Mechanisms of the Locus Coeruleus-Norepinephrine System in Attention

Authors: Xing Lianzi, Yujie Chen, Miao Chengguo, Zhang Yang, Miao Chengguo, Zhang Yang

Date: 2025-10-11T00:00:00+00:00

Abstract

The locus coeruleus-norepinephrine system (LC-NE) is a crucial neuromodulatory system in the brain that plays a pivotal role in attention regulation. This article provides a systematic review of the mechanisms through which LC-NE functions in attention, encompassing: 1) the firing patterns and activity dynamics of LC-NE during attentional processes; 2) effective behavioral and neuroelectrophysiological indices of LC-NE activity; 3) the mechanisms of LC-NE within the three attentional subsystems—alerting, orienting, and executive control; and 4) the mechanistic associations between LC-NE and various attention-processing-related dysfunctions. Future research urgently necessitates the integration of pupillometry, event-related potentials, intracranial electroencephalography, high-precision neuroimaging, and neuromodulation techniques, employing high spatiotemporal precision tracking and causal intervention studies to further elucidate the dynamic regulatory mechanisms of LC-NE in attentional processing, thereby furnishing theoretical underpinnings for interventions in attention disorders.

Full Text

The Mechanisms of Locus Coeruleus-Norepinephrine System in Attention

XING Lianzi, CHEN Yujie, MIAO Chengguo, ZHANG Yang
(Department of Psychology, Soochow University, Suzhou 215000, China)

Abstract: The locus coeruleus-norepinephrine (LC-NE) system is a critical neuromodulatory system in the brain that plays an essential role in attentional regulation. This article provides a systematic review of the mechanisms by which the LC-NE system contributes to attention, including: 1) the firing patterns and activity dynamics of LC-NE neurons during attentional processes; 2) behavioral and neurophysiological indicators that reliably reflect LC-NE activity; 3) the role of LC-NE in the three attentional subsystems—alerting, orienting, and executive control; and 4) the associations between LC-NE function and various attention-related disorders. Future studies should integrate techniques such as pupillometry, event-related potentials, intracranial electroencephalography, high-resolution neuroimaging, and neuromodulation. Combining high spatiotemporal resolution tracking with causal intervention approaches can further elucidate the dynamic regulatory mechanisms of the LC-NE system in attentional processing, thereby providing a theoretical basis for interventions in attentional disorders.

Keywords: LC-NE system, attention, alerting, orienting, executive control
Classification Code: B482

Attention serves as a core cognitive mechanism for information selection and processing (Posner, 1980) and has long been a focal point in cognitive science research. It determines how individuals effectively filter and allocate limited cognitive resources in their environment and directly influences the efficiency of goal-directed behavior. Neurotransmitter systems are believed to play crucial roles in cognitive functions such as attention, alertness, and cognitive control (Aston-Jones & Cohen, 2005; Boyle et al., 2024; Ghosh & Maunsell, 2024; Pajkossy et al., 2018). Among these, the locus coeruleus-norepinephrine system (LC-NE), with its extensive neural projection network and norepinephrine (NE) release mechanisms, functions as a hub in dynamically regulating brain functional states and is considered one of the core neuromodulatory systems (Berridge et al., 2012; Dahl et al., 2022; Maness et al., 2022; Poe et al., 2020; Thiele & Bellgrove, 2018; Usher et al., 1999; Verguts & Notebaert, 2009).

Research from rodents, non-human primates, and humans consistently demonstrates that the LC-NE system plays a key role in attentional regulation (Aston-Jones & Cohen, 2005; Bari et al., 2020; Bouret & Sara, 2005; Dahl et al., 2020; Ghosh & Maunsell, 2024; Janitzky et al., 2015; McBurney-Lin et al., 2019; McGaughy et al., 2008; Unsworth & Robison, 2017). Notably, attention is not a unitary psychological process but comprises multiple functionally distinct yet interconnected subsystems. Classic attention theory posits that attention can be divided into three main subsystems: alerting, orienting, and executive control (Fan et al., 2002; Petersen & Posner, 2012). Although these subsystems exhibit relative independence in function and neural basis (Fan et al., 2005), some studies have found interactions among them (MacLeod et al., 2010). While numerous studies have revealed that the LC-NE system is broadly involved in regulating each attentional subsystem (Bari et al., 2020; Bast et al., 2018; Gabay, Pertzov, et al., 2011; Geva et al., 2013; Ghosh & Maunsell, 2024; Grueschow et al., 2020, 2022; Unsworth & Robison, 2017), consensus on its specific mechanisms in attentional regulation has not been reached. In particular, how tonic and phasic firing of LC neurons function across different subsystems and their interrelationships remain poorly articulated. Meanwhile, existing theories show certain disagreements. For example, the "adaptive gain theory" emphasizes that LC balances alertness and exploration through gain modulation, whereas the "network reset theory" highlights its triggering role in attentional shifting. While each view has supporting evidence, they have not been integrated within a unified framework. Moreover, generalizing findings from animal studies to human cognition and clinical applications faces multiple challenges, including cross-species differences, limited imaging resolution, and insufficient causal evidence. These challenges constrain both our deep understanding of the LC-NE system' s regulatory mechanisms in attentional processing and its potential application in treating attention-related disorders. Therefore, this article aims to comprehensively review the neurophysiological mechanisms of the LC-NE system in attentional regulation, summarize behavioral and neurophysiological markers of LC-NE activity, and delineate the system' s specific roles across attentional subsystems and its potential impact on various attention disorders, thereby providing a theoretical framework and methodological reference for future research.

1.1 LC-NE System and Attention-Related Neurophysiological Characteristics

The locus coeruleus (LC) is a NE nucleus unique to vertebrates, located deep in the dorsal brainstem, and serves as the primary synthesis and release center for NE in the brain (Manger & Eschenko, 2021; Poe et al., 2020). LC neurons influence multiple key cortical and subcortical structures through extensive axonal projections (Berridge & Waterhouse, 2003; Ma et al., 2023; McBurney-Lin et al., 2019; Poe et al., 2020; Sara & Bouret, 2012), including the prefrontal cortex (PFC), anterior cingulate cortex (ACC), parietal cortex, thalamus, and amygdala (Berridge & Waterhouse, 2003; Poe et al., 2020). These brain regions are closely associated with critical processes such as attention maintenance and orienting (Bang et al., 2023; Katsuki & Constantinidis, 2012; Petersen & Posner, 2012; Sarrias-Arrabal et al., 2023), collectively forming the core anatomical basis for LC-NE modulation of attentional processing.

