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REVIEW ARTICLE

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Beyond the role in motor function, entopeduncular nucleus, a critical neural hub in psychiatric disorders and sleep regulation

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ABSTRACT

Background: The entopeduncular nucleus (EP) is a major output nucleus of the basal ganglia and plays a critical role in integrating motor, emotional, and behavioral processes. Although traditionally linked to motor control, accumulating evidence indicates that the EP is deeply involved in psychiatric disorders, sleep regulation, addiction, and mood-related behaviors. As the rodent homolog of the human internal Globus pallidus (GP) the EP represents a key translational structure bridging preclinical and clinical neuroscience.

Methods: This narrative review was conducted following established narrative review methodology. Relevant literature was identified through a structured search of major biomedical databases. Peer-reviewed experimental and clinical studies investigating EP anatomy, connectivity, neurotransmitter systems, and functional roles were included. The review synthesizes findings from mouse and rat models employing optogenetic and chemogenetic manipulation, electrophysiological recording, neuroanatomical tracing, molecular approaches, and behavioral assays, alongside human neuroimaging, lesion, and deep brain stimulation studies.

Results: Evidence from rodent models demonstrates that the EP functions as a convergence hub integrating GABAergic, glutamatergic, dopaminergic, serotonergic, and endocannabinoid signaling. EP projections to the lateral habenula regulate aversive processing, addiction-related behaviors, and mood states. Cell-type-specific mouse studies identify entopeduncular circuits implicated in anxiety regulation. Dysregulation of EP circuits is implicated in depression, anxiety, and Parkinsonian motor dysfunction. Clinical and preclinical neuromodulation studies further support the therapeutic relevance of targeting EP circuits.

Conclusion: The EP is a multifunctional neural hub extending beyond motor control. Integrating evidence from rodent and human studies highlights its importance in psychiatric and sleep disorders and supports its potential as a translational therapeutic target.

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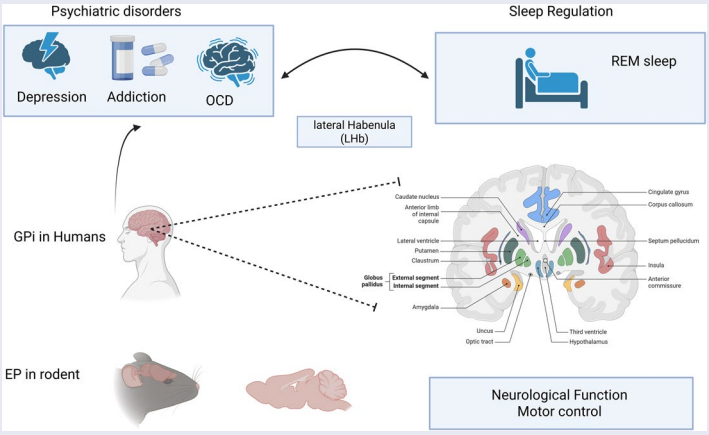
GRAPHICAL ABSTRACT



KEY MESSAGES

- The entopeduncular nucleus (EP) functions extend beyond motor control to psychiatric regulation and sleep modulation.
- EP-lateral habenula projections are crucial for addiction and aversive behaviors.
- EP's endocannabinoid system plays a vital role in sleep regulation and mood control.
- Deep brain stimulation of EP shows therapeutic potential for Parkinson's disease and treatment-resistant depression.
- Novel therapeutic approaches targeting EP circuits are emerging for psychiatric disorders, including anxiety, Obsessive-compulsive disorder (OCD), and schizophrenia.
- Translation of preclinical findings to human applications remains a key challenge.

Introduction

The EP [1], a critical component of the basal ganglia [2], has emerged as a significant area of interest in neuroscience due to its multifaceted roles in psychiatric disorders, sleep regulation, and potential clinical applications. Recent research has significantly expanded our understanding of the EP beyond its traditional role as a motor output nucleus, showing that EP neuronal activity encodes both reward-related and movement-related signals in freely moving mice, suggesting that the EP functions as a limbic-motor interface involved in valence, motivation, and behavioral outcome processing [3]. The entopeduncular nucleus exists as a distinct nucleus in rodents, while in humans and other primates, it is considered homologous to the internal segment of the globus pallidus (GPi), highlighting a key evolutionary difference in basal ganglia organization between species (Figure 1).

Recent research has highlighted the EP's involvement in modulating the aversive effects of substances like cocaine. Studies have shown that EP projections to the lateral habenula (LHb) are crucial for processing cocaine's aversive effects and influencing addiction vulnerability [1]. This finding opens new avenues for understanding and potentially treating substance abuse disorders.

The EP also plays a pivotal role in sleep regulation, primarily through the endocannabinoid system. Activation of cannabinoid receptor 1 (CB1R) in the EP has been found to promote non-rapid eye movement sleep (NREMs) and modulate mood [4]. This discovery suggests potential therapeutic applications for sleep disorders and mood-related conditions.

Furthermore, the Relationship between endocannabinoids and dopamine within the EP influences basal ganglia output, affecting action selection and decision-making processes [5]. This interaction may have implications for psychiatric conditions characterized by impaired decision-making.

From a clinical perspective, high-frequency stimulation (HFS) of the EP, similar to deep brain stimulation (DBS) used in Parkinson's disease, has been explored for its effects on neurotransmitter dynamics and motor behavior. While HFS in the EP increases extracellular glutamate levels in the striatum, its neuroprotective and functional improvement effects in Parkinson's disease models differ from those observed in the subthalamic nucleus [6,7]. Furthermore, the discovery of mixed GABA/glutamate cotransmission within these pathways suggests a highly nuanced mechanism for encoding choice direction and outcome [8].

