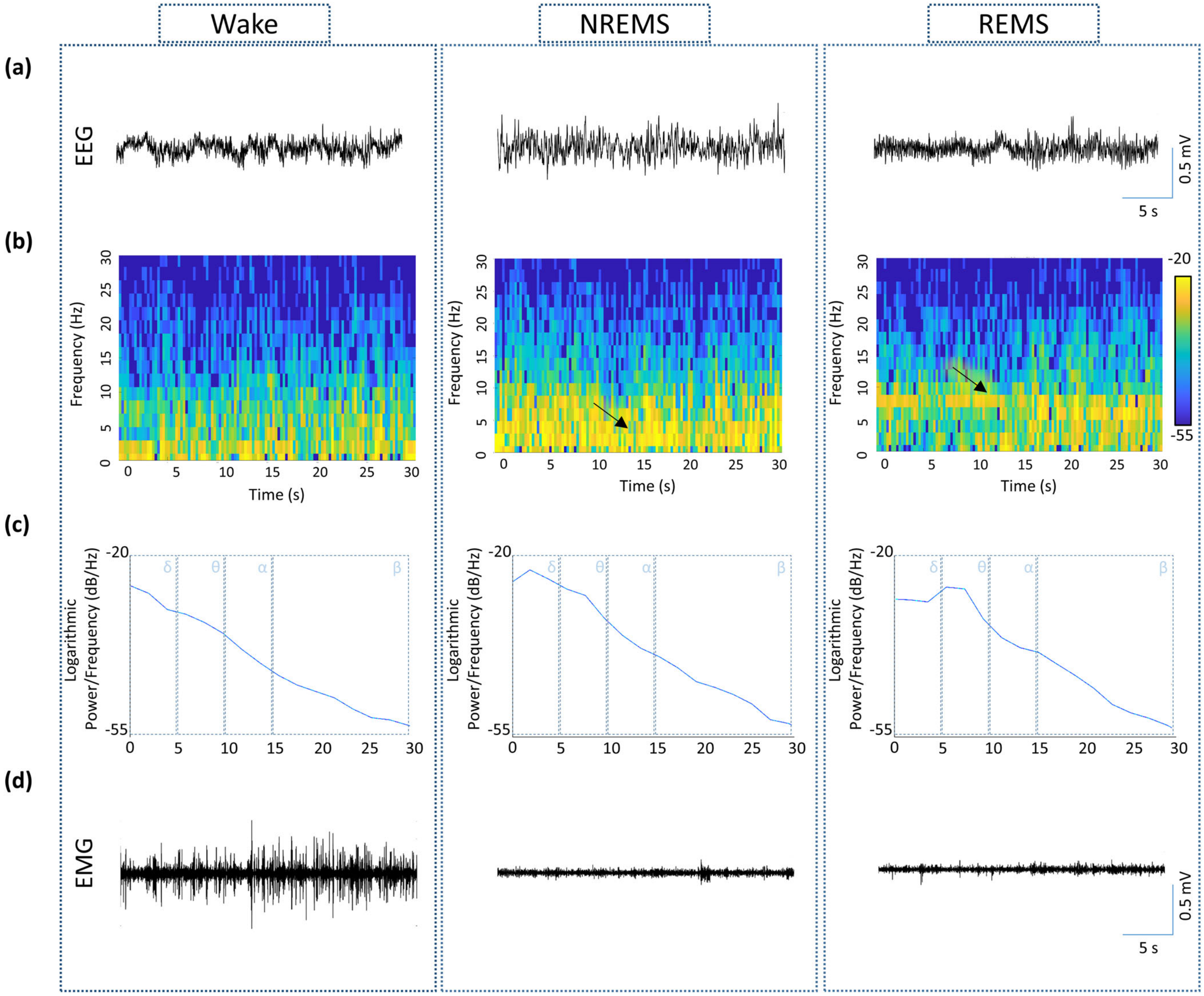

FIGURE 1 Discrimination of vigilance states based on EEG (electroencephalogram) and EMG (electromyogram) signals. (a) A representative 30 s EEG recording from the occipital cortex of an adult mouse during wakefulness (Wake), rapid eye movement sleep (REMS), and non-rapid eye movement sleep (NREMS). Wake and REMS share some visual similarities (Rahimi et al., 2023b). (b) The density spectral array of the corresponding EEG indicates a more prominent delta power (0.1–5 Hz) in NREMS (arrow) and theta power (5–10 Hz) in REMS (arrow), while Wake exhibits mixed frequencies. (c) Logarithmic power spectral analysis of the same EEG signal shows a clear peak of delta in NREMS and theta in REMS. δ, delta; θ, theta; α, alpha; β, beta. (d) EMG recordings corresponding to the same EEG signal reveal that during Wake, the EMG has a significantly higher amplitude, aiding in the discrimination from REMS (Rahimi et al., 2023b). The mouse EEG signals underwent 1000 times amplification before digitization with a high-pass filter of 0.1 Hz. The EMG signal was processed with a high-pass filter at 10 Hz.The mouse EEG data were recorded at the Department of Anesthesiology & Intensive Care, School of Medicine, Technical University of Munich, under licence: ROB-55.2-2532.Vet_02-19-121.

and archicortical neurons in regulating wakefulness has been largely overlooked.

It is known that the substantial set of genes and proteins in the ventral hippocampus exhibit circadian oscillations in healthy mice, which could influence various circadian rhythms in the brain (Debski et al., 2020). While the functions of the hippocampus in generating brain oscillations and facilitating memory consolidation during sleep have been examined extensively (Pronier et al., 2023), its possible crosstalk with sleep–wake regulation is still largely unexplored. This review centres its focus on the subiculum, the main output region of the hippocampal formation (Kishi et al., 2000). We provide a brief overview of the subiculum, report its structural changes in individuals with sleep disorders, explore its projection with brain regions involved in sleep–wake regulation, and discuss how the subicular function changes in sleep-deprived mice. These findings emphasise the importance of studying the interaction between the subiculum and sleep–wake regulation.

