Improving the adaptive and continuous learning capabilities of artificial neural networks: Lessons from multi-neuromodulatory dynamics

Jie Mei [1,2,3,*,†,§], Alejandro Rodriguez-Garcia [4,*], Daigo Takeuchi [5], Gabriel Wainstein [6,7], Nina Hubig [1,8], Yalda Mohsenzadeh [9,10], Srikanth Ramaswamy [4,11,†,§]

[1] IT:U Interdisciplinary Transformation University Austria, Linz, Austria
[2] International Research Center for Neurointelligence, The University of Tokyo, Tokyo, Japan
[3] Department of Anatomy, University of Quebec in Trois-Rivieres, Trois-Rivieres, QC, Canada
[4] Neural Circuits Laboratory, Biosciences Institute, Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom
[5] Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
[6] Brain and Mind Centre, The University of Sydney, Sydney, NSW, Australia
[7] Helsinki Institute of Life Science (HILIFE), University of Helsinki, Helsinki, Finland
[8] Department of Neuroscience, Medical University of South Carolina (MUSC), Charleston, SC, USA
[9] Department of Computer Science, Western University, London, Ontario, Canada
[10] Vector Institute for Artificial Intelligence, Toronto, Ontario, Canada
[11] Theoretical Sciences Visiting Program (TSVP), Okinawa Institute of Science and Technology Graduate University, Okinawa, Japan
[*] These authors contributed equally.
[†] Senior authors. [§] Lead contacts: jie.mei@it-u.at; srikanth.ramaswamy@newcastle.ac.uk.

Abstract

[*] Continuous, adaptive learning – the ability to adapt to the environment and improve performance – is a hallmark of both natural and artificial intelligence. Biological organisms excel in acquiring, transferring, and retaining knowledge while adapting to dynamic environments, making them a rich source of inspiration for artificial neural networks (ANNs). This study explores how neuromodulation, a fundamental feature of biological learning systems, can help address challenges such as catastrophic forgetting and enhance the robustness of ANNs in continuous learning scenarios. Driven by neuromodulators including dopamine (DA), acetylcholine (ACh), serotonin (5-HT) and noradrenaline (NA), neuromodulatory processes in the brain operate at multiple scales, facilitating dynamic responses to environmental changes through mechanisms ranging from local synaptic plasticity to global network-wide adaptability. Importantly, the relationship between neuromodulators, and their interplay in the modulation of sensory and cognitive processes are more complex than expected, demonstrating a "many-to-one" neuromodulator-to-task mapping. To inspire the design of novel neuromodulation-aware learning rules, we highlight (i) how multi-neuromodulatory interactions enrich single-neuromodulator-driven learning, (ii) the impact of neuromodulators across multiple spatial and temporal scales, and correspondingly, (iii) strategies for approximating and integrating neuromodulated learning processes in ANNs. To illustrate these principles, we present a case study to demonstrate how neuromodulation-inspired mechanisms, such as DA-driven reward processing and NA-based cognitive flexibility, can enhance ANN performance in a Go/No-Go task. By integrating multi-scale neuromodulation, we aim to bridge the gap between biological learning and artificial systems, paving the way for ANNs with greater flexibility, robustness, and adaptability.

1 CONTINUAL LEARNING IN NATURAL AND ARTIFICIAL INTELLIGENCE

Learning is the dynamic process by which a system reconfigures itself to improve its performance on a task through experience (Kandel and Hawkins, 1992; Kudithipudi et al., 2022; Wang et al., 2024a). However, real-world scenarios are not stationary, which presents unique challenges to maintaining good performance over time (Hadsell et al., 2020; Neftci and Averbeck, 2019). Through evolution, biological organisms have developed the ability to learn a variety of tasks over their lifetime with minimized cross-task interference. This ability to integrate new knowledge without forgetting previously acquired representations has enabled them to adapt to the environment, thereby maintaining and optimizing survival (Chen and Liu, 2018; Flesch et al., 2023; Hassabis et al., 2017; Rodriguez-Garcia et al., 2024; Wang et al., 2024a). In addition to the ability of biological organism to **(i)** progressively learn new tasks, they can also **(ii)** transfer knowledge across successive tasks, **(iii)** incorporate new examples of previously learned tasks, and **(iv)** both detect and adapt to changes in their environment – all in a robust and efficient manner. Consequently, in recent years, these abilities to continuously learn in a dynamic environment have been increasingly understood in a broader context, often merging their concept with that of lifelong learning (Chen and Liu, 2018; Hadsell et al., 2020; Kudithipudi et al., 2022; Wang et al., 2024a).