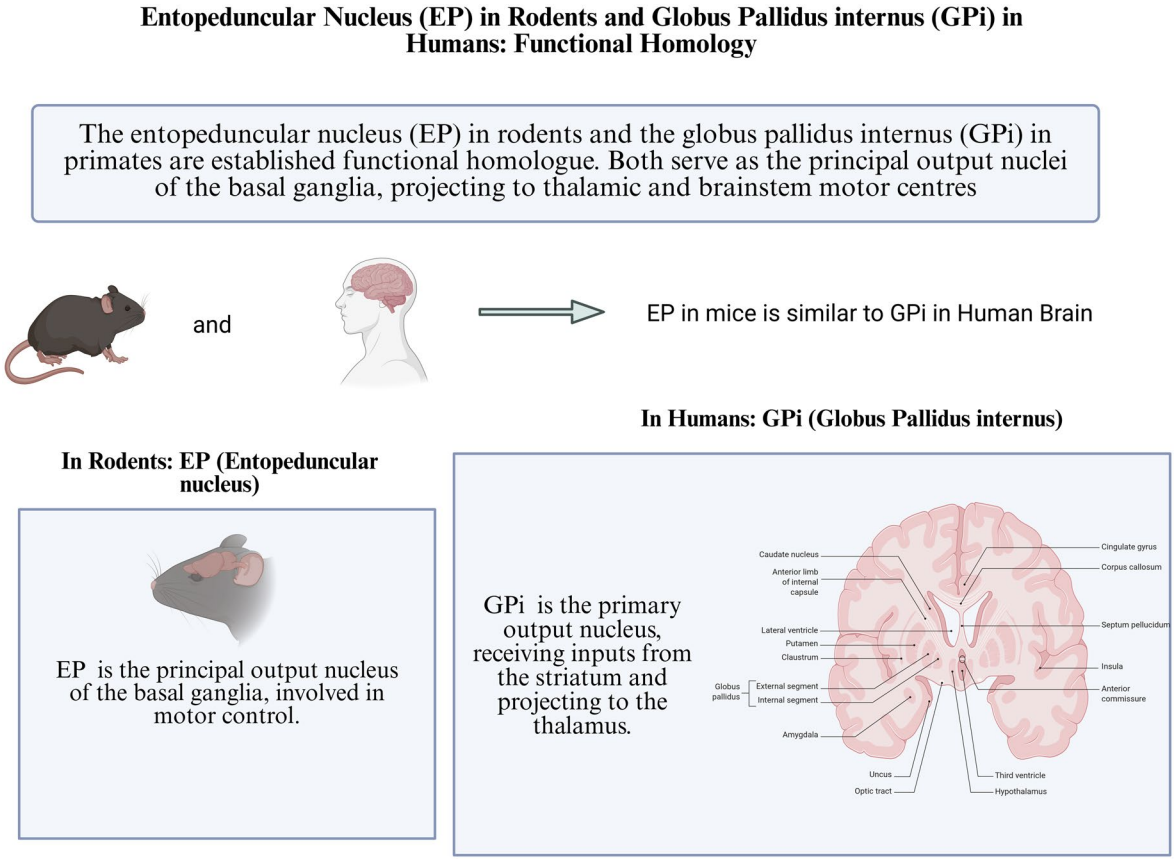


Figure 1. Functional homology between the entopeduncular nucleus (EP) in rodents and the globus pallidus internus (GPi) in humans.
Schematic illustration comparing the anatomical location and functional equivalence of the entopeduncular nucleus (EP) in rodents and the globus pallidus internus (GPi) in humans. Both structures serve as the principal output nuclei of the basal ganglia, integrating inputs from the striatum and projecting to the thalamus to regulate motor control. The EP in rodents is shown to be functionally homologous to the GPi in primates, highlighting conserved basal ganglia circuitry across species.

Coherent neuronal firing between the EP and motor cortex has been documented in parkinsonian rats with levodopa-induced dyskinesias, the functional integration of this circuit [9] in hemiparkinsonian rats, the EP modulates motor control through inhibitory projections to thalamic motor regions, thereby influencing motor cortical activity and movement execution [10]. These findings underscore the complex involvement of the EP in both psychiatric and neurological disorders. This comprehensive narrative review aims to synthesize and expand upon recent findings on the EP's multifaceted roles in these domains, discussing its underlying mechanisms, influence on behavior, and prospects for clinical translation. By delving deeper into the intricate networks and molecular pathways involving the EP, we can better appreciate its significance in brain function and its potential as a therapeutic target. These recent cell-type-specific discoveries now demand a translational roadmap that links rodent EP circuits to human GPi interventions This review is organized as follows. We first describe the comparative anatomy and circuit architecture of the EP. We then systematically examine its involvement in five psychiatric domains addiction, mood disorders, anxiety, schizophrenia, and OCD integrating pathophysiological mechanisms, preclinical evidence, and therapeutic implications within each subsection. Next, we discuss the EP's emerging role in sleep regulation and circadian rhythms, followed by its relevance to Parkinson's disease and motor neuromodulation. We conclude with a translational roadmap that identifies priorities for bridging rodent EP findings to human GPi-targeted interventions.

Review registration and methodology statement

This narrative review follows a structured approach to literature synthesis, though it was not formally registered due to its narrative nature. A comprehensive literature search was conducted using PubMed, Web of Science, and Scopus databases Search terms included "entopeduncular nucleus," "internal globus

pallidus," "basal ganglia," "psychiatric disorders," "sleep regulation," and "motor control." Additional searches were performed combining these terms with "addiction," "mood disorders," "anxiety," "schizophrenia," "OCD," "Parkinson's disease," and "deep brain stimulation." Articles were selected based on relevance, methodological quality, and contribution to current understanding of EP function. Priority was given to peer-reviewed original research articles, systematic reviews, and meta-analyses. This review synthesizes findings from both preclinical and clinical studies to provide a comprehensive overview of EP's role in various neurological and psychiatric conditions.