During attentional regulation, the LC dynamically modulates neural activity in target brain areas by releasing NE and activating different receptor types, thereby playing a central role in maintaining selective attention, regulating arousal levels, and enabling flexible allocation of attentional resources. NE receptors primarily include three types: high-affinity α_2 receptors (more sensitive to NE, activated at relatively low NE levels), which mainly participate in inhibitory regulation by reducing neuronal background noise to enhance signal-to-noise ratio; and lower-affinity α_1 and β receptors (requiring higher NE concentrations for activation), which are typically associated with excitatory effects (Atzori et al., 2016; Zhang et al., 2023). In attention-related brain regions such as the PFC, different NE concentrations can selectively activate different receptor types: moderate NE levels preferentially activate high-affinity α_2 receptors, enhancing neuronal firing and thereby improving working memory performance and executive function (Arnsten, 2009; Ramos & Arnsten, 2007); whereas under high-stress or high-arousal states, elevated NE levels activate low-affinity α_1 and β receptors, suppressing PFC neuronal firing and impairing its function, ultimately leading to decreased attention and executive function (Arnsten, 2009; Ramos & Arnsten, 2007). Beyond receptor-mediated excitatory and inhibitory effects, NE can also regulate neuronal plasticity by enhancing synaptic transmission efficacy and reducing spontaneous firing frequency, thereby improving the response flexibility of neural networks (Berridge & Waterhouse, 2003; Woodward et al., 1979). In summary, the unique anatomical projections, receptor characteristics, and neuromodulatory mechanisms of the LC-NE system collectively constitute its physiological basis for attention regulation.

1.2 LC-NE System Firing Patterns and Attention Regulation

LC neuronal firing activity manifests primarily in two modes: tonic and phasic. The tonic mode reflects baseline activity and is mainly related to overall alertness, task engagement, and behavioral flexibility; the phasic mode involves brief, high-frequency discharges in response to target stimuli or unexpected events and is considered a key neural mechanism for attentional focusing and selection (Unsworth & Robison, 2017). Electrophysiological studies in non-human primates have revealed significant functional distinctions between these two modes in cognitive-behavioral regulation (Rajkowski et al., 1994).

Phasic mode typically occurs when individuals encounter sudden, salient, or task-relevant stimuli, exhibiting high temporal specificity. These brief, high-frequency discharges can enhance prioritized processing of target stimuli while suppressing responses to irrelevant information, thereby improving attentional selection efficiency (Aston-Jones & Cohen, 2005). Additionally, phasic mode is closely associated with event-related potential (ERP) components such as the P3, providing electrophysiological evidence for the LC-NE system' s role in rapid identification of "unexpected events" and behavioral updating (Nieuwenhuis et al., 2005). At the behavioral level, phasic mode facilitates rapid focusing on and responding to critical signals, supporting target detection, motivation-driven behavior execution, and adaptive adjustment—representing an important mechanism through which the LC-NE system modulates task performance. In contrast, tonic firing level is closely related to overall alertness state and exhibits a classic inverted-U-shaped modulation pattern. When tonic LC neuronal activity is too low, individuals show attentional dispersion and inability to maintain task focus, resulting in poor behavioral performance and absent task-related phasic responses; when tonic activity is at moderate levels, phasic responses to target stimuli are enhanced, yielding optimal performance; when tonic activity is too high (e.g., under high stress or arousal), it may suppress phasic discharges, causing attentional resource dispersion and difficulty maintaining targets, leading to performance decline (Chamberlain & Robbins, 2013; Unsworth & Robison, 2017).

This inverted-U relationship reflects the nonlinear modulation of cortical excitability by the LC-NE system and aligns closely with the classic Yerkes-Dodson law regarding the relationship between arousal and performance (Yerkes & Dodson, 1908). Based on these mechanisms, Aston-Jones and Cohen (2005) proposed the "adaptive gain theory," which posits that the LC-NE system dynamically balances "exploitation" (utility-driven behavior) and "exploration" (environmental exploration) by regulating the degree to which cortical neurons respond to signals (or "signal gain"). When task utility is high, LC neurons maintain moderate tonic firing accompanied by strong phasic discharges to enhance processing efficiency of target information and suppress interference from irrelevant information, thereby improving goal-directed behavior efficiency. Conversely, when task utility declines, LC neurons show enhanced tonic firing and reduced phasic discharges, making attention more easily dispersed and prompting individuals to shift toward exploring new cues or behaviors.

Building upon these findings regarding the two firing modes and their behavioral functions, current research increasingly focuses on the switching mechanisms between them and their regulatory conditions. Evidence indicates that behavioral states (e.g., target utility), task difficulty, and cognitive load changes can all influence the dynamic switching of LC neuronal firing modes (Gabay, Pertzov, et al., 2011; Sara & Bouret, 2012). For example, the "network reset theory" proposes that sudden salient stimuli can evoke synchronized phasic discharges in LC neurons, thereby interrupting current neural activity patterns and initiating new attentional states (Sara & Bouret, 2012). Unlike the adaptive gain theory' s emphasis on how phasic and tonic modes regulate neural activity and responses, the network reset theory highlights the unique role of LC neurons in promoting neural network reorganization (a comparative summary of the two theories is presented in Table 1). This theory suggests that phasic LC activation is not merely a response to stimuli but a key mechanism triggering network dynamic reorganization. By altering functional connectivity between different brain regions, the LC-NE system enables the brain to flexibly adjust attentional and behavioral strategies to cope with unexpected events (Bouret & Sara, 2005). In the model proposed by Bouret and Sara (2005), phasic and tonic LC discharge activities cooperatively support a flexible attentional system. When tonic activity and overall NE release levels are low, it helps maintain task engagement when expecting target-relevant stimuli and prevents premature behavioral shifts; when tonic activity and NE release levels are elevated, it increases attentional dispersion and the likelihood of behavioral shifts, reflecting a more exploratory mode. Furthermore, Totah et al. (2021) noted that phasic discharges are often accompanied by highly synchronized activity in LC neuron populations, a process that may be regulated by the PFC-LC circuit. Future research should further explore the switching mechanisms of LC firing modes and their relationship with PFC regulatory circuits.

In summary, LC-NE regulation of attention does not stem from simple neural excitability enhancement but rather from the dynamic coordination of tonic and phasic firing modes to achieve fine-tuned regulation of cognitive system responsiveness. This mechanism provides a crucial neurophysiological foundation for task maintenance and strategy switching in complex environments.