On the contrary, while state-of-the-art artificial neural networks (ANNs) excel at learning from fixed datasets and can outperform humans on certain tasks, they exhibit inherent limitations that prevent

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them from being considered as 'lifelong learning machines' (Kudithipudi et al., 2022). Examples of such limitations include catastrophic forgetting (Goodfellow et al., 2013; McCloskey and Cohen, 1989; Ratcliff, 1990), the reliance on large and often labeled datasets (D'Angelo and Henning, 2021; Wang et al., 2024a), the inability to generalize to out-of-distribution data (Zador, 2019), high energy consumption that limits scalability (Kudithipudi et al., 2022; Pfeiffer and Pfeil, 2018), and the credit assignment problem (Kriegeskorte and Golan, 2019).

In this work, we explore continual learning in its broader conceptualization, recognizing it as an essential component for fostering intelligence in artificial intelligence (AI) systems, which is instrumental in the advancement towards artificial general intelligence (Chen and Liu, 2018). We will illustrate how mechanisms of different neuromodulatory systems can support continual learning and contribute to various relevant learning paradigms, and offer insights into how computations inspired by neuromodulators including dopamine (DA), serotonin (5-HT), acetylcholine (ACh) and noradrenaline (NA) can be integrated into ANN architectures across multiple spatio-temporal scales, leading to more adaptive and resilient AI systems.

The catastrophic forgetting problem

One major challenge to the advancement of continuous learning systems lies in the learning methods employed. State-of-the-art ANNs rely on gradient-based methods, in particular, the backpropagation algorithm (Kriegeskorte and Golan, 2019; LeCun et al., 2015). However, there is currently no widely accepted mechanism within the brain that can explain the backward transmission of error signals along one-way synapses (Hwu and Krichmar, 2020; Lillicrap et al., 2020; Whittington and Bogacz, 2019). Furthermore, a critical limitation of backpropagation is catastrophic forgetting (Goodfellow et al., 2013; McCloskey and Cohen, 1989), which occurs when the acquisition of new information interferes with previously learned data, causing the system to forget its prior knowledge when trained on sequential tasks. In contrast, biological systems are capable of integrating learnings throughout their lifetime, thereby ensuring and optimizing the survival of the species (Hadsell et al., 2020; Hassabis et al., 2017; Mei et al., 2022).

Catastrophic forgetting does not originate from a deficiency in memory storage. Rather, it is caused by the overwriting of memory without preserving prior knowledge (Goodfellow et al., 2013; Kudithipudi et al., 2022). To address this challenge and protect synaptic weights from being overwritten regularized gradient-based methods such as Elastic Weight Consolidation (Kirkpatrick et al., 2017), Synaptic Intelligence (Zenke et al., 2017), Memory Aware Synapses (Aljundi et al., 2017), or Sliced Cramer Preservation (Kolouri et al., 2020) have been proposed. Moreover, alternative approaches seek to mitigate catastrophic forgetting by emulating sleep-like states of the brain to preserve memories (González et al., 2020; Krishnan et al., 2019).

Some studies have been inspired by neurogenesis in the hippocampus, using dynamic network architectures to overcome catastrophic forgetting by incorporating new neurons or layers, thereby preserving previously acquired knowledge (Parisi et al., 2019; Rusu et al., 2016). Other approaches employ modular architectures to maintain learning across sequential tasks (Ellefsen et al., 2015; Hadsell et al., 2020). Furthermore, novel architectures that realized heterogeneous neural populations have demonstrated the ability to learn across timescales through multi-stable dynamic regimes (Gast et al., 2024; Stern et al., 2023). In addition, emerging perspectives suggest neuron-specific neuromodulation as a means to enhance adaptability (Munn et al., 2023; Rodriguez-Garcia et al., 2024) and to address credit assignment in spiking neural networks (Liu et al., 2021).