Anatomical and functional overview of the entopeduncular nucleus

Comparative anatomy: rodent EP vs. primate GPi

EP is a small, lens-shaped structure located in the ventral forebrain, forming part of the ventral pallidum. Quantitative Golgi studies of the primate substantia nigra reveal diverse dendritic morphologies among nigral output neurons, providing a comparative structural framework that has informed analyses of basal ganglia output organization more broadly [11] dedicated Golgi-level morphological mapping of the EP itself remains comparatively sparse. In rodents, it exists as a distinct nucleus, while in primates, it is considered homologous to the internal segment of the globus pallidus [12]. This anatomical positioning allows the EP to serve as a critical interface between the basal ganglia and various downstream targets, including the thalamus, lateral habenula, and brainstem nuclei [13].

Cytoarchitecturally, the EP is primarily composed of GABAergic projection neurons, with a smaller population of interneurons ,Similar GABAergic organization characterizes the external globus pallidus (GPe), where distinct neuronal populations contribute to basal ganglia output across basal ganglia nuclei [14]. These neurons exhibit complex dendritic arborizations, allowing for intricate information processing [15]. Recent studies have revealed neurochemical heterogeneity within the EP, with subpopulations of neurons expressing different combinations of neuropeptides and receptors [16]. Neurochemical diversity has also been documented in the GPe, which contains distinct prototypic and arkypallidal neuronal subtypes [17]

Neurochemical heterogeneity and circuitry

Cytoarchitecturally, the EP is primarily composed of GABAergic projection neurons. However, recent mapping a study has revealed distinct subregions defined by the expression of Substance P and Cannabinoid Type-1 Receptors (CB1R), indicating a high degree of functional specialization [2].

Afferent inputs

EP manifests a sophisticated connectivity framework that is fundamental to its multifaceted functional responsibilities. Principal afferent inputs to the EP consist of striatal projections originating from both direct and indirect pathway neurons, thereby establishing an essential connection within the cortico-basal ganglia-thalamo-cortical loop. Coherent activity between the EP and motor cortex further supports the functional integration of this circuit [8,9]. Entopeduncular lesions facilitate spontaneous and drug-evoked motor behavior in hemiparkinsonian rats, whereas thalamic lesions depress it, revealing the inhibitory influence of EP output on motor control [10]. Inputs of dopaminergic nature from the substantia nigra pars compacta (SNc) serve to modulate EP activity [11], while serotonergic innervation arising from the dorsal raphe nucleus exerts influence over mood and emotional processing [18].

Efferent projections

The principal efferent projections of the EP are similarly varied. GABAergic outputs directed towards motor, associative, and limbic regions of the thalamus comprise a significant portion of its efferent connections [19]. The EP additionally conveys excitatory projections to the lateral habenula (LHb), which are

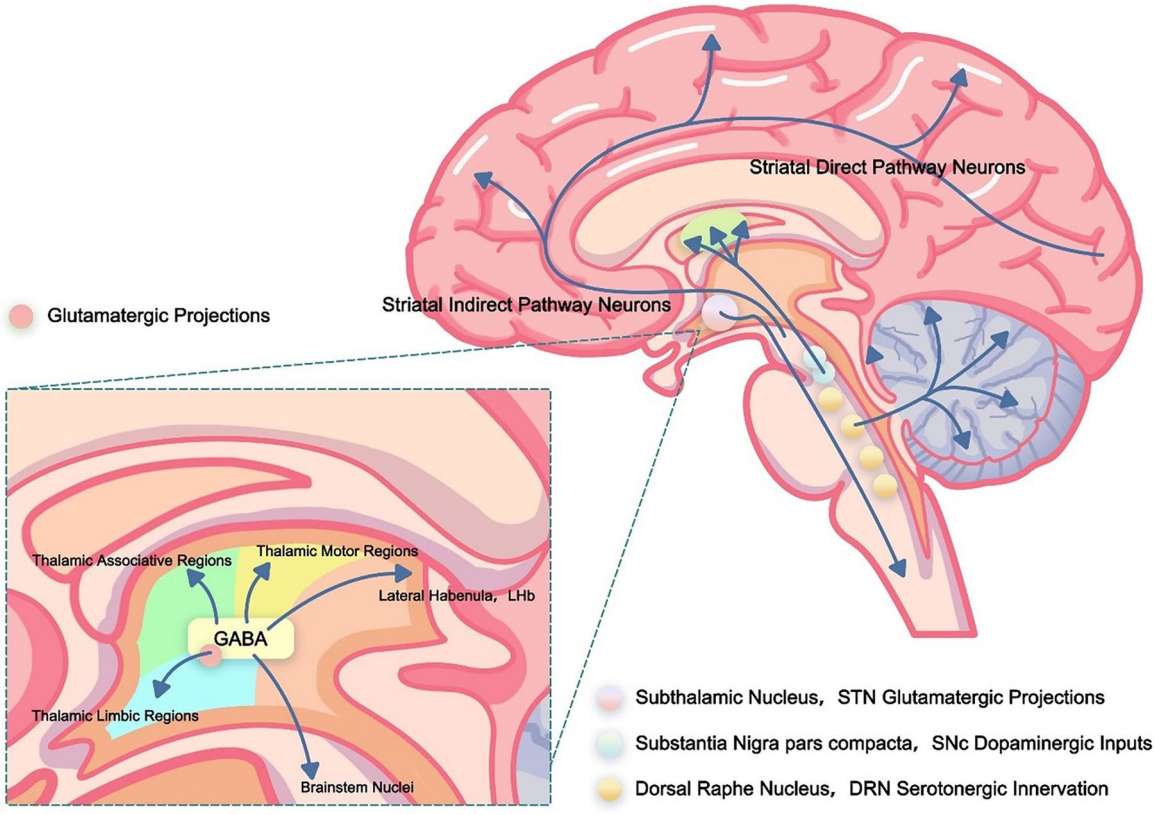


Figure 2. Synaptic architecture and circuit connectivity of the EP.
The major afferent and efferent connections of the entopeduncular nucleus EP. The EP receives inputs from striatal direct and indirect pathway neurons, glutamatergic projections from the subthalamic nucleus STN, dopaminergic inputs from the substantia nigra pars compacta SNc, and serotonergic innervation from the dorsal raphe nucleus DRN. EP outputs project to thalamic motor, associative, and limbic regions, the lateral habenula LHb, and brainstem nuclei, highlighting its role as an integrative hub linking motor, limbic, and associative basal ganglia circuits.

vital for the processing of aversive behaviors and are suppressed by serotonin [20]. Moreover, descending projections to a range of brainstem nuclei, including the pedunculopontine nucleus and the superior colliculus, further enhance the EP's influence [21]. This intricate connectivity framework positions the EP as a pivotal integrator of diverse neural information, thereby affecting motor, cognitive, and emotional processes [22]. GABAergic and glutamatergic projections to the LHb and VTA, which are vital for reward and aversion processing synaptic architecture is shown in (Figure 2).