2 | SUBICULUM AND ITS INTERACTION WITH SLEEP

2.1 | Anatomy and primary function of the subiculum

The subiculum comprises three distinct layers, arranged from outermost to innermost: the molecular layer, the pyramidal cell layer, and the polymorphic layer (O'Mara, 2005; O'Mara et al., 2001). Despite its adjacency to sector CA1, the subiculum exhibits distinct molecular profiles. Studies demonstrate a clear cytoarchitectural boundary between the subiculum and CA1, underscoring their separate molecular organisations (Lein et al., 2004). Traditionally, the subiculum in rodents was not extensively divided and was roughly segmented into proximal and distal subiculum, based on its proximity to CA1 (Fujise et al., 1995; Ishihara & Fukuda, 2016), or along the dorso-ventral axis into dorsal and ventral subiculum (Ding et al., 2020).

The predominant neuronal population in the subiculum consists of pyramidal cells (PCs), which release glutamate as their neurotransmitter. Most PCs in the subiculum have a primary apical dendrite that is innervated by the hippocampus through the molecular layer, and they also possess axonal collaterals that are entering the polymorphic layer (Harris et al., 2001). Varicosities and axonal extensions within the pyramidal cell layer and apical dendritic region suggest intrinsic connectivity, while the presence of these features on axons projecting to the presubiculum, entorhinal cortex (EC), or CA1 classifies them as projection cells (Harris et al., 2001). PCs are regulated by various GABAergic interneurons (GABA-INs). GABA-INs can divide further into three main groups, including parvalbumin expressing INs (PV-INs), somatostatin expressing INs (SOM-INs), and vasoactive intestinal (poly)peptide expressing INs (VIP-INs). PV-INs are the most abundant GABA-INs in the Subiculum, providing perisomatic inhibition to PCs (Drexel et al., 2017). Subicular SOM-INs predominantly target PC's proximal dendrites (Nichol et al., 2018), and VIP-INs, often target other groups of subicular INs, and are key participants in the subiculum's disinhibitory circuitry (Rahimi et al., 2023a).

The subiculum has been extensively studied for its role in the spatial navigation (Kitanishi et al., 2021), contextual memory (Anderson & Petrovich, 2017), reward (Lindenbach et al., 2019), spatial memory consolidation (Contreras et al., 2018), emotional regulation (Subhadeep et al., 2022; Yan et al., 2022), and the stress response (Mu et al., 2020). It is important to note that poor sleep quality can directly or indirectly affect all these primary functions of the subiculum. Recent research has indicated that sleep facilitates spatial memory (Simon et al., 2022) and poor sleep quality can impact spatial orientation (Valera et al., 2016), suggesting a potential alteration in subicular function. Insufficient sleep has been shown to affect how individuals learn from reward or punishment (Gerhardsson et al., 2021), and REMS deprivation can alter reward memory (Shahveisi et al., 2022). Interactions between insomnia, sleep duration and emotional processes have also been observed (Baglioni et al., 2023), and several studies in humans have linked fear and extinction recall/retention to both REMS and slow wave sleep (SWS) (Bottary et al., 2023). However, it is crucial to recognise that various brain regions participate in the execution of these cognitive functions. Consequently, further research is necessary to explore whether the literature suggests anatomical and/or functional connections between the subiculum and sleep–wake behaviour.

2.2 | Clinical studies

Five studies found structural changes in the subiculum in patients with sleep disorders. The studies used automatic segmentation in magnetic resonance imaging (MRI) to measure the size of the various parts of the hippocampal formation. However, it is important to interpret studies with automatic segmentation carefully (Zeidman et al., 2015). Specifically, using T1-weighted MRI for automatic segmentation has been criticised for not accurately distinguishing certain specific parts, such as the molecular layer (Wisse et al., 2021).

Macey et al. collected T1-weighted MRI images from 66 newly diagnosed, untreated Patients with obstructive sleep apnea (OSA) (mean age ± SD: 46.3 ± 8.8 years; 50 males) and 59 healthy age-matched control participants (46.8 ± 9.0 years; 38 males) (Macey et al., 2018). Male patients exhibited a higher bilateral volume throughout CA1 and subiculum, with greater right-hemispheric increases and lower bilateral volumes in the mid- and posterior-CA3/ dentate gyrus (DG). Female patients showed right-hemispheric differences with increased volumes in CA1 and the subiculum/uncus, and decreased volumes in the posterior CA3/DG. Lee et al. calculated cortical thickness and hippocampal subfield volumes from T1-weighted MRI images of 45 controls (age 15.43 ± 1.73 years, 21 males) and 53 adolescent children with OSA (age 15.26 ± 1.63 years, 32 males) to investigate the association of childhood OSA with alterations in cortical structure and hippocampal subfield structural changes (Lee et al., 2023). They observed that in adolescents with OSA, only the volume of the right-hemispheric subiculum-head area of the hippocampus was larger compared with the control group. This enlargement was positively correlated with both the apnea–hypopnea index (AHI) and the arousal index.

Recently, the association of sleep-disorder-related breathing impairments and medial temporal lobe atrophy in cognitively unimpaired amyloid-positive older adults was assessed (André et al., 2023). T1-weighted MRI images were collected between 2016 and 2020 as part of the Age-Well Randomized Controlled Trial conducted under the Medit-Ageing European Project. The AHI interacted with the volumes of the EC, subiculum, CA1, and DG. This interaction revealed that in individuals with amyloid-positive status, higher severity of sleep apnea was associated with reduced volumes of subregions in the medial temporal lobe. Notably, this relationship did not hold true for individuals who were amyloid-negative.