2.1 LC-NE System and Attention: Evidence from Pupil Dilation

Pupil dilation (PD) is a sensitive and stable physiological indicator for measuring arousal level and cognitive effort. Wang and Li (2024) noted in their review that pupillary responses are closely related to LC-NE system activity. Numerous pharmacological and neurophysiological studies further demonstrate that PD is closely associated with LC neuronal firing patterns (Beatty, 1982; Dragone et al., 2018; Gabay, Chica, et al., 2011; Unsworth & Robison, 2017) and can serve as an indirect indicator of LC-NE system activity (R. H. Hou et al., 2005; Joshi et al., 2016; Morad et al., 2000; Phillips et al., 2000; Varazzani et al., 2015). For instance, pharmacological studies show that modafinil, a drug that increases central NE levels, enhances subjective alertness and induces PD, whereas clonidine, which reduces NE levels, decreases alertness and causes pupil constriction (R. H. Hou et al., 2005). Animal electrophysiological studies also reveal a significant positive correlation between PD and LC discharge frequency (Joshi et al., 2016; Rajkowski et al., 1994; Reimer et al., 2016; Varazzani et al., 2015), with noticeable pupil dilation observed approximately 300 ms after LC discharge. Notably, although other brain regions (e.g., thalamus) are also associated with pupillary changes, LC neuronal discharge activity shows the most significant predictive effect on pupil changes (Joshi et al., 2016).

Human behavioral studies also support the association between PD and LC neuronal activation levels during attentional guidance. For example, Dragone et al. (2018) found that high-predictability cues elicited stronger PD responses compared to low-predictability cues, suggesting that phasic LC discharge participates in attentional regulation. Moreover, baseline pupil size gradually decreased across trials, indicating a dynamic adjustment process of tonic LC discharge activity during task performance. In other words, tonic LC activation is typically reflected in baseline pupil size, whereas phasic activation triggered by external events manifests as changes in PD. It is worth noting that PD may also be influenced by other neurotransmitter systems. While short-term PD changes are primarily related to the NE system, sustained PD during motor activity is more likely associated with sustained activation of the cholinergic system (Reimer et al., 2016). Therefore, PD can serve not only as an indicator of LC-NE system activity but also as a measure of other neural systems regulating bodily functions, providing an important perspective for investigating the coordinated regulation of arousal and attention by multiple neuromodulatory systems.

However, using PD as an indicator of LC-NE system activity has limitations. The main issue is that pupil size is highly susceptible to task-irrelevant variables such as environmental brightness and blinking, which can weaken its validity as an indicator of LC-NE system activity (Gabay, Pertzov, et al., 2011; Mathôt et al., 2018). To reduce interference from brightness and other irrelevant variables, researchers have proposed analyzing pupillary responses using contrast methods between task conditions. For example, Gabay and Pertzov et al. (2011) designed two tasks with identical visual attributes but different attentional loads (a simple localization task vs. a complex discrimination task) and found that the complex task elicited more significant phasic PD compared to the simple task. Furthermore, if PD indeed reflects LC-NE system activity, its phasic changes should temporally correspond closely with behavioral responses. Based on this, the study employed time-lock analysis anchored to behavioral responses to more accurately extract pupillary changes related to LC-NE system activation during attentional processing. Results showed that significant phasic PD was observed only in the high-demand complex task. These findings not only support the feasibility of using PD as an indicator of LC-NE system activity in specific tasks but also highlight the flexibility of the LC-NE system in attentional regulation.

Notably, using PD as a valid indicator of LC-NE system activity requires two key prerequisites. First, LC neuronal activation should be primarily related to behavioral responses rather than being directly driven by stimulus presentation (Rajkowski et al., 2004). Second, changes in arousal state should be manifested through phasic pupillary changes time-locked to behavioral responses, not merely through alterations in baseline pupil size (Beatty, 1982). When these prerequisites are met, PD can serve as an effective non-invasive physiological indicator reflecting the dynamic characteristics of the LC-NE system in attentional regulation.

2.2 LC-NE System and Attention: Evidence from Event-Related Potentials

Event-related potentials (ERP) are a neurophysiological technique with high temporal resolution commonly used to study dynamic brain responses during attentional processing. ERP components are widely employed as indirect neurophysiological indicators of LC-NE system activity when investigating its attentional modulation mechanisms. Current research primarily focuses on the P3 and N2 components, which are considered closely related to LC-NE system function (Martín & René, 2012; Nieuwenhuis et al., 2005; Warren et al., 2011; Warren & Holroyd, 2012).

The P3 (also called P300) is an important ERP component viewed as a neurophysiological indicator reflecting the reallocation of attentional resources to novel or salient stimuli (Polich, 2007). Studies show that damage to the LC region or its NE ascending pathways in both rodents and primates attenuates cortical P3 activity (Ehlers & Chaplin, 1992; Nieuwenhuis et al., 2005; Pineda et al., 1989), suggesting that the LC is a key modulatory source of the P3. Additionally, NE agonists such as clonidine reduce P3 amplitude in humans (Halliday et al., 1994) and non-human primates (Swick et al., 1994), further supporting the close link between P3 and the LC-NE system. Temporally, phasic LC neuronal discharge typically occurs approximately 150–200 ms after stimulus presentation, while NE-induced cortical modulatory effects occur 100–200 ms post-stimulus, which aligns closely with the classic P3 latency (Berridge & Waterhouse, 2003; Foote et al., 1983). Based on this, Nieuwenhuis et al. (2005) proposed the "LC-P3 theory," which posits that the P3 reflects phasic enhancement of cortical neural responses triggered by NE release from the LC. Subsequently, Martín and René (2012) further noted that this enhancement primarily manifests in the processing of task-relevant stimuli—when NE is released, the responsiveness of target neurons in the brain is enhanced, which can improve the signal-to-noise ratio of subsequently processed target neurons, enabling the brain to capture and process relevant information more efficiently. More direct evidence comes from Vazey et al. (2018), who used optogenetics to induce phasic discharge in rat LC neurons and observed ERP responses similar to human N1 and P3 components in the rat cortex, providing experimental evidence for a causal relationship between LC neuronal discharge and ERP components. Additionally, in cognitive control tasks, the NoGo-P3 is considered related to response inhibition. Studies have found that at the individual level, PD indicators reflecting LC-NE system activity can predict NoGo-P3 amplitude, suggesting that the LC-NE system also participates in regulating response inhibition processes (Chmielewski et al., 2016). Overall, the LC-P3 theory supports the core hypothesis of the adaptive gain theory at the electrophysiological level—that phasic LC discharge can enhance the responsiveness of task-relevant neurons, thereby optimizing attention and cognitive control processes.