Neurotransmitter systems and functional roles

The functionality of the EP is subject to modulation by multiple neurotransmitter systems. GABA is recognized as the principal neurotransmitter of EP projection neurons, which is essential for its inhibitory output [14]. Glutamate is identified within a subset of EP neurons projecting to the LHb and in afferent projections stemming from the STN [23]. Dopamine exerts modulation on EP activity *via* D1 and D2 receptors, impacting synaptic plasticity [24]. Serotonin interacts with multiple receptor subtypes in the EP, thereby influencing mood and emotional processing [18]. Cholinergic inputs from the brainstem modulate striatal and nucleus accumbens activity, affecting attention and arousal [25]. These cholinergic systems might also influence EP function through their actions within the broader basal ganglia circuitry Endocannabinoids play an instrumental role in synaptic plasticity and neurotransmitter release within the EP [26].

The EP's extensive connectivity and neurochemical intricacy underpin its engagement in various functional domains, including motor execution and learning, reward processing, value-based decision-making, emotional regulation, and sleep-wake cycles. Understanding these diverse functional roles is crucial for appreciating the EP's involvement in various neuropsychiatric disorders and its potential as a target for therapeutic intervention (Figure 2).

The EP's role in psychiatric disorders

Addiction and rewarding

The EP has been recognized as an essential component in the neurobiological framework of addiction, particularly through its projections to the LHb and its interactions with the mesolimbic dopamine system [27]. Endocannabinoid signaling in the LHb directs stress coping strategies and modulates anxiety and depressive like behaviors under conditions of stress [28]. In parallel, cocaine withdrawal diminishes GABAergic cotransmission at EP-LHb synapses, shifting the GABA/glutamate balance and driving aversive states that heighten relapse vulnerability. Furthermore, endocannabinoid/GABA interactions within the EP have been shown to modulate alcohol intake, suggesting a broader role for EP signaling in substance use disorders [29,30].

Mood disorders and anxiety

The EP's role in mood regulation is increasingly linked to its connectivity with the prefrontal cortex (PFC) reduced EP–PFC functional connectivity correlates with MDD severity. Translating this circuit to humans, a 2016 randomized, double-blind, crossover trial of deep-brain stimulation targeted to the ventral anterior limb of the internal capsule (vALIC) enrolled 25 adults with treatment-resistant depression. After a 52-week open-label optimisation phase, 40% of patients (10/25) achieved responder status (≥ 50% reduction on the 17-item Hamilton Depression Rating Scale). During the subsequent 12-week blinded crossover, active stimulation yielded a mean HAMD-17 score of 13.6 versus 23.1 during sham ($p < 0.001$), confirming the antidepressant effect beyond placebo. The study reported a favorable safety profile; however, serious psychiatric adverse events, including suicide attempts and suicidal ideation, occurred during the open-label phase [31].

Schizophrenia and OCD

EP dysfunction is also implicated in the impaired sensorimotor gating (measured by prepulse inhibition, PPI) seen in schizophrenia, as evidenced by studies showing that lesions or stimulation of the EP can modulate apomorphine-induced PPI deficits [32,33]. Mechanistically, the EP contributes to thalamic gating, where its inhibitory output regulates the flow of sensory information to the cortex, disruption of this gating is linked to the cognitive symptoms and sensory overload characteristic of schizophrenia in OCD models, high-frequency stimulation (HFS) of the EP has been shown to reduce compulsive-like behaviors, likely by normalizing the overactive output to the thalamocortical loops [34]. This suggests that the EP is a key node in the Cortico-Striato-Thalamo-Cortical (CSTC) circuits, where its hyperactivity may drive error-monitoring deficits and compulsive checking.

EP-LHb pathway in drug aversion

Recent investigations have clarified the distinct function of the EP-LHb pathway in mediating the aversive consequences associated with drug use. A study demonstrated that projections from the EP to the LHb play a pivotal role in aversive behavioral responses observed in rodent models [35]. The optogenetic activation of this pathway was adequate to elicit conditioned place aversion, whereas its inhibition diminished the avoidance behavior induced by cocaine.

Cocaine withdrawal diminishes GABAergic cotransmission at EP-LHb synapses, shifting the GABA/glutamate balance and driving aversive states that heighten relapse vulnerability [36]. Additionally, thalamic inputs to the nucleus accumbens have been shown to mediate opiate dependence [37], highlighting the distributed nature of addiction-related circuit adaptations [36].

EP interactions with the reward system

The EP's role in addiction extends beyond aversion, it involves complex interactions with the brain's reward circuitry. Faget et al. (2018) demonstrated that ventral pallidum neurons receive inputs from both the direct and indirect pathway neurons of the nucleus accumbens, allowing for nuanced modulation of reward-related behaviors [38]. In parallel, the EP may influence addiction-related aversive states through

its projections to the LHb. Furthermore, the projections of the EP to the ventral tegmental area (VTA) may, similar to pallidal-VTA circuitry, provide GABAergic modulation of VTA neuronal excitability, with opioid-sensitive inhibition potentially influencing dopaminergic tone in the nucleus accumbens, a process implicated in reward learning and addiction. [39].