Subicular volume changes were also reported in connection with other sleep impairments. To assess the relationship between sleep duration, sleep impairments, perceived stress, and hippocampal subfield volumes in later life, adults (aged 68.8 ± 7.3; 46% males) from the Irish Longitudinal Study on Ageing completed a questionnaire along with multiparametric brain T1-weighted MRI (de Looze et al., 2022). No cross-sectional and follow-up associations between sleep and total hippocampal volume, and between stress and total hippocampal volume, were found. In contrast, a long sleep duration (≥9–10 h per night) was linked to smaller volumes of the molecular layer, hippocampal tail, presubiculum, and subiculum. On the other hand, the combination of short sleep duration (≤6 h) and higher perceived stress was associated with smaller volumes of CA1, molecular layer, subiculum, and hippocampal tail. Sleep impairments, independently and in conjunction with higher stress, together with the severity of sleep impairments were associated with smaller volumes of these same subfields. Similarly, Liu et al. reported that poor sleep was associated with smaller hippocampal subfields in healthy elderly individuals (Liu et al., 2021). Sleep quality was self-assessed using the Pittsburgh Sleep Quality Index (PSQI), and hippocampal volumes were measured from T1-weighted MRI images. A total of 67 cognitively normal elderly individuals aged 60–83 years were classified into 30 normal sleepers with a PSQI <5 and 37 poor sleepers with a PSQI ≥5. Compared with normal sleepers, poor sleepers exhibited significantly lower normalised volumes in the left CA1, DG, and subiculum, and the global PSQI was negatively associated with the normalised volumes of these regions (only in the left hemisphere).

2.3 | Animal studies

2.3.1 | The anatomical connections between the subiculum and sleep–wake regulating areas

The subiculum receives its primary input from two critical regions, namely the CA1 region and the EC (O'Mara, 2005; Witter, 2006). Notably, PCs located in the proximal CA1, close to sector CA2, innervate the distal subiculum (adjacent to the presubiculum), while PCs of the distal CA1 innervate the proximal portion of the subiculum close to sector CA1 (Matsumoto et al., 2019). Cells in layer III of the lateral and medial EC (LEC and MEC) mainly terminate in the stratum lacunosum-moleculare of area CA1 and the molecular layer of the subiculum (Witter et al., 2000).

While there is accumulating evidence indicating that the subiculum also sends backward projections to sector CA1, the major outputs from the subiculum are directed towards the EC, exhibiting a precise spatial organisation. The proximal half of the dorsal subiculum innervates the LEC, whereas the distal part is connected to the MEC (Witter, 2006). Projections from the ventral hippocampus target both the dorsal and ventral MEC (Ohara et al., 2023). Additionally, the ventral subiculum is composed of multiple distinct neuronal populations that send parallel, long-range projections to various areas, including the prefrontal cortex, nucleus accumbens shell (Wee & MacAskill, 2020), amygdalohippocampal area, antero-dorsal thalamic nucleus, medial hypothalamus (Tang et al., 2016), and several brain regions involved in sleep regulation, which will be discussed in the following (Table 1). Here, we explore the subiculum's projection to regions with a confirmed causal role in initiating and sustaining wakefulness, NREMS, or REMS. Consequently, areas such as the prefrontal and retrosplenial cortices, which receive substantial projections from the subiculum (Kinnavane et al., 2018; Tang et al., 2016) and exhibit clear associations with state-dependent brain oscillations (Alexander & Shelley, 2018; Brady et al., 2023; Del Koike et al., 2017; Feliciano-Ramos et al., 2023), but lack an established causal role, were omitted from the discussion.

The extensive subicular projections to sleep–wake modulating regions strongly suggest potential interactions between subiculum and sleep–wake regulation.

Thalamus

The thalamus is composed of distinct subnuclei that exert strong control over cortical oscillations during both wakefulness and sleep (Gent et al., 2018; Honjoh et al., 2018). The paraventricular nucleus of the thalamus (PVT) shows heightened activity during wakefulness, and suppressing PVT neuronal activity reduces wakefulness. Conversely, activating PVT neurons induces a shift from sleep to wakefulness (Ren et al., 2018). Tonic optogenetic activation of neurons in the centromedial nucleus of the thalamus (CMT) induces NREMS–wake transitions (Gent et al., 2018). Optogenetic stimulation of ventromedial thalamic nucleus (VM) cells rapidly awoke all mice from NREMS and consistently caused EEG activation during slow wave anaesthesia, with no arousal observed from REMS (Honjoh et al., 2018). In addition, several other thalamic nuclei, such as the nucleus reuniens and anterior thalamic nuclei, play a role in the generation of state-dependent brain oscillations (Hauer et al., 2019; Latchoumane et al., 2017; Szabó et al., 2022; Tsanov et al., 2011; Viena et al., 2021).

Using herpes simplex virus 1 (HSV-1) tracing (injected into the ventral subiculum) in mice, the monosynaptic connection of ventral subiculum to PVT, nucleus reuniens and CMT was observed (Tang et al., 2016). Projection from both dorsal and ventral subiculum to nucleus reuniens was also found using retrograde Fluoro-Gold tracing (injected into the nucleus reuniens) (Scheel et al., 2020). In rat, it was observed that the projections to the anteromedial nucleus favoured the proximal subiculum, while those to the anteroventral nucleus predominantly arose in the distal subiculum (Christiansen et al., 2016). Furthermore, in the macaque, subicular inputs to the anteromedial thalamic nucleus predominantly arose from the anterior subiculum (Christiansen et al., 2016).

TABLE 1 Neuronal connectivity between the subiculum and sleep–wake promoting areas.