The brain's ability to regulate its own plasticity, known as metaplasticity, plays a crucial role in enabling continual learning. This principle is reflected in learning-to-learn algorithms, which leverage inner and outer learning loops to capture adaptation processes operating at two distinct time scales (Hadsell et al., 2020; Miconi, 2022). Recently, meta-learning approaches have become increasingly important due to their ability to integrate brain-inspired neuromodulatory learning techniques, particularly in reinforcement scenarios (Bellec et al., 2020; Miconi, 2022; Schmidgall and Hays, 2023; Schweighofer and Doya, 2003; Wert-Carvajal et al., 2022).

Overall, bridging the gap between meta-plasticity-driven learning mechanisms and heterogeneous neural architectures presents a promising avenue for the mitigation of catastrophic forgetting. This can be precisely modulated through the release of neuromodulators that act in a neuron-specific manner, thereby fine-tuning plasticity and exploiting the population diversity of heterogeneous SNNs (Rodriguez-Garcia et al., 2024). Additionally, this approach can help tackle the credit assignment problem (Liu et al., 2022b) and promotes multi-task learning by regulating different modes of neuronal dynamics (Munn et al., 2023; Williams et al., 2024), offering a more robust framework for continuous and adaptive learning in artificial neural systems.

Learning across multiple tasks

ANNs are typically trained using supervised or unsupervised learning paradigms, relying heavily on the quality and diversity of the training datasets. As a result, these datasets play a critical role in shaping the learned task representations (Pfeiffer and Pfeil, 2018; Zador, 2019), limiting the network's ability to generalize to out-of-distribution (OOD) data (examples that significantly differ from training distribution) and reduces its effectiveness in processing entirely novel samples (D'Angelo and Henning, 2021; Wang et al., 2024a). Furthermore, for ANNs to adequately learn a given task, a substantial number of training samples is required. This results in the training datasets consuming a significant amount of memory space (Kudithipudi et al., 2022; Pfeiffer and Pfeil, 2018; Schuman et al., 2022).

In contrast, biological organisms acquire knowledge in a self-supervising or reinforcing manner through direct interactions with uncertain and noisy environments (Neftci and Averbeck, 2019). This exposure has facilitated the refinement of their ability to transfer knowledge across tasks in a forward or in a backward fashion (Hadsell et al., 2020; Kudithipudi et al., 2022; Wang et al., 2024a). Furthermore, they possess genetically encoded capabilities that have been developed through evolution and are inherent to their biology (Kar and DiCarlo, 2024; Zador, 2019). Hence, biological systems are capable of rapid and efficient learning from a limited number of trials, a phenomenon commonly described in the framework of few-shot learning (Kudithipudi et al., 2022; Wang et al., 2024a). In a similar vein, continual learning systems have sought inspiration in the aforementioned features of biological learning: Some notable examples include SNNs in neuromorphic chips trained with surrogate gradients (Stewart et al., 2020), as well as SNNs trained with eligibility propagation (e-prop) (Bellec et al., 2020), which have demonstrated the capacity for few-shot learning.

The biological brain learns continuously and adaptively

In the biological brain, learning occurs in response to changes in the environment, task demands, and/or the state of the organism. To learn continuously in a complex and ever-changing environment, a series of actions with different cognitive demands are performed. These actions often involve **(i)** acquiring, and tracking knowledge acquired in a completed task, **(ii)** recognizing a new task, **(iii)** determining task statistics and similarities across tasks, **(iv)** encoding, reusing and exploiting acquired knowledge, **(v)** updating and transmitting task-specific variables, and **(vi)** updating internal states during and after learning. In real-world scenarios, task shifts and environmental changes do not always occur sequentially - instead, an organism sometimes learns to meet the requirements of multiple tasks simultaneously, which requires not only the storage of past tasks, but also the distinction between parallel, concurrent tasks, and across time scales. In brain circuits, these components of continuous learning processes are supported by a collective of computations, with the help of neuromodulatory systems. For example:

- **Encoding task sequences:** Encoding takes place in brain areas such as the prefrontal cortex (PFC), anterior cingulate cortex (ACC) and basal ganglia, where representations of task sequences are stored and retrieved, allowing for the flexible execution of complex multi-step behaviors (Jin and Costa, 2015; Takeuchi et al., 2022; Tanji and Shima, 1994). Such processes involve the formation of associations between contextual cues, specific actions and their outcomes, facilitated by synaptic plasticity mechanisms (e.g., LTP and LTD).