The N2 is another ERP component considered closely related to the LC-NE system, typically associated with conflict monitoring and inhibitory control. In classic psychological paradigms such as Go/NoGo and Flanker tasks, conflicting or incongruent stimuli generally elicit larger N2 amplitudes (Fong et al., 2018; Gajewski & Falkenstein, 2013; Nieuwenhuis et al., 2003). For example, in Go/NoGo tasks, individuals must suppress automatic response tendencies elicited by frequent Go trials, and the rare NoGo trials therefore evoke more significant N2 components (Falkenstein et al., 1999; Kopp, Mattler, et al., 1996). Similarly, in Flanker tasks, distractor stimuli (flankers) activate response options that conflict with the target, also enhancing N2 (Kopp, Rist, et al., 1996). While the N2 component is less commonly used to directly measure LC activity, recent research has begun exploring its relationship with the LC-NE system, particularly in high cognitive load and conflict situations where N2 may reflect early modulatory effects of the LC-NE system (Patel & Azzam, 2005). For instance, Warren et al. (2011) found in a face oddball task that N2 scalp distribution changes with task conditions, potentially reflecting differential involvement of cortical regions under NE modulation. Based on this, Warren and Holroyd (2012) further revised the "LC-P3 theory," proposing that N2 may correspond to initial NE release during early LC neuronal discharge, while P3 reflects subsequent NE depletion. This theory naturally explains the temporal sequence between N2 and P3 and emphasizes the critical role of the LC-NE system in generating both ERP components. Research by Hong et al. (2014) also supports this theory, finding that both N2 and P3 amplitudes correlate with baseline pupil size, suggesting both are closely related to LC function. Overall, ERP research provides important evidence for understanding the temporal characteristics of the LC-NE system during attentional processes. However, due to its limited spatial resolution, researchers have recently begun using functional magnetic resonance imaging (fMRI) to compensate for ERP’ s spatial localization limitations. For example, Walz et al. (2013) used simultaneous EEG-fMRI and found that brain activity during the N2 time window was functionally coupled with activity in midbrain regions during the P3 phase, suggesting these regions may coordinately participate in attentional neuromodulation through the LC-NE system.

2.3 Comparison and Integration of LC-NE System Measurement Indicators

Most current research on LC-NE modulation of attention uses PD and ERP components as primary measures, with some studies also incorporating fMRI to supplement spatial evidence. These three approaches each have distinct advantages and limitations in temporal resolution, spatial resolution, and applicable scenarios: PD and ERP are better suited for revealing dynamic temporal processes, while fMRI provides spatial localization and network-level evidence.

PD offers high temporal resolution for real-time tracking of LC-NE system dynamics and has been validated in both human and animal studies (Dragone et al., 2018; Joshi et al., 2016; Joshi & Gold, 2020; Reimer et al., 2016). PD is also widely used in tasks requiring continuous tracking of arousal levels, attentional dynamics, and changes in cognitive effort (Gabay, Pertzov, et al., 2011; Murphy et al., 2011, 2014). However, PD is easily disrupted by non-task factors such as environmental brightness, blinking, and emotion, making its validity as an indirect indicator of LC-NE system activity in attentional regulation controversial (Joshi & Gold, 2020). ERP, on the other hand, can track the temporal characteristics of the LC-NE system in attentional processing with millisecond precision, particularly the P3 component’s close relationship with phasic LC discharge (Murphy et al., 2011; Nieuwenhuis et al., 2005). This method is suitable for target detection, inhibitory control, and conflict monitoring tasks (Warren & Holroyd, 2012), but its low spatial resolution only allows indirect reflection of LC activity through scalp electrical signals, making precise localization difficult. In contrast, fMRI offers high spatial resolution for observing functional connectivity with cortical and subcortical regions. Studies using resting-state and task-based fMRI have revealed network interactions between the LC and regions such as the PFC, ACC, thalamus, and amygdala (Liebe et al., 2020; Murphy et al., 2014). However, its limited temporal resolution typically requires combination with pupillometry or ERP to achieve high spatiotemporal precision tracking of LC-NE activity.

2.4 Multimodal Measurement Evidence Strengthening the LC-NE System-Attention Relationship

Multimodal measurement provides a richer and more precise perspective for revealing the LC-NE system’ s mechanisms in attention. Murphy et al. (2014) simultaneously recorded PD and fMRI signals and found significant correlations between PD and blood oxygen level-dependent signal changes in the LC region during both resting state and oddball tasks, further supporting the validity of PD as an indirect indicator of LC-NE system activity. Additionally, Ding et al. (2021) combined positron emission tomography (PET), fMRI, and norepinephrine transporter (NET) radiotracers to conduct multimodal imaging studies of LC-NE system function across different ethnic groups. Results showed that the LC-NE system function declined faster in African American populations compared to other groups, suggesting they may face higher risks of attention dysfunction. These findings not only demonstrate the methodological advantages of multimodal techniques in validating the LC-NE system-attention relationship but also showcase their potential for revealing group differences and attention deficit disorders.

3.1 LC-NE Regulatory Mechanisms in Attentional Alerting

Attentional alerting refers to a state in which individuals proactively increase sensitivity and response readiness to upcoming stimuli before receiving external information (Petersen & Posner, 2012). Maintaining attentional alertness primarily depends on coordinated regulation by the right-hemisphere frontoparietal network, thalamus, and LC-NE system. Neuroimaging studies have found that right frontal and parietal regions are activated when individuals perform alerting or sustained attention tasks, suggesting this network plays a central role in maintaining alertness (Coull et al., 1996; Sturm & Willmes, 2001). Meanwhile, the thalamus, as an arousal regulation center, participates in regulating phasic and tonic alertness through coordination with frontoparietal cortex (Sturm & Willmes, 2001). Additionally, the LC-NE system influences various cognitive processes including visual attention by modulating overall arousal levels and setting baseline states for cortical activity through its extensive projection network (Euler et al., 1946). In spatial cueing tasks, researchers assess alerting effect strength by comparing reaction times between alerting cue and no-cue conditions, finding that this effect is modulated by LC-NE system functional state (Fernandez-Duque & Posner, 1997), providing behavioral evidence for the LC-NE system' s role in attentional alerting regulation.