EP plasticity in addiction

Chronic drug exposure drives significant plasticity across pallidal output nuclei, altering the functional output of the EP and its primate homolog the GPI. Creed et al. (2016) discovered that repeated cocaine exposure enhances ventral tegmental area dopamine neuron activity via calcium-impermeable NMDA receptors, thereby augmenting dopaminergic drive that modulates reward-related behavior [40]. This plasticity encompasses changes in both Pre and post-synaptic mechanism including modifications in neurotransmitter release probability and receptor expression [41] sketch is shown in Figure 3.

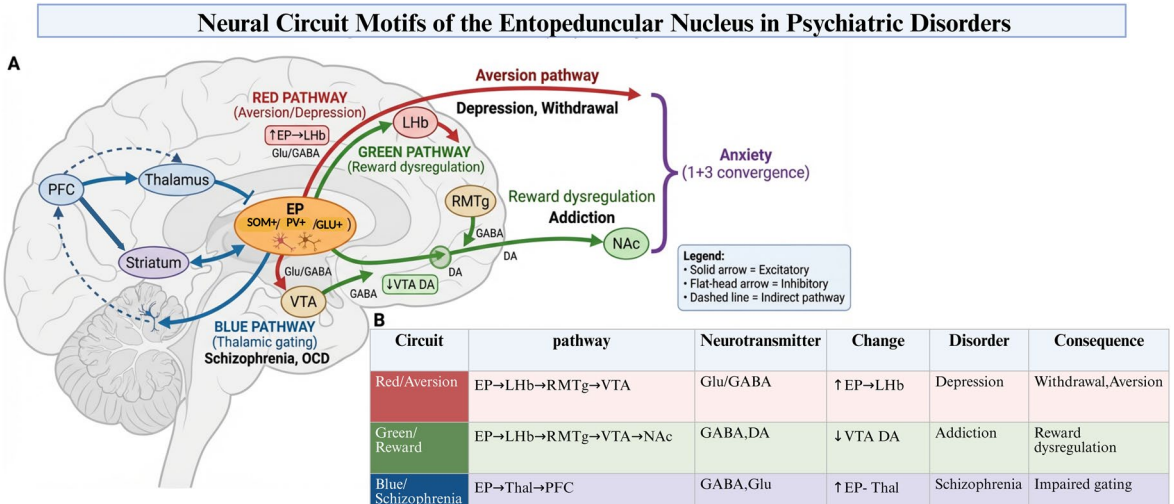
Therapeutic implications

Mood disorders

The EP's role in mood regulation has become increasingly apparent, with evidence implicating EP dysfunction in both depression and bipolar disorder.Structural neuroimaging meta-analyses reveal reduced basal ganglia volume in major depressive disorder relative to healthy controls, with structural alterations further distinguishing depressive from bipolar phenotypes [42].

EP and depression

Neuroimaging studies have shown alterations in EP activity and connectivity in patients with MDD. Structural and functional abnormalities in the amygdala and prefrontal cortex have been documented in major depressive disorder, particularly in patients with suicide attempts [43]. These alterations in limbic-prefrontal connectivity may parallel dysfunction in EP-prefrontal circuits, although EP-specific connectivity studies in MDD remain limited. Preclinical models using rodents have also revealed changes in EP neuronal activity and synaptic plasticity associated with depression. Neuroimaging meta-analyses



Circuit	pathway	Neurotransmitter	Change	Disorder	Consequence
Red/Aversion	EP→LHb→RMTg→VTA	Glu/GABA	↑EP→LHb	Depression	Withdrawal,Aversion
Green/ Reward	EP→LHb→RMTg→VTA→NAc	GABA,DA	↓VTA DA	Addiction	Reward dysregulation
Blue/ Schizophrenia	EP→Thal→PFC	GABA,Glu	↑EP- Thal	Schizophrenia	Impaired gating
Blue/OCD	PFC→Str→EP(GPi)→Thal→PFC	GABA,Glu	Hyperactive loop	OCD	Repetitive Behaviour
Purple/ Anxiety	Red+ Blue Convergence	Mixed	combined ↑	Anxiety	Multi-circuit dysfunction

Figure 3. EP-centered neural circuits in psychiatric disorders.
(a) Schematic of three EP pathways: red (EP→LHb) mediating aversion/depression; green (EP→LHb→RMTg→VTA→NAc) regulating reward and addiction via dopaminergic output; and blue (EP→thalamus→PFC/striatal loops) controlling thalamocortical gating, linked to schizophrenia and OCD. Convergence contributes to anxiety. Solid arrows, excitatory; flat-headed arrows, inhibitory; dashed lines, indirect.
(b) Summary of pathways, neurotransmitters (Glu, GABA, DA), direction of change, and associated disorders.

have identified structural and functional neural differences in anxiety disorders compared to healthy controls [44]. Preclinical studies further suggest that chronic stress leads to dendritic remodeling and altered excitability in basal ganglia neurons, effects that may be reversed by antidepressant treatment.

EP in bipolar disorder

Neuroimaging studies have consistently identified widespread cortical structural abnormalities in patients with bipolar disorder, reflecting disruptions in brain networks involved in emotional and cognitive regulation [45]. Furthermore, dysregulation of glutamatergic and GABAergic neurotransmission is considered a key neurobiological feature of bipolar disorder and is thought to contribute to its underlying pathophysiology [46]. Circadian rhythm disruption, including alterations in sleep–wake cycles and chronotype, is another hallmark of the disorder and has been associated with symptom severity, disease progression, and relapse [47]. Although direct evidence linking the EP to bipolar disorder remains limited, its central role within basal ganglia circuits and its involvement in affective, motor, and circadian regulation suggest that it may contribute to the neural mechanisms underlying the disorder.

Therapeutic approaches in mood disorders

EP has emerged as a promising target for treating mood disorders through various approaches. Neuromodulation techniques, particularly deep brain stimulation, have shown encouraging results in treatment-resistant depression [31]. Pharmacological management of bipolar disorder targets monoaminergic and glutamatergic systems, with ongoing development of mechanism-based therapies that indirectly influence basal ganglia output [48]. Given the EP's role in circadian regulation, chronotherapeutic approaches may be particularly effective for mood disorders that involve circadian components [49].