Species	Which region of subiculum	Which area	Which technique (injection site)	Monosynaptic or disynaptic	Reference
Mouse	Ventral	Thalamus (PVT, nucleus reuniens and CMT)	HSV-1 tracing (injected ventral subiculum)	Monosynaptic	Tang et al. (2016)
Mouse	Dorsal and ventral	Thalamus (nucleus reuniens)	Retrograde Fluoro-Gold tracing (injected in nucleus reuniens	Monosynaptic	Scheel et al. (2020)
Rat	Distal	Thalamus (anteromedial nucleus)	Multiple retrograde tracers (injected in anterior thalamic nuclei)	Monosynaptic	Christiansen et al. (2016)
Rat	Proximal	Thalamus (anteroventral nucleus)	Multiple retrograde tracers (injected in anterior thalamic nuclei)	Monosynaptic	Christiansen et al. (2016)
Macaque	Anterior	Thalamus (anteromedial thalamic nucleus)	HRP tracing (injected in anterior thalamic nuclei)	Monosynaptic	Christiansen et al. (2016)
Mouse	Ventral	LH	Retrograde labelling through CTB-488 (injected in LH) and anterograde rabies virus injection (injected in ventral subiculum)	Monosynaptic	Wee et al. (2023)
Rat	Dorsal and ventral (ventral significantly more)	LH	Anterograde PHA-L tract-tracing method (in subiculum)	Monosynaptic	Köhler (1990)
Mouse	Ventral	LH	HSV-1 tracing (injected ventral subiculum)	Monosynaptic	Tang et al. (2016)
Rat	Temporal two-thirds	MnPO	Anterograde PHA-L (injected in subiculum) and retrograde CBT subunit (injected in hypothalamus)	Monosynaptic	Kishi et al. (2000)
Rat	Not specified	MnPO	Wheat germ agglutinin conjugated to HRP (injected in MnPO)	Monosynaptic	Chiba and Murata (1985)
Rat	Ventral	MnPO	Retrograde (injected in MnPO) and anterograde (injected in ventral subiculum) axonal transport techniques (amino acid, true blue, SITS, or wheat germ agglutinin)	Monosynaptic	Simerly and Swanson (1986)
Rat	Ventral	VLPO	Retrograde tracer CTB subunit (injected in VLPO)	Monosynaptic	Chou et al. (2002)
Mouse	Dorsal	MB	Retrograde labelling through CTB (injected in MB)	Monosynaptic	Kinnavane et al. (2018)
Rat	Dorsal	MB	Multiple retrograde tracers (injected in RSC) and anterograde BDA tracing (injected in dorsal subiculum)	Monosynaptic	Kinnavane et al. (2018)
Rat	Full longitudinal extent	Anterior, tuberal, and mammillary regions of hypothalamus	Anterograde PHA-L (in subiculum) and retrograde CTB subunit (in hypothalamus)	Monosynaptic	Kishi et al. (2000)
Mouse	Ventral	BF (medial septal nucleus and diagonal band nucleus)	HSV-1 tracing (injected ventral subiculum)	Monosynaptic	Tang et al. (2016)
Mouse	Dorsal	BF (dorsolateral septum)	Pseudo-typed rabies virus trans-synaptic retrograde tracing	Monosynaptic	Besnard et al. (2019)

(Continues)

TABLE 1 (Continued)

Species	Which region of subiculum	Which area	Which technique (injection site)	Monosynaptic or disynaptic	Reference
Mouse	Ventral	VTA	Anterograde PHA-L (injected ventral subiculum) and retrograde CTB (injected in VTA)	Disynaptic (through BNST)	Glangetas et al. (2015)
Rat	Dorsal	VTA	Anterograde transsynaptic tracing using AAV-1 (in dorsal subiculum)	Disynaptic (through medial mammillary nucleus)	Umaba et al. (2021)
Mouse	Ventral	LC	HSV-1 tracing (injected ventral subiculum)	Disynaptic	Tang et al. (2016)
Mouse	Ventral	MRN	HSV-1 tracing (injected ventral subiculum)	Disynaptic	Tang et al. (2016)
Mouse	Ventral	LDT	HSV-1 tracing (injected ventral subiculum)	Monosynaptic	Tang et al. (2016)
Rat	Ventral	SCN	Retrograde CTB subunit (injected in SCN)	Monosynaptic	Krout et al. (2002)

Lateral hypothalamus (LH)

The LH houses both sleep-active and wake-active neurons. Sleep-active neurons expressing melanin-concentrating hormone (MCH) in the LH are most active during REMS (Hassani et al., 2009; Kroeger et al., 2019; Varin et al., 2018). These neurons promote the initiation of REMS by inhibiting wake-promoting neurons in various brain areas, including the tuberomammillary nucleus (TMN), the locus coeruleus (LC), and the dorsal raphe nucleus (DRN) (Jego et al., 2013). The chronic activity of MCH neurons influences not only REMS but also NREMS (Konadhode et al., 2013). Additionally, hypocretin/orexin neurons in the LH play a crucial role in regulating the sleep–wake cycle (Latifi et al., 2018). Loss of these neurons leads to narcolepsy in various species, including humans (Thannickal et al., 2000) and mice (Chemelli et al., 1999). Glutamatergic and GABAergic neurons in the LH region are crucial in inducing and maintaining wakefulness, and their inhibition enhances sleep (Herrera et al., 2016; Venner et al., 2016).

Connections between the LH and the subiculum were indicated by retrograde labelling through cholera toxin B (CTB)-488 (injected in LH) as well as anterograde rabies virus injection (injected into the ventral subiculum) (Wee et al., 2023), HSV-1 tracing (injected into the ventral subiculum) (Tang et al., 2016), and anterograde *Phaseolus vulgaris* leucoagglutinin (PHA-L) tract-tracing (injected into the subiculum) (Köhler, 1990).