The LC-NE system participates in dynamic regulation of attentional alerting by modulating NE release levels. Animal studies show that alarm stimuli can activate LC neurons and promote NE release, thereby enhancing alertness (Aston-Jones & Cohen, 2005); conversely, blocking the NE system significantly weakens the alerting effect of warning signals (Marrocco et al., 1994). Pharmacological studies further support this mechanism—drugs that inhibit NE release (e.g., clonidine and dexmedetomidine) attenuate attentional alerting effects, while drugs that enhance NE release amplify them (Petersen & Posner, 2012). Additionally, Coull et al.' s (1999) PET study found that administration of α_2 receptor agonists at rest weakened functional connectivity between frontal cortex, thalamus, and visual cortex, but during attentional tasks, it significantly enhanced activity in the parietal cortex-centered attentional network, indicating that LC-NE system regulation of attentional states is highly context-dependent.

Beyond NE release level modulation, LC neuronal firing patterns also participate in attentional alerting regulation. Research shows that LC firing patterns are closely related to attentional performance: both excessively high and low discharge frequencies lead to attentional dispersion, while moderate frequencies typically correspond to optimal task performance (Aston-Jones et al., 1991). The adaptive gain theory suggests that appearance of task-relevant targets can shift LC neurons into phasic firing mode, thereby inducing an attentional alerting state that enhances processing of target stimuli and utilization of cognitive resources; when task utility remains consistently low, LC neurons tend to shift to tonic firing mode, where they respond to any stimulus, prompting individuals to disengage from the current task and explore other potentially valuable activities (Aston-Jones & Cohen, 2005). This mechanism supports dynamic balance between "task maintenance" and "strategy switching." Notably, transitions in LC firing mode are extremely rapid, with phasic discharge activity decreasing within approximately 50–60 ms after stimulus onset (Foote et al., 1980). This rapid dynamic adjustment enables the LC-NE system to flexibly regulate sensitivity to external stimuli, optimizing attentional resource allocation and facilitating processing of task-relevant information.

3.2 LC-NE Regulatory Mechanisms in Attentional Orienting

Attentional orienting refers to the process of shifting attention from its current focus to a target stimulus that will be selected or attended to (Petersen & Posner, 2012). Numerous studies have shown that two key neural networks in the cerebral cortex jointly participate in attentional processing of external stimuli: the dorsal attention network (DAN) and the ventral attention network (VAN) (Corbetta & Shulman, 2002). The DAN is primarily associated with top-down attentional control (Chica et al., 2013), with core regions including the intraparietal sulcus (IPS), superior parietal lobule (SPL), and frontal eye field (FEF) (Corbetta et al., 2008). Neuroimaging studies show that when individuals need to focus attention on specific spatial locations based on cues, the DAN including FEF and IPS is significantly activated (Corbetta & Shulman, 2002). In contrast, the VAN primarily participates in bottom-up attentional shifting, with core regions including the temporoparietal junction (TPJ) and ventral frontal cortex (VFC) (Corbetta et al., 2008). When salient stimuli appear at non-cued locations, TPJ activation increases significantly, driving attention to shift from the previous focus to the new target (Corbetta et al., 2000; Corbetta & Shulman, 2002). Notably, DAN and VAN are not independent but can dynamically switch under LC-NE system regulation according to task demands and environmental changes. According to the network reset theory, when salient stimuli appear, the LC-NE system can promote rapid attentional reorienting through phasic discharge activity, specifically by evoking signal transmission in TPJ that shifts attention from the task-oriented DAN to the externally novel stimulus-sensitive VAN (Corbetta et al., 2008). Recent research further shows that during salient stimulus processing, increased phasic LC discharge activity is accompanied by enhanced effective connectivity from the salience network

(SN) to the DAN, suggesting that the LC-NE system specifically modulates DAN functional integration through the SN to promote dynamic allocation of attentional resources (He et al., 2023). Additionally, Bouret and Richmond (2015) proposed that LC neuronal activity is related to the energy investment required for goal-directed behavior. Based on this, research has further applied this to attentional regulation in different contexts: when individuals process high-reward or target-relevant cues, LC-NE system activation increases, preferentially activating the DAN to support goal-directed attention; conversely, when processing low-reward or non-target cues, LC-NE activation decreases, DAN activation reduces, and the VAN maintains sensitivity to external novel stimuli (Hofmeister & Sterpenich, 2015). These findings collectively demonstrate that the LC-NE system flexibly allocates attentional resources between goal-directed and stimulus-driven behaviors through specific modulation of the DAN and VAN, thereby maintaining adaptive behavior and task performance.

As a crucial regulatory component of VAN-mediated exogenous attention, the LC-NE system also participates deeply in specific regulation of exogenous attentional orienting through dynamic changes in firing patterns. In classic exogenous spatial cueing tasks, if a target appears at the cued location after a short stimulus onset asynchrony (SOA), individuals respond faster; conversely, when SOA is long (greater than 300 ms), responses are faster when targets appear at noncued locations—a phenomenon known as “inhibition of return” (IOR) (Posner & Cohen, 1984). The mechanism involves suppressing reflexive attention to facilitate strategic attention deployment, thereby improving visual search efficiency (Okon-Singer et al., 2020). Notably, the onset time of IOR is influenced by task type: it appears later in difficult discrimination tasks and earlier in simple detection tasks (Lupiáñez et al., 1997). This difference may be related to different firing modes of the LC-NE system: in difficult tasks, LC neurons activate in phasic mode, allocating more attentional resources to target stimuli while suppressing attention to peripheral cues, thus delaying IOR onset; in simple tasks, LC neurons exhibit more tonic firing, reducing attentional resources allocated to targets, allowing peripheral cues as distractors to receive more processing and causing IOR to appear earlier (Gabay, Pertzov, et al., 2011; Gabay & Henik, 2010). Additionally, external threat cues can enhance LC-NE system activation and induce stronger IOR effects, further emphasizing the important role of the LC-NE system in exogenous attention regulation (Okon-Singer et al., 2020).

Research from animal models also provides more direct causal evidence for the LC-NE system’ s function in attentional orienting. For example, Janitzky et al. (2015) used optogenetics to temporarily suppress LC neuronal activity in mice and found that this manipulation severely disrupted flexible switching of attention between dimensions, suggesting that LC-NE plays a critical role in regulating attentional orienting shifts. Similarly, Vazey et al. (2018) used optical stimulation to evoke phasic LC discharge activity and found that this induced electrophysiological responses similar to human ERP N1 and P3 components in rat cortex. This rapid phasic discharge not only enhanced neural responses in sensory cortex to stimuli but also improved goal-directed information processing and attentional reorienting, further confirming the fine regulatory role of the LC-NE system in attentional orienting.