Anxiety and EP mechanisms

Optogenetic studies have identified key pathways, such as the EP–LHb circuit, which transmits aversive signals, activation of this pathway drives real-time place avoidance, consistent with its role as an antireward signal [20]. Although the EP lacks direct projections to the amygdala, it modulates amygdalar activity through thalamic nuclei, thereby influencing fear and anxiety responses[50]. The EP regulates prefrontal cortical circuits through thalamic projections, contributing to the cognitive and affective dimensions of anxiety [12].

Molecular mechanisms within the EP may significantly influence anxiety regulation. GABAergic transmission plays a central role, with selective modulation of GABA(A) receptor subtypes potentially demonstrating bidirectional effects on anxiety levels [51]. Neurons expressing corticotropin-releasing factor (CRF) and neuropeptide Y (NPY) in the amygdala exhibits opposing effects on anxiety-like behaviors [52],while related peptidergic systems in other basal ganglia structures, including the EP, may contribute to anxiety modulation through interconnected circuits and NPY in the bed nucleus of the stria terminalis (BNST) exerts anxiolytic effects [53]. Given the interconnectedness of the EP with extended amygdala structures, these neuropeptidergic mechanisms may indirectly influence EP-mediated anxiety responses. The increasing understanding of the EP's role in anxiety has inspired novel therapeutic approaches, including the development of subtype-selective GABA(A) receptor modulators [52] Reverse translational strategies for developing animal models have also advanced our understanding of mood and anxiety disorders more broadly [54], refined neuromodulation techniques, and potential biomarker identification [55].

Schizophrenia and EP dysfunction

Dysfunction of the EP appears increasingly relevant to the pathophysiology of schizophrenia. Dopaminergic and glutamatergic dysregulation in schizophrenia disrupts basal ganglia-thalamo-cortical circuits, implicating downstream output nuclei such as the EP in the pathophysiology of early-stage disease [56]. Animal models demonstrate that disrupted GABAergic signaling in cortical and subcortical circuits during development can lead to schizophrenia-like phenotypes ,Maternal immune activation selectively impairs

parvalbumin interneuron function in the medial prefrontal cortex and given the interconnectedness of the basal ganglia with cortical GABAergic networks, similar disruptions may extend to EP circuits [57].

The EP's involvement spans multiple symptom domains in schizophrenia. Through its influence on thalamocortical circuits, EP dysfunction may contribute to deficits in working memory and impaired executive function,Drug-induced plasticity in prefrontal cortical regions, such as long-term potentiation alterations following repeated cocaine exposure [58] may illustrates how circuit-level disruptions can impair executive functions. Alterations in EP-mediated sensory gating might underlie positive symptoms [59], Alterations in EP-mediated sensory gating consistent with the prepulse-inhibition findings described above [32,33] might underlie positive symptoms, while its role in motivation and reward processing suggests involvement in negative symptoms [60]. These insights have prompted explorations of novel drug targets [61], neuromodulation approaches [62], and early intervention strategies [63].

OCD and EP circuitry

The EP's position within the cortico-striato-thalamo-cortical circuit makes it particularly relevant to the pathophysiology of obsessive-compulsive disorder (OCD).Monoamine abnormalities in the SAPAP3 knockout model contribute to obsessive-compulsive disorder-related behaviors [64]. Abnormal activity in EP projections to the thalamus may further contribute to CSTC circuit hyperactivity observed in OCD, highlighting the potential convergence of neurochemical and circuit-level mechanisms. Specific frontostriatal circuits are implicated in impaired cognitive flexibility and goal-directed planning in OCD [65], The EP-LHb pathway may additionally contribute to error detection and aversive signaling, which could relate to excessive concerns about making mistakes. Aberrant pulvinar connectivity has been documented in social anxiety disorder [66], suggesting that thalamic and related subcortical structures, including the EP, may contribute to anxiety phenotypes through their influence on amygdalar activity. Research findings support the involvement of cortico-striato-thalamo-cortical circuits in OCD, with neuroimaging meta-analyses identifying altered orbitofrontal and subcortical activity in patients. Given the EP's central position within these circuits, it may contribute to the underlying network dysfunction [67], and electrophysiological recordings revealing abnormal subthalamic theta activity as a potential biomarker for OCD [68], Whether EP neurons exhibit similarly altered firing patterns in OCD remains an important question for future research. Animal studies demonstrate that striatal circuits governing habit formation are critically implicated in obsessive-compulsive disorder, with downstream pallidal output modulating compulsive behavioral patterns [69]. Therapeutic approaches targeting the EP, including deep brain stimulation [70] and novel pharmacological interventions, show promise for treatment-resistant OCD. Understanding EP circuits may also inform the development of more effective cognitive-behavioral therapy approaches and neurofeedback techniques.

The EP's role in sleep regulation and circadian rhythms

The EP's involvement in sleep regulation has gained significant attention in recent years. Mammalian sleep is regulated by interactions among multiple neurotrans [71]. Nicotinic receptor modulation has been explored as a strategy for targeting neuronal dysfunction in schizophrenia [63],Separately, the endocannabinoid system within the EP has been implicated in sleep regulation, with CB1R activation promoting NREM sleep[4] the newly discovered Som + neurons are essential for REM sleep maintenance and its associated emotional processing [72]. CB1R activation in the EP reduces the release of neurotransmitters that promote wakefulness, thereby facilitating the transition to NREM sleep. In contrast, EP Som + neurons exhibit high firing rates during REM sleep, projecting to the LHb to modulate the emotional content of dreams and post-sleep anxiety levels. Furthermore, N-arachidonoyl-serotonin (AA-5-HT) has been identified as a modulator of sleep-wake architecture and homeostasis [73].Together with endocannabinoid signaling within the EP, these findings highlight the chemical diversity of mechanisms underlying sleep regulation

The EP may also contributes to circadian rhythm regulation through its communication with the SCN. EP neurons show diurnal firing patterns, with peak activity during the active phase, which is entrained by

SCN-derived signals. This rhythmic activity is essential for coordinating the basal ganglia's output with the body's internal clock, ensuring that motor and cognitive functions are optimized for the appropriate time of day.