Preoptic hypothalamus area (POA)

The ventrolateral preoptic nucleus (VLPO) and median preoptic nucleus (MnPO) regions contain a dense population of neurons responsible for regulating sleep (Horner & Peever, 2017). Selective lesions in the rat VLPO significantly reduce NREMS (Lu et al., 2000). During sleep, GABAergic neurons in the VLPO and MnPO regions inhibit arousal regulatory systems, including the LH, posterior hypothalamus, dorsal raphe nucleus (DRN), LC, ventral periaqueductal grey matter (vPAG), and parabrachial nucleus (PB), thereby promoting sleep (Weber & Dan, 2016).

The temporal two-thirds of the subiculum are connected to the MnPO, as confirmed by anterograde PHA-L (injected into the subiculum) and retrograde CTB subunit injections (in hypothalamus) (Kishi et al., 2000). Additionally, the ventral subiculum's connection to the MnPO was identified using wheat germ agglutinin (injected into the MnPO) (Chiba & Murata, 1985). Furthermore, employing diverse retrograde (injected into the MnPO) and anterograde axonal transport techniques (injected into the ventral subiculum), the MnPO displayed reciprocal connections with the ventral subiculum (Simerly & Swanson, 1986). A direct connection between the VLPO and the ventral subiculum was described using retrograde tracer CTB subunit injection (injected into the VLPO) (Chou et al., 2002).

TMN

The hypothalamus's TMN serves as the exclusive supplier of histamine in the brain (Panula et al., 1984). Neurons within the histaminergic TMN project extensively to different sleep–wake regulatory areas, such as the VLPO (Sherin et al., 1998). These histaminergic TMN neurons exhibit the highest firing rates during active wakefulness, decrease their activity during quiet wakefulness, and remain inactive during both NREMS and REMS (Takahashi et al., 2006). Silencing histaminergic TMN neurons not only impairs arousal but also rapidly and selectively induces SWS (Fujita et al., 2017).

The subiculum was found to have connections with various hypothalamic regions, including the anterior, tuberal, and mammillary regions, established through anterograde PHA-L (injected in subiculum) and retrograde CTB subunit (injected into the hypothalamus) tracings (Kishi et al., 2000). In the rat, using multiple retrograde tracers (injected into the mammillary bodies, MB) and anterograde biotinylated dextran amine (BDA) tracing (injected into the dorsal subiculum), the monosynaptic connection of MB and subiculum was reported (Kinnavane et al., 2018). In the same study, the connections between the dorsal subiculum and MB was also confirmed in mice by retrograde labelling through fluorescent retrograde tracer fast blue (FB, injected in MB) (Kinnavane et al., 2018).

Basal forebrain (BF)

Adjacent to the POA, basal forebrain is a critical region for both sleep and wakefulness (Takahashi et al., 2009). The BF comprises three predominantly non-overlapping subpopulations, including glutamatergic neurons expressing vesicular glutamate transporter subtype 2 (McKenna et al., 2021), cholinergic neurons (Han et al., 2014), and GABAergic neurons (McKenna et al., 2020). Glutamatergic neurons in the BF influence REMS by modulating the theta rhythm (Xu et al., 2015). The BF GABAergic neurons exhibit mixed functions, with PV-expressing neurons involved in rapid transitions from NREMS to wakefulness (McKenna et al., 2020), while SOM-expressing neurons promote NREMS (Xu et al., 2015). Cholinergic neurons are active during wakefulness and REMS, inhibiting slow-wave delta oscillations (Han et al., 2014).

Monosynaptic projection of the subiculum to BF (medial septal nucleus and diagonal band nucleus) was observed by HSV-1 tracing (injected into the ventral subiculum) (Tang et al., 2016), as well as pseudo-typed rabies virus trans-synaptic retrograde tracing (injected into the BF, dorsolateral septum) (Besnard et al., 2019).

Ventral tegmental area (VTA)

Within the VTA, a region containing numerous dopaminergic, glutamatergic, and GABAergic neurons, the dopaminergic neurons predominantly regulate sleep and wakefulness (Morales & Margolis, 2017). Optogenetic and chemogenetic stimulation of VTA dopaminergic and glutamatergic neurons induces wakefulness (Eban-Rothschild et al., 2016; Oishi et al., 2017), while inhibiting these neurons results in robust NREMS activation (Eban-Rothschild et al., 2016; Yu et al., 2019). GABAergic VTA neurons restrict wakefulness by inhibiting arousal-promoting VTA glutamatergic and/or dopaminergic neurons, as well as through projections to the LH (Yu et al., 2019).

The VTA exhibited disynaptic connections to the ventral subiculum, as demonstrated by anterograde PHA-L (injected in ventral subiculum) and retrograde CTB tracing techniques (injected in VTA) (Glangetas et al., 2015) and anterograde transsynaptic tracing using adeno-associated virus serotype 1 (AAV-1, injected into the dorsal subiculum) (Umaba et al., 2021).

LC

The LC serves as a vital arousal-centre, with its noradrenergic neurons promoting wakefulness (Liang et al., 2021). Their activity decreases during NREMS and ceases during REMS (Aston-Jones & Bloom, 1981; Hobson et al., 1975).

Using a HSV-1 tracing technique (injected into the ventral subiculum) disynapses projection of the ventral subiculum to the LC was observed (Tang et al., 2016).