Although numerous studies indicate that the LC-NE system participates in attentional orienting, controversy remains regarding whether it directly regulates this process. One view suggests that LC-NE primarily modulates attentional alerting while the orienting process is dominated by the cholinergic system (Slater et al., 2022). For instance, Ikeda et al. (2017) found that the NE agonist modafinil increased alerting activation levels in occipital regions but did not significantly affect orienting responses. However, other perspectives propose that the LC-NE system has common regulatory effects on both alerting and orienting: as a core mechanism for regulating neural activity gain, LC-NE can act on continuously changing alertness, orienting, and task-related attentional processes (Aston-Jones & Cohen, 2005; Bouret & Sara, 2005; Sara & Bouret, 2012). Geva et al. (2013) used PD as an LC-NE system activity indicator and found that temporal cues elicited larger early PD components compared to no-cue conditions, while spatial cues containing location information further accelerated this component' s activation, suggesting that it may integrate neural processing of both alerting and orienting. Bast et al. (2018) also noted that phasic LC activity can simultaneously modulate both alerting and orienting attentional subsystems. Moreover, more direct causal evidence comes from Ghosh and Maunsell' s (2024) non-human primate neurophysiological study, which found that LC neurons discharged only when contralateral visual stimuli were effectively attended, and this discharge was closely related to enhanced perceptual sensitivity. Importantly, activating LC neurons via optogenetics significantly improved monkeys' detection ability for contralateral stimuli, demonstrating that the LC-NE system not only regulates overall arousal levels but also possesses spatially specific attentional regulatory functions, providing strong support for its simultaneous modulation of both alerting and orienting.

3.3 LC-NE Regulatory Mechanisms in Attentional Control

Attentional executive control refers to the ability to monitor and resolve conflicts between expectations, stimuli, and responses (Petersen & Posner, 2012). This process depends on the coordinated action of attentional and inhibitory processes. Attentional processes involve the ability to effectively focus or shift attention to task-relevant information sources (Miyake et al., 2000), while inhibitory processes help individuals shield against interference from irrelevant stimuli, with the core mechanism being the suppression of automatic or impulsive behavioral responses to achieve cognitive control (Friedman & Miyake, 2004). These highly interactive and mutually constraining cognitive functions are not only crucial for maintaining goal-directed behavior but also enable individuals to flexibly respond to changing environmental demands. Neuroimaging research has identified the ACC and PFC within the frontoparietal network as important nodes in the attentional control network, with the ACC primarily responsible for conflict monitoring and the PFC dominating cognitive control execution (Kerns et al., 2004). The LC-NE system plays a vital role in regulating this attentional control demand-based neural network (Cohen et al., 2004). Specifically, the LC dynamically modulates PFC neural activity through widespread NE release, thereby regulating attentional control and other higher-order cognitive functions (Aston-Jones & Cohen, 2005; Sara & Bouret, 2012).

Empirical studies show that NE-enhancing drugs can improve PFC functional activity, thereby enhancing performance in attention and response inhibition tasks (Chamberlain et al., 2009; Nagashima et al., 2014). Interestingly, LC-NE modulation of attentional control exhibits an inverted-U-shaped pattern: moderate NE levels are most beneficial for attentional control, while excessively high or low NE levels lead to attentional maintenance failure (Aston-Jones et al., 1999; Ramos & Arnsten, 2007). Based on this mechanism, Unsworth and Robison (2017) proposed that tonic activity levels of the LC-NE system play a decisive role in attentional control systems during task execution. Only when tonic NE levels are in the moderate range can LC neurons generate effective phasic discharge responses to appropriately modulate PFC activation states and achieve attentional resource allocation for goal-directed processing. Robison et al. (2023) further confirmed this hypothesis, finding a stable association between phasic LC discharge responses and individual attentional control capabilities, supporting the central role of the LC-NE system in attentional regulation.

At the behavioral regulation level, NE not only enhances attention but also effectively suppresses impulsive responses—that is, inhibitory drive effects from irrelevant or distracting stimuli. Both animal and human studies provide supportive evidence. For example, Bari et al. (2020) used optogenetics to modulate LC neuronal activity in mice and found that activating the LC-NE system enhanced goal-directed attention and reduced impulsive responses, while suppressing LC activity led to attentional dispersion and increased impulsive responses. Similar results have been observed in human studies, where pharmacological intervention in NE reuptake processes effectively improved individuals' response inhibition abilities (Chamberlain et al., 2006). Functional neuroimaging research has further revealed functional interactions between the LC-NE system and cognitive control networks, showing significant functional connectivity between LC activation patterns and regions including the dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex (VLPFC), dorsal parietal lobe (DPL), motor, and visual areas, suggesting that the LC-NE system plays a key regulatory role in cognitive conflict resolution (Köhler et al., 2016). Furthermore, Grueschow et al. (2020) found in a response conflict task that reaction time changes in conflict trials were highly correlated with functional coupling strength between the conflict monitoring region—the dorsomedial prefrontal cortex (DMPFC)—and the LC-NE system, with stronger coupling associated with more efficient conflict resolution. Animal tracing studies also support the existence of structural and functional connections between the DMPFC and LC-NE system (Chandler, Gao, et al., 2014; Chandler, Waterhouse, et al., 2014). Additionally, Grueschow et al. (2022) found in an emotional Stroop task that functional coupling between the LC-NE system and frontoparietal cortex as well as parts of the striatum was significantly enhanced during conflict trials, with coupling strength positively correlated with individual conflict resolution efficiency. These findings indicate that dynamic interactions between the LC-NE system and cognitive control networks play a central regulatory role in goal-directed behavior and response inhibition.