EP and the endocannabinoid system in sleep regulation

The endocannabinoid system within the EP has emerged as a key modulator of sleep. Activation of cannabinoid receptor 1 (CB1R) in the EP promotes NREM sleep [4], while lateral hypothalamic circuits regulate wakefulness through distinct inhibitory mechanisms [74]. This effect is mediated through the modulation of GABAergic and glutamatergic transmission within the EP. Furthermore, the endocannabinoid system in the EP has been implicated in the homeostatic regulation of sleep, with increased endocannabinoid signaling during sleep deprivation promoting subsequent sleep recovery.

EP interactions with sleep-wake circuits

The EP's role in sleep regulation may extends beyond the endocannabinoid system, involving complex interactions with various sleep-wake circuits. The lateral hypothalamus, a key center for wakefulness regulation containing glutamatergic orexin neurons [75], may influence basal ganglia output nuclei including the EP. The thalamic reticular nucleus plays a crucial role in the generation of sleep spindles and the maintenance of NREM sleep [76]. The EP may also modulates the activity of the pedunculopontine tegmental nucleus, a brainstem region involved in REM sleep regulation [77]. Given the anatomical position of the EP within basal ganglia-thalamic circuits, these sleep-wake structures may interact with EP-mediated pathways.

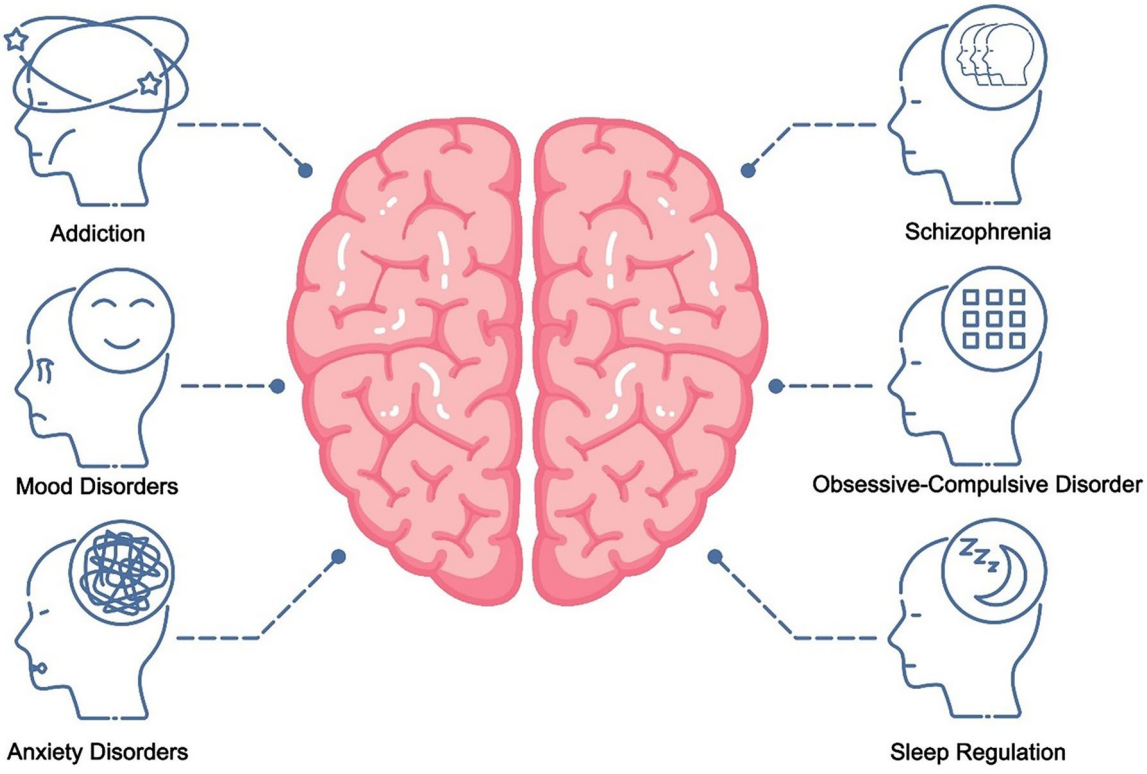


Figure 4. The pathophysiological implications of entopeduncular nucleus dysfunction. The EP acts as a critical hub where motor, limbic, and associative circuits converge. Dysfunction within the EP may contribute to widespread disturbances in downstream neural systems and is associated with addiction, mood disorders, anxiety disorders, schizophrenia, obsessive-compulsive disorder, and sleep regulation abnormalities. This schematic summarizes the broad clinical and behavioral domains potentially influenced by EP dysfunction.

Table 1. Circuit-specific therapeutic targets and modalities across neuropsychiatric disorders, with corresponding evidence levels.

Disorder	Therapeutic target	Treatment modality	Evidence level
Addiction	EP-LHb Aversion Circuit	Optogenetics / Chemogenetics	Preclinical
Depression	vALIC (adjacent to GPi)	*DBS*	*Clinical*
Anxiety	EP–LHb aversive signaling	Optogenetics	Preclinical (aversive behavior)
OCD	GPi (TS + OCD comorbidity)	*open-loop GPi-DBS*	*case series*
Parkinson's	GPi motor output nuclei	*GPi-DBS*	*Clinical*

Circadian rhythm regulation and the EP

Primate homolog of EP (GPi)'s involvement in circadian rhythm regulation has been highlighted by recent studies.The primate homolog of the EP, the globus pallidus internus, exhibits diurnal variations in neuronal activity across the sleep–wake cycle, though the directionality varies across individuals [78]. This rhythmicity is entrained by the master circadian clock in the suprachiasmatic nucleus (SCN) through both direct and indirect projections [79]. Circadian rhythm disruption can arise from genetic mutations affecting photic entrainment, as demonstrated by the duper mutation in Syrian hamsters [80].Whether EP-specific lesions or manipulations similarly alter circadian rhythms remains to be directly tested

The EP's role in sleep regulation and circadian rhythms has significant therapeutic implications. Targeting the endocannabinoid system within the EP may provide novel approaches for the treatment of sleep disorders, such as insomnia [81]. Modulation of EP activity through deep brain stimulation or pharmacological interventions may also prove beneficial for conditions characterized by circadian disruptions, such as shift work disorder or jet lag.