Raphe nuclei

The DRN and median raphe nucleus (MRN) contribute to sleep regulation through serotonergic neurons (Sulaman et al., 2023). The firing pattern of DRN serotonergic neurons increases during wakefulness and decreases during REMS (Trulson & Jacobs, 1979). These serotonergic neurons promote relaxed wakefulness while inhibiting REMS (Jacobs & Fornal, 1993). Rasmussen et al. reported a group of presumed 5-HT neurons in the MRN with similar activity patterns to “classic” 5-HT neurons in the DRN (Rasmussen et al., 1984). Recent research in mice has shown that GABAergic neurons in the LH selectively suppress GABAergic neurons in the DRN, leading to increased activity in a significant portion of LH neurons, thereby promoting arousal (Gazea et al., 2021). MRN suppresses or blocks the theta rhythm during NREMS, while silencing the MRN during REMS allows its expression (Vertes, 2010).

The MRN was found to receive projections from the ventral subiculum, as identified through HSV-1 tracing (injected into the ventral subiculum) (Tang et al., 2016). This projection has the first synapsis on the connection between the MRN and interpeduncular nucleus and then reaches MRN.

Laterodorsal tegmental nucleus (LDT)

The LDT houses cholinergic neurons, maximally active during wakefulness and REMS, and GABAergic neurons, active solely during REMS (Boucetta et al., 2014).

Using the HSV-1 tracing technique (injected into the ventral subiculum), monosynaptic projection of subiculum to LDT was identified (Tang et al., 2016).

Suprachiasmatic nucleus (SCN)

The SCN is associated with various sleep–wake regulating nuclei, playing a crucial role in circadian rhythm regulation. Lesions to the SCN abolish the daily rhythm in sleep–wake states and lead to sleep fragmentation in non-human primates (Edgar et al., 1993) and rat (Chou et al., 2003; Wurts & Edgar, 2000), which indicates the important role of the SCN in regulating the circadian timing of sleep. However, the specific pathways and functions of the SCN in sleep–wake synchronisation and sleep quality still require further investigation.

The SCN displayed connections with the ventral subiculum, as revealed through retrograde CTB subunit tracing (injected in SCN) (Krout et al., 2002).

These findings provide insight into the intricate projection of the subiculum, particularly ventral subiculum, to sleep–wake promoting areas (Figure 2), hinting at its potential direct involvement in regulating sleep and wakefulness, however, no study has yet assessed this possibility. It is noteworthy that, despite frequent reports of GABAergic projections from CA1 (Honoré et al., 2021), there is currently no documentation of any GABAergic projection from the subiculum in mice and rats. Consequently, these projections are deemed to be primarily glutamatergic (Lodge et al., 2023). However, it is crucial to acknowledge a limitation in the current understanding, as the studies under discussion employed anterograde and retrograde tracer injections in the subiculum and target areas, respectively, without the ability to differentiate between specific cell types. In addition, we should acknowledge that the glutamatergic projections from the subiculum to various areas may not necessarily induce the activation of those regions, as the subicular glutamergic projections can also target other cell types (for example GABAergic neurons of BF (Besnard et al., 2019)). Consequently, the ultimate impact of subicular