As mentioned previously, PD is an important physiological indicator of LC-NE system activity. Building on this, research has further shown that PD not only reflects overall attentional state but also systematically reveals the regulation of all three attentional subsystems—alerting, orienting, and executive control (see Table 2) (Geva et al., 2013; Joshi et al., 2016). At the attentional alerting level, high alertness is typically accompanied by larger and more stable baseline pupil diameter, while fatigue or low alertness states are characterized by reduced and more fluctuating baseline pupil diameter (R. H. Hou et al., 2005; Morad et al., 2000). In sustained attention tasks, individuals' baseline pupil diameter and task-evoked pupillary responses gradually decrease over time, reflecting attenuation of attentional alertness (Beatty, 1982; Fried et al., 2014; Unsworth & Robison, 2016). The adaptive gain theory also suggests that pupil diameter is smaller during low arousal and low tension states, significantly larger during high arousal states, and moderate pupil diameter corresponds to optimal attentional performance, reflecting phasic LC activation (Aston-Jones & Cohen, 2005). Additionally, PD is highly coupled with α-β band desynchronization in EEG, suggesting both may depend on NE release mechanisms. Moreover, individuals' PD response intensity to fearful stimuli can effectively predict their attentional task performance, with stronger PD responses associated with better performance (Dahl et al., 2020), further supporting the LC-NE system' s role in attention and alertness regulation. In spatial orienting tasks, PD is also considered an important indicator of LC-NE system activity. For example, Gabay and Pertzov et al. (2011) found that PD is highly sensitive to task processing demands: in difficult tasks, PD shows response-locked phasic characteristics corresponding to phasic LC discharge, whereas in simple tasks, PD changes are more similar to baseline fluctuations associated with tonic discharge. This demonstrates that LC-NE modulation of attentional orienting can also be reflected through PD and shares similar neural regulatory mechanisms with alerting attention. Furthermore, at the executive control level, research shows that executive control processes are accompanied by significant late PD responses, with amplitude increasing with conflict level (Geva et al., 2013), suggesting executive control is also closely related to PD triggered by LC activation. In summary, PD is not only a sensitive indicator of LC-NE system activity but also systematically reflects the dynamic regulatory characteristics of the three major attentional subsystems: alerting, orienting, and executive control.

4.1 LC-NE and ADHD

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood neurocognitive disorder characterized by inattention, hyperactivity, and impulsive behavior (Gawrilow et al., 2014). Although the underlying pathophysiological mechanisms of ADHD remain unclear, research indicates that NE plays a crucial role in its development (Huang et al., 2022; Liao et al., 2019).

Molecular and neuroimaging studies show that individuals with ADHD exhibit abnormalities in NE signaling function (Liao et al., 2019; Sigurdardottir et al., 2021), typically accompanied by reduced activity in attention-processing brain regions, most notably abnormal PFC activity (B. A. Anderson, 2021). As one of the most extensively impaired brain regions in ADHD, PFC dysfunction is considered the core neural basis for attentional control deficits in ADHD individuals (Arnsten, 2009). Animal studies provide further experimental evidence for this mechanism. Research shows that optogenetic inhibition of LC projections to the PFC in mice leads to significantly increased attentional dispersion and impulsive behavior, indicating that this pathway has important effects on executive control function (Bari et al., 2020). These findings collectively reveal the critical role of the LC-NE system in frontoparietal network regulation and provide important empirical evidence for understanding the neural mechanisms of ADHD-related symptoms. Building on this, clinical research further views the LC-NE system as an important target for pharmacological intervention. The norepinephrine transporter (NET) is considered one of the key targets for ADHD medication (Vanicek et al., 2014). Drugs such as methylphenidate (MPH) can improve attentional function and behavioral control by inhibiting NET activity to block NE reuptake and enhance NE neurotransmission efficiency in the PFC region (Hannestad et al., 2010). Related studies show that NET inhibitors have good efficacy in alleviating core ADHD symptoms (Angyal et al., 2018; Huang et al., 2022). Zhang et al. (2023) noted in their review that the LC-NE system not only plays an important role in attentional regulation but also serves as a key target for treating attentional dysfunction. In summary, the LC-NE system plays a critical role in attentional deficits and impulse control disorders in ADHD by regulating prefrontal function and related neural network activity. Its functional imbalance not only provides support for revealing the neurophysiological basis of ADHD but also offers an important target direction for precise pharmacological intervention.

4.2 LC-NE and ASD

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by core features of social communication impairment (Dawson et al., 2012), often showing abnormal attentional processing, particularly reduced selective attention to social stimuli (Bast et al., 2018). Specific manifestations include weakened phasic alerting abilities (Orekhova & Stroganova, 2014) and impaired attentional orienting function (Jaworski & Eigsti, 2017).

Increasing research finds that the LC-NE system plays an important role in ASD pathophysiology. Studies suggest that the LC-NE system may participate in broader pathophysiological regulation in ASD (London, 2018), and its functional abnormalities may directly affect attentional processing performance in

ASD individuals (Bast et al., 2018). Pupillary changes are considered peripheral physiological indicators of LC-NE system activity, and the two are highly coupled during attentional regulation (Wang & Li, 2024). Research shows that atypical pupillary response patterns in children with ASD reflect LC-NE system functional abnormalities (W. Hou et al., 2024). Specifically, in resting states, children with ASD show significantly larger pupil diameters than typically developing children (C. J. Anderson & Colombo, 2009; W. Hou et al., 2024; Keehn et al., 2021; Kim et al., 2022), suggesting their LC is in a state of sustained hyperactivation that may affect environmental information filtering and effective allocation of attentional resources. During task states, attentional disengagement ability is significantly reduced in children with ASD, and disengagement speed negatively correlates with resting pupil diameter (Keehn et al., 2021), further revealing potential links between sustained hyperactivation of the LC-NE system and impaired attentional regulation.

Research has found that ASD individuals show clear deficits in attentional processing (Hames et al., 2016; Landry & Parker, 2013; Mutreja et al., 2016). For example, in tasks requiring attentional orienting, they show longer reaction times (Mutreja et al., 2016) and lower accuracy (Hames et al., 2016). A meta-analysis also confirmed that ASD individuals show moderate effect size orienting attention deficits across all age stages (Landry & Parker, 2013). Neuroimaging studies found that in resting state, functional connectivity between the SN and other attentional systems is abnormal in children with ASD (Green et al., 2016), suggesting the LC-NE system may fail to effectively coordinate dynamic allocation of attentional resources. In summary, LC-NE system dysfunction may be key to abnormal attentional processing in ASD individuals. With the development of neurotechnologies such as pupillometry and functional imaging, LC-NE system dysfunction is expected to become an important biomarker for identifying ASD neural phenotypes and provide potential neuromodulation targets for precision intervention strategies.