- **Updating task representations:** As new information is encountered, the brain updates its internal models of the task environment by modifying existing representations or creating new ones. Neuromodulators may play crucial roles in such model-based learning processes, signaling the need for behavioral adjustments and triggering synaptic changes necessary to adapt to changing circumstances (Akam and Walton, 2021).

- **Maintaining task fidelity:** To ensure stable execution of learned task sequences, the brain needs to avoid catastrophic forgetting. Some regularization methods in ANN learning are able to achieve this and exhibit parallels with NMDA-mediated plasticity and the clustering of closely related synapses in biological neurons (Acharya et al., 2022; Bono and Clopath, 2017; Kastellakis et al., 2016; Limbacher and Legenstein, 2020; Pagkalos et al., 2024). However, while these methods have demonstrated exceptional fidelity in supervised image classification tasks, their broader potential remains unexplored across a wider range of real-world applications.

Given the brain's resilience and capacity for learning continuously, catastrophic forgetting, also referred to as catastrophic interference, which takes the form of full erasure of previously learned representations upon acquisition of new information, is rarely reported in healthy subjects in the study of human cognition (French, 1999). Rather, phenomena that are to some extent comparable to catastrophic forgetting, e.g., interference in declarative memory caused by overlapping information, have been observed in patients with amnesia (Merhav et al., 2014). Such interference has also been observed in motor learning, where loss of previously acquired motor skills occur when new skills are learned. When new locomotor tasks are present (e.g., learning a new sport that is similar to a learned sport but with different rules

and court area), there can be interference with existing motor memories, leading to negative transfer of learned motor skills (Seidler, 2010). Reduced motor learning and transfer abilities have been shown in brain pathologies: For example, although cerebellar damage doesn't affect online motor adjustments, it compromises adaptive performance in motor learning processes (Morton and Bastian, 2006; Smith and Shadmehr, 2005). Furthermore, neurodegenerative disorders such as Parkinson's or Huntington's disease can lead to performance decrease in kinematic adaptation tasks (Laforce and Doyon, 2002).

Overall, when brain pathologies are excluded, it is difficult to pinpoint cognitive processes that are comparable in nature and functionally analogous to catastrophic forgetting. Nevertheless, studies have focused on identifying the neural correlates of learning and memory, providing a substantial body of evidence on how the nervous system supports learning in a continuous, sustained, and robust manner (Grossman and Cohen, 2022).

Neuromodulators in diverse continual learning settings

Neuromodulators such as DA, NA, 5-HT and ACh contribute to a diverse range of adaptive learning and decision-making processes. Although the link between experimental and theoretical studies still remains limited, neuromodulators likely balance stabilization and flexibility in a diverse range of adaptive learning paradigms that overlap in goals and techniques with continual learning. Some examples of these paradigms include transfer learning, meta-learning, multi-task learning, incremental learning and online learning (see Table 1 for comparison of each learning paradigms; see also (Avery and Krichmar, 2017; Doya, 2002; Lee et al., 2024; Montague et al., 2012) for discussions). Therefore, understanding the contributions of neuromodulators to these learning paradigms, and their biological correlates, will help us improve the robustness and flexibility of existing models.

Definition of continual learning settings

The constraints imposed by each learning setting require the use of distinct computational formalizations (Hoi et al., 2021; Hospedales et al., 2021; Long et al., 2015; Pan and Yang, 2010; Sener and Koltun, 2018; Shalev-Shwartz, 2011; Wang et al., 2024a; Zhang and Yang, 2022; Zhuang et al., 2021). While there is a variety of formalizations for each learning setting, depending on the contexts and algorithms with which the learning problem is formalized, we describe here some representative formulations:

1. **Transfer learning:** Transfer learning refers to the problem of extracting and retaining the knowledge learned in one or more source tasks and applying this knowledge to a target task (Hospedales et al., 2021; Long et al., 2015; Pan and Yang, 2010; Zhuang et al., 2021). The general goal is to adapt models trained on one domain to a new domain by minimizing the discrepancy between the source and target tasks:

$$\theta_t = \arg\min_{\theta} \left(L_t(\theta; D_t) + \lambda R(\theta) \right), \tag{1}$$

   where parameters θ are initialized from θ_s that are learned from the source task T_s, and L_t is the task-specific loss function with D_t being the data from target task T_t. The regularization term R, (e.g., L$_2$ norm, $||\theta - \theta_s||^2$) ensures that the current model retains relevant knowledge from the source task by penalizing deviations between the current parameters θ and the pre-trained source model parameters θ_s.