EP stimulation and neuroprotection in Parkinson's disease

DBS of the EP has emerged as a potential therapeutic approach for Parkinson's disease (PD). While DBS of the subthalamic nucleus (STN) is more commonly used, EP stimulation has shown promise in preclinical studies, though dedicated clinical case reports remain scarce [82].

Neuroprotective effects of EP stimulation

High-frequency stimulation (HFS) of thesubthalamic nucleus (STN) has demonstrated both motor and cognitive performance in animal models of PD. In a study by Temel et al, [83],While EP stimulation represents a related therapeutic avenue, the neuroprotective effects of STN stimulation have been more extensively characterized. These neuroprotective effects were associated with increased expression of brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) in the striatum [84]. Whether similar neurotrophic mechanisms underlie EP stimulation effects remains to be determined

Modulation of neurotransmitter release

High-frequency stimulation of basal ganglia output nuclei can modulate striatal neurotransmitter dynamics. Stimulation of the substantia nigra pars reticulata (SNr) has been shown to influence conditioned reward behaviors in addiction models [85],while stimulation of the EP affects striatal glutamate levels in the context of motor disorders [7]. Pathological beta-band synchronization in the STN correlates with both bradykinesia and rigidity in Parkinson's disease [86]. EP stimulation may similarly influence basal ganglia oscillatory dynamics, although direct evidence remains limited.

Comparison with STN stimulation

While EP stimulation shares some similarities with STN stimulation, there are notable differences in their effects. EP stimulation might be expected to have a more pronounced influence on the limbic and

associative territories of the basal ganglia, whereas STN stimulation primarily targets motor regions; this direct comparison has not yet been empirically tested and remains an important direction for future work [87]. This difference may have implications for the selection of stimulation targets based on the predominant symptoms of individual patients (Figure 4).

To provide a structured overview of the translational relevance of EP circuitry, Table 1 summarizes disorder-specific therapeutic strategies, underlying circuit mechanisms, and the current level of supporting evidence.

Clinical applications and future directions

Building on the therapeutic framework summarized in Table 1,Clinical applications of entopeduncular nucleus circuitry have matured through globus pallidus internus deep brain stimulation in Parkinson's disease, where marked motor improvements and durable benefits over multi-year follow-up are firmly established. The pallidal complex further represents a promising target for neuropsychiatric conditions, with adjacent ventral capsule circuits demonstrating efficacy in treatment-resistant depression and basal ganglia-thalamo-cortical modulation showing potential in obsessive-compulsive and addiction-related phenotypes. Future research must focus on refining stimulation parameters through directional and closed-loop architectures, coupled with precise patient stratification based on circuit-specific biomarkers. Bridging rodent EP connectomics with human GPi imaging will be critical to advance these interventions from empirical programming to mechanism-guided neuromodulation.

Limitations

The review follows a narrative rather than systematic or meta-analytic format, so selection bias and incomplete literature coverage cannot be excluded. Evidence for the EP remains sparse relative to other basal ganglia structures, and much of the clinical discussion relies on inference from the primate GPi internus or neighbouring circuits rather than on dedicated EP studies. Accordingly, the proposed roles of the EP should be interpreted in the context of the evolving evidence base. Cross-species translation is further complicated by anatomical divergence in thalamic and brainstem connectivity. Several therapeutic strategies are supported only by preclinical models or small case series, with scant longitudinal data on long-term efficacy or adverse events.These boundaries define the interpretive limits of this study.

Conclusion

The EP has emerged as a critical hub in the basal ganglia circuitry, with far-reaching implications for neurological and psychiatric disorders. Its diverse roles in addiction, mood disorders, anxiety, schizophrenia, OCD, sleep regulation, and Parkinson's disease underscore its significance as a potential therapeutic target.

Recent advances in our understanding of the EP's anatomical and functional organization have provided new insights into the mechanisms underlying its involvement in these conditions. The EP's complex interactions with various neurotransmitter systems, including GABA, glutamate, dopamine, and endocannabinoids, highlight the importance of a systems-level approach to understanding its functions.

As we continue to unravel the intricacies of the EP's circuitry and its role in brain disorders, new avenues for therapeutic interventions will emerge. From targeted pharmacological approaches to refined neuromodulation techniques, the EP holds promise as a key target for the development of more effective treatments.

However, significant challenges remain in translating these preclinical findings into clinical practice. Future research should focus on bridging the gap between animal models and human studies, as well as identifying biomarkers that can guide patient selection and treatment optimization.

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HZW contributed to the conception of the study; SS contributed significantly and equally to the analysis and manuscript preparation; NNY & SS & HZW performed the analysis with constructive discussions. HZW & NNY performed the analysis with constructive discussions and figures. DW performed the supervision and examined the structure of this article. All authors contributed to the article and approved the submitted version.

Ethical approval

As the structure of the study is a review, no IRB was obtained.

Authors contributions

CRediT: **Huaizhi Wang**: Conceptualisation, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing; **Saboor Saeed**: Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing; **Nana Yan**: Data curation, Formal analysis, Investigation, Validation, Visualisation, Writing – review & editing; **Dan Wang**: Conceptualisation, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Visualisation, Writing – review & editing.

Disclosure statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement

The data supporting the results of this study can be obtained from authoritative databases (PubMed, Embase, Medline, and Web of Science), as its review article so no new data was generated.

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