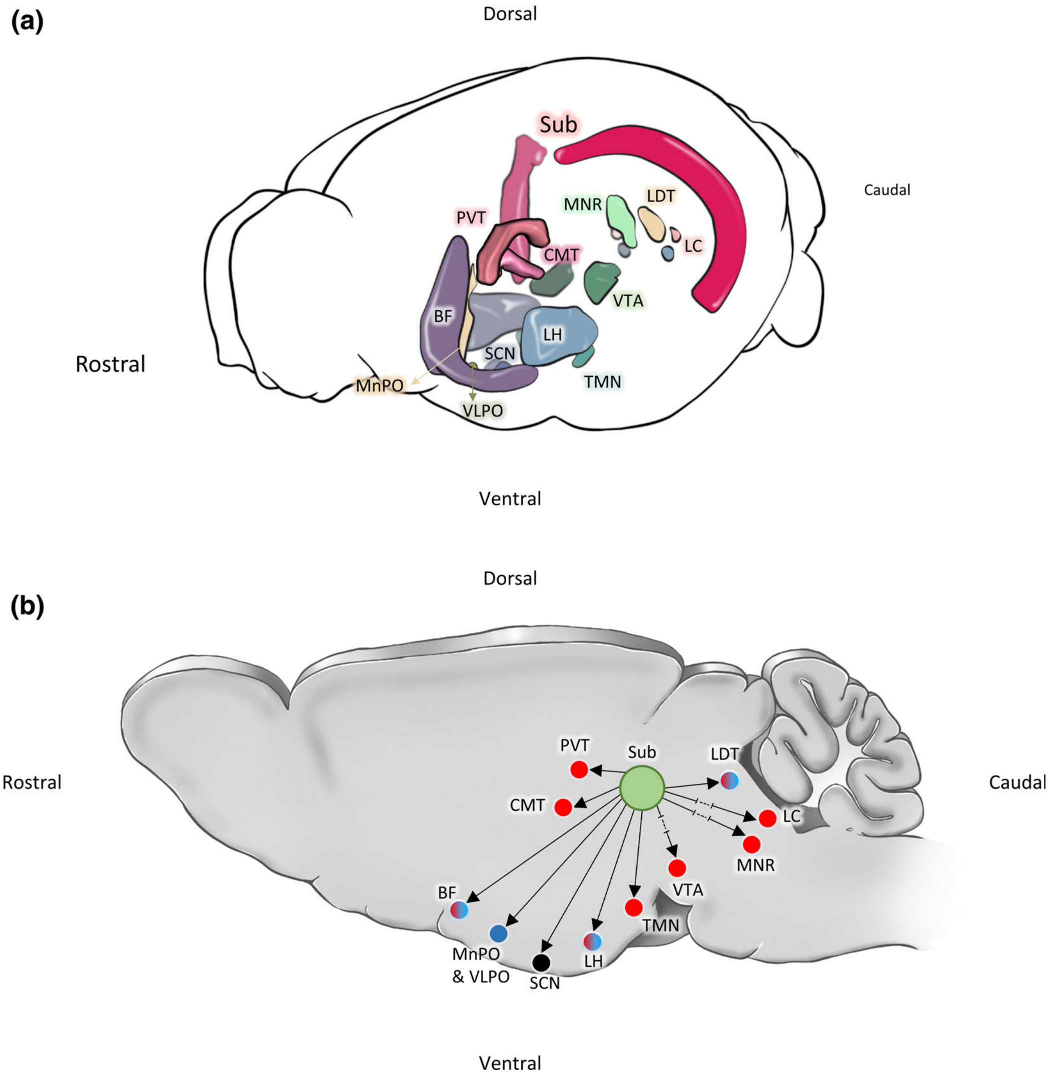

FIGURE 2 Three-dimensional reconstruction (a) and the schematic projections (b) of the subiculum to the brain areas involved in the regulation of vigilance states. Disynaptic projections are shown by sign. Nuclei highlighted in red indicate wake-promoting areas, blue indicates sleep-promoting areas, and red/blue signifies a dual role. The SCN is emphasised in black due to its crucial role in the circadian rhythm of vigilance states (Wurts & Edgar, 2000); however, no definitive sleep/wake-promoting function has been established for it. BF, basal forebrain; CMT, centromedial nucleus of the thalamus; LC, locus coeruleus; LH, lateral hypothalamus; LDT, laterodorsal tegmentum nucleus; MnPO, median preoptic nucleus; MRN, median raphe nucleus; PVT, paraventricular nucleus of the thalamus; SCN, suprachiasmatic nucleus; SLD, sub-laterodorsal (tegmental) nucleus; TMN, tuberomammillary nucleus; VLPO, ventral lateral preoptic nucleus; VTA, ventral tegmental area.

projections on different sleep–wake regulatory areas remains uncertain, as these projections have the potential to elicit either wake-promoting or sleep-promoting effects. Further comprehensive investigations are warranted to unravel the specific functional implications of subicular projections in the modulation of sleep–wake cycles.

2.3.2 | Change in subicular function in context of sleep–wake regulation

The pioneering study by Hagan et al. in 1992 explored the role of the subiculum in spatial navigation and also reported changes in sleep behaviour in rats (Hagan et al., 1992), which have received much less attention. Bilateral ibotenic acid injections induced lesions in the EC/subiculum, resulting in increased diurnal SWS and spindle incidence, along with decreased REMS. Additionally, there was a reduction in theta power during REMS and quiet waking, but not during SWS. However, the study was limited to the techniqal fact that the subiculum was not solely assessed and the result could be caused also by EC. Using in situ hybridisation for 222 genes in multiple brain regions following 6 h of sleep deprivation in mice, significant alterations in the expression of several genes (associated with learning and memory) in the subiculum were observed (Thompson et al., 2010), highlighting interactions between the subiculum and sleep. Additionally, observations indicated that a substantial set of genes and proteins in the ventral hippocampus (containing the ventral subiculum) exhibited circadian oscillations in healthy mice, which could influence various circadian rhythms in the brain (Debski et al., 2020). Despite the limited exploration of the direct relationship between the subiculum and sleep–wake behaviour, the role of the subiculum in generating sleep oscillations has been well discussed.

The subiculum has been found to act as an intrinsic generator of hippocampal theta rhythm (Jackson et al., 2014), the oscillation which plays a significant role in the consolidation of contextual memories during REMS (Boyce et al., 2016). Ibotenic acid lesioning of the ventral subiculum increased the absolute theta power in the CA1 area, with no noticeable change in its relative power (Laxmi et al., 2000). Conversely, this lesioning led to a decrease in both the absolute and relative power of EC theta power, indicating that the subicular output may play a modulatory role in the synchronous neuronal activity of EC and CA1-PCs during REMS. Bandarabadi et al. explored the dynamics of theta–gamma band interactions, utilising multiple frequency and temporal scales during simultaneous recordings from hippocampal CA3, CA1, subiculum, and parietal cortex in freely moving mice (Bandarabadi et al., 2019). Interestingly, they found that coupling during REMS was significantly stronger than during active wake within the subiculum and parietal cortex, but no such differences were observed within CA3 and CA1. The theta power exhibited no significant changes across REMS, except within the subiculum with notable alterations. Additionally, the theta phase significantly modulated the ultrahigh gamma band (160–250 Hz) in pyramidal cell layers of CA3 and the subiculum exclusively. It was suggested that the role of the subiculum in theta- and gamma oscillations is modulated by cholinergic inputs to the ventral subiculum, as the elimination of these inputs significantly reduced subicular theta, and enhanced gamma, activity during active wake and REMS states (Rastogi et al., 2014). Intriguingly, an autoradiographic study revealed that after 96 h of REMS deprivation, a decrease in muscarinic receptor binding in the EC and subiculum could be recorded, but not in other parts of the hippocampal formation (Nunes et al., 1994).

Recent work by Raquet et al. demonstrated that neonatal exposure to the novel sedative/hypnotic drug, 3β-OH, resulted in reduced subicular delta- and sigma band oscillations during NREMS (Fine-Raquet et al., 2023). In contrast, a previous study by the same authors found that neonatal exposure to the common anaesthetic agent ketamine increased subicular gamma band oscillations during NREMS and significantly suppressed subicular long-term potentiation in adolescent rats (Manzella et al., 2020). These findings suggest that exposure to different sedative/hypnotic agents during a critical period of brain development may induce distinct functional changes in subiculum circuitry that persist into adolescence. Recently, through anatomically restricted inactivation of VIP-INs in the ventral subiculum of epileptic mice, we observed a significant shift in the circadian rhythm of seizures (Rahimi et al., 2023a), implying a prominent interaction between the ventral subiculum and circadian rhythm. However, the epileptic brain exhibits distinct functional connectivity compared with a non-epileptic one (Morgan et al., 2015); therefore, in-depth studies in normally behaving animals are essential to reveal the complexities and mechanisms underlying this relationship.