4.3 LC-NE and Anxiety and Depressive Disorders

Anxiety and depressive disorders are the most common types of mood disorders, both showing varying degrees of impaired attentional control function. According to attentional control theory, anxiety weakens individuals' top-down attentional control and reduces attentional switching flexibility (Eysenck et al., 2007). Research shows that both children and adults with anxiety disorders exhibit attentional control deficits (Mogg et al., 2015; Pacheco-Unguetti et al., 2011), while major depressive disorder (MDD) patients tend to persistently attend to negative information (Rudich-Strassler et al., 2022). These abnormal attentional patterns are believed to be closely related to hyperactivation of the LC-NE system (Zhang et al., 2023). Animal studies provide direct evidence for this hypothesis. For example, McCall et al. (2015) used optogenetics to activate endogenous projections from corticotropin-releasing hormone neurons in the amygdala to the LC, which induced tonic LC discharge and significant anxiety-like behavior. Subsequent research found that activating LC-to-amygdala NE projection pathways also enhanced amygdala neural activity and triggered anxiety responses (McCall et al., 2017). Additionally, threatening stimuli can directly evoke LC neuronal discharge (Morris et al., 2020), and under stress states, high-frequency tonic LC discharge releases large amounts of NE that overactivate α_1 and β receptors, suppressing PFC function (Birnbaum et al., 1999; Ramos et al., 2005) and exacerbating attentional dispersion and impulse control deficits (Arnsten et al., 2007). These findings collectively reveal that the LC-NE system may constitute the neural basis for attentional dysfunction in mood disorders. Clinically, NE reuptake inhibitors (e.g., reboxetine) can effectively alleviate anxiety, fear anticipation, and depressive symptoms by enhancing NE synaptic transmission function (Montgomery, 1997; Versiani et al., 2002), further confirming the validity of the LC-NE system as a drug target for mood disorders. In summary, the LC-NE system plays a key role in attentional control deficits caused by mood disorders by regulating neural activity in the PFC and amygdala, providing important support for understanding the neurobiological mechanisms of mood disorders and drug-targeted interventions.

5 Summary and Outlook

As the brain’ s primary neuromodulatory center, the LC-NE system plays a key role in attentional regulation through its extensive neural projections, diverse receptor modulation mechanisms, and flexible firing patterns. The system not only participates in modulating multiple attentional subsystems including alerting, orienting, and executive control, but its dysfunction is also associated with attentional disorders such as ADHD and ASD, and it may become an effective neural target for intervening in various attentional disorders. The application of non-invasive physiological indicators (such as pupil dilation PD and event-related potentials ERP) has already provided evidence for revealing the mechanisms of LC-NE system regulation of attention, and the development of multimodal measurement techniques has provided new opportunities for understanding LC-NE system function. Despite significant progress in recent research on the LC-NE system in attentional regulation, several challenges remain, and future research urgently needs to deepen in the following aspects:

First, current indirect indicators used to assess LC-NE system activity (such as PD and ERP) remain controversial regarding their reliability and specificity. Taking PD as an example, its changes are regulated not only by the LC-NE system but also by multiple neurotransmitter systems including acetylcholine and serotonin (Cazettes et al., 2021; Reimer et al., 2016), limiting its explanatory power as a specific functional indicator of LC-NE. Furthermore, Megemont et al. (2022) found in mouse studies that PD is highly correlated with LC discharge activity only during events with significantly increased amplitude and is affected by brain state fluctuations. This suggests that single indicators have limitations in reflecting LC-NE system activity, and future research urgently needs to conduct cross-validation of multiple neural and physiological indicators such as

PD and ERP components, using multimodal fusion modeling to replace single assessment approaches and improve the sensitivity and specificity of LC-NE system activity representation. Notably, despite these limitations, methods such as pupillometry and ERP still offer the advantage of millisecond-level temporal resolution, effectively capturing the rapid dynamic regulation of attentional processes by the LC-NE system. However, temporal advantages alone cannot solve spatial localization challenges. Due to the small size and deep brainstem location of the LC, conventional 3T fMRI cannot achieve precise imaging of its activity. Future research could utilize ultra-high-field 7T fMRI (Berger et al., 2023; Koshmanova et al., 2023) to improve spatial resolution and combine it with the temporal resolution advantages of pupillometry and ERP to achieve high spatiotemporal precision tracking of LC-NE in attentional regulation. Additionally, under clinically indicated conditions, intracranial electroencephalography (iEEG) technology, which offers both millisecond-level temporal and spatial resolution, could be used to reveal the regulatory effects of the LC-NE system on attentional network nodes such as the PFC, parietal cortex, and TPJ.

Second, although observational studies have revealed correlational features between LC-NE activity and attentional performance, the lack of systematic intervention studies prevents clear identification of causal mechanisms of LC-NE in attentional regulation. Future research could combine pharmacological stimulation, transcranial magnetic stimulation (TMS), and transcranial electrical stimulation (tES) to reveal the neural mechanisms of LC-NE system regulation of attention from a causal perspective. Additionally, deep brain stimulation (DBS) could serve as an invasive causal intervention method, acting on key network nodes highly coupled with the LC-NE system in clinically indicated individuals to provide critical evidence for clarifying its causal role in attentional regulation. Furthermore, combining these neuromodulation approaches with observational indicators such as pupillometry, ERP, and fMRI signals can achieve complementarity between causal manipulation and dynamic recording, thereby more comprehensively revealing the functional characteristics of the LC-NE system during attentional regulation.

Finally, the functional connectivity mechanisms between the LC and multiple key regions in attentional networks (such as PFC, parietal cortex, TPJ, etc.) require further investigation. Although existing research has revealed interaction patterns between the LC and attentional networks in subsystems such as alerting, orienting, and executive control through animal models (Bari et al., 2020; Ghosh & Maunsell, 2024; Janitzky et al., 2015; Marrocco et al., 1994), dynamic functional connectivity in human tasks still lacks systematic research support. Additionally, the LC-NE system may show functional differences across different age stages—for example, its supportive role in attention development during childhood and adolescence and its potential association with attention decline in elderly populations—making this developmental perspective worthy of further exploration. Meanwhile, emerging computational modeling frameworks (such as predictive coding and gain control frameworks) provide new theoretical tools for explaining the dynamic role of LC-NE in different task contexts and are expected to combine with empirical research to promote the establishment of unified mechanism models. Overall, deepening our understanding of the LC-NE system' s role in attention will not only help build more complete neural mechanism models of attentional regulation but also provide more precise pathways and theoretical foundations for interventions in attentional disorders.

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Note: Figure translations are in progress. See original paper for figures.