3 | LIMITATIONS

In this review, we explored the projections from the subiculum to various sleep–wake regulatory regions and examined the anatomical and functional changes in the subiculum observed in patients with sleep problems and in rodents. However, it is important to acknowledge our limitation regarding the use of the term "subiculum". The subiculum is part of the subicular complex, which includes the prosubiculum, subiculum, presubiculum, postsubiculum, and parasubiculum (Ding, 2013). While our focus in this review was specifically on studies discussing the role of the subiculum, it is worth noting that some studies did not mention whether they differentiated between these areas. Therefore, we cannot be certain whether the term "subiculum" in their text refers only to the subiculum or to the entire subicular complex.

As highlighted in the review, the subiculum has extensive reciprocal connections to other parts of the hippocampal formation and the EC. While changes in the hippocampal formation and EC were reported in some studies, we emphasised the subiculum due to its status as the main output region of the hippocampal formation. Particularly, the ventral subiculum sends diverse long-range projections to almost all sleep–wake regulatory regions. However, the interaction between the subiculum, EC, and the hippocampal formation prevents us from claiming that the observed effects by the subiculum are a unique role.

Numerous functional and anatomical studies have proposed that the hippocampus is generally homologous across mammals, despite shifts in its spatial position within the brain during evolution (Poppenk et al., 2013; Strange et al., 2014). The hippocampal longitudinal axis is dorsoventrally oriented in mice, while it is rotated into the posterior–anterior direction in primates and humans, leading to the belief that the mouse dorsal subiculum is homologous to the human posterior subiculum, and the mouse ventral subiculum is homologous to the anterior human subiculum (Bienkowski et al., 2021; Fanselow & Dong, 2010). Considering the projection of the ventral subiculum to diverse sleep–wake regulatory areas in mice, it is reasonable to expect a similar projection in the human anterior subiculum. However, technical challenges have hindered studies from assessing these projections in humans. The MRI studies discussed in this review did not distinguish between posterior and anterior subiculum in humans, and the use of T1-weighted images alone makes precise discrimination challenging (Wisse et al., 2021). The use of a combination of T1-weighted and T2-weighted images is recommended for optimal segmentation (Iglesias et al., 2015) and to validate automatic segmentation against high-reliability manual segmentation (bronze-standard approach) or direct comparison with histological samples (gold standard approach) (de Looze et al., 2022; Wisse et al., 2021). However, none of these measures were conducted in the studies listed.

4 | CONCLUSIONS AND PERSPECTIVES

In this review, we have examined the subiculum's projections to the areas involved in regulating sleep–wake cycles and explored alterations in the anatomy and function of the subiculum in both humans and rodents with sleep disorders. However, existing studies have primarily focussed on the connection of the subiculum to these areas and the 'bottom-up' changes in subicular function following sleep deprivation. There is a notable gap in the literature regarding the possibility that changes in subicular function could impact sleep–wake regulation through a 'top-down' mechanism. Indeed, while sleep–wake states are typically associated with neocortical and hippocampal rhythms, the potential role of neocortical and archicortical neurons in regulating wakefulness has been largely overlooked. A few recent studies have started exploring this less-researched 'top-down' pathway, discussing the change in the sleep–wake pattern after direct modulation of the neocortical layer 5 PCs (Krone et al., 2021), PCs within the medial prefrontal cortex (Hong et al., 2023), and cortical SOM-expressing neurons (Funk et al., 2017; Spano et al., 2022; Tossell et al., 2023). Given the critical place of the hippocampus in brain-wide circuitry involved in memory and temporal processing (Eichenbaum, 2017; Pronier et al., 2023), one could speculate that this structure may have a so far unrecognised role in encoding the time spent awake or asleep. By discussing the projections of the subiculum, the primary output region of the hippocampus (Kishi et al., 2000), to sleep–wake regulatory regions, we would like to highlight the unexplored possibility of a 'top-down' role of the subiculum in sleep–wake regulation. Although studies such as Hagan et al (Hagan et al., 1992), which induced lesions in the subiculum/EC resulting in sleep disturbance, and our recent work, demonstrating significant changes in the circadian rhythm of seizures by silencing VIP-INs in the ventral subiculum of epileptic mice (Rahimi et al., 2023a), provide insights into this possibility, further research is essential. Notably, the first experiment was not exclusively localised to the subiculum, and the second involved epileptic animals, making it imperative to conduct additional studies to thoroughly evaluate this hypothesis.

We found the subiculum as a promising focus for future research on sleep neurobiology. Exploring its precise neurophysiological mechanisms in interaction with sleep-regulatory regions and understanding the molecular and cellular processes during sleep–wake transitions could provide deeper insights into the regulation of sleep cycles. Investigating the subiculum's neural pathways may enhance our understanding of the connections between brain oscillations and vigilance states. Furthermore, interventions such as pharmacological and neuromodulatory approaches targeting the subiculum may offer innovative strategies for improving sleep disorders and overall sleep quality.

AUTHOR CONTRIBUTIONS

Sadegh Rahimi: Conceptualization; writing – original draft; writing – review and editing; visualization; validation. **Leesa Joyce:** Visualization; writing – original draft; writing – review and editing. **Thomas Fenzl:** Writing – review and editing; conceptualization; methodology; project administration; supervision; validation. **Meinrad Drexel:** Funding acquisition; writing – review and editing; methodology; project administration; supervision; validation; conceptualization.

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CONFLICT OF INTEREST STATEMENT

All authors declare that this research was conducted in the absence of any commercial or financial interests that could be a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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