2. **Meta-learning:** The general goal of meta-learning, or learning-to-learn, is to train a model on a variety of learning tasks, such that the model (or the meta-learner) is able to learn a meta-knowledge about what, when and how to learn, adapts quickly to a new task from a few examples, and continues to adapt as more data become available (Andrychowicz et al., 2016; Finn et al., 2017; Hospedales et al., 2021). In contrast to other learning paradigms, meta-learning generally involves bi-level optimization in learning the meta-knowledge ω from the source task (i.e., meta-training stage) where one optimization contains another optimization as a constraint (Hospedales et al., 2021). Then, in the meta-testing stage, the meta-knowledge ω^* obtained in the meta-training stage is used to train the model for each task ("base-model") on each previously unseen target task T_i:

Meta-training stage

$$\omega^* = \arg\min_{\omega} \sum_{i=1}^{N} L^{\text{meta}} \left(D_s^{\text{val}(i)}, \theta_i^*, \omega \right) \tag{2}$$

$$\text{s.t. } \theta_i^*(\omega) = \arg\min_{\theta} L^{\text{task}} \left(D_s^{\text{train}(i)}, \theta, \omega \right), \quad i = 1, \ldots, N \tag{3}$$

Meta-testing stage

$$\theta_i^* = \arg\min_{\theta} L^{\text{task}} \left(D_t^{\text{train}(i)}, \theta, \omega^* \right), \quad i = 1, \ldots, N \tag{4}$$

4

Task Learning paradigm and goal	Key properties (i) Sequential or concurrent learning? (ii) Is performance in the original domain preserved after learning? (iii) Memory demand and computational cost	Similar paradigms and concepts in experimental studies	Learning objective, loss function and parameter optimization
Transfer learning Efficient adaptation to new domains	(i) Sequential (ii) Lower performance due to catastrophic forgetting (iii) Memory demand does not change significantly	Transfer of learning (Haskell, 2006; Woodworth and Thorndike, 1901) Mapping of knowledge (Gentner, 1983) Schema learning (Tse et al., 2007) Structure learning (Tervo et al., 2016)	$\theta_n = \arg\min_\theta \left(L_s(\theta, D_i) + \lambda R(\theta) \right),$ with initial $\theta = \theta_s$.
Meta-learning Efficient adaptation to new tasks and contexts	(i) Sequential (ii) Lower performance due to catastrophic forgetting (iii) Data memory increases in learning inner and outer processes	Learning-to-learn (Harlow, 1949) Meta-cognitive learning (He and Lieder, 2023)	$\theta_i^*(\omega) = \arg\min_\theta L^{\text{task}}(D_s^{\text{train}(i)}, \theta, \omega),$ where ω^* is obtained in the meta-training stage.
Multi-task / Joint learning Promoting learning by using shared patterns across tasks and domains	(i) Concurrent (ii) Performance is maintained, as learning occurs using data from all domains (iii) Data memory and computational cost increases as the number of domains increases	Dual task paradigm (Pashler, 1994) Task switching (Rushworth et al., 2004; Takeuchi et al., 2022)	$\theta^* = \arg\min_\theta \sum_{i=1}^{N} \lambda_i L_i(\theta; D_i)$
Incremental learning Assimilating new information and efficiently updating models while avoiding catastrophic forgetting	(i) Sequential (ii) Performance is maintained, as algorithms suppress catastrophic forgetting (iii) Memory demand does not change as the number of domains increases (model parameters in the original domain are inherited but training data is not); computational cost is comparatively low	Retroactive interference (Anderson, 2003) Task switching (Rushworth et al., 2004; Takeuchi et al., 2022) Set-shifting (Dias et al., 1996; Konishi et al., 1998; Robbins, 2007)	$\theta^* = \arg\min_{\theta_t} \left(L_t(\theta_t; D_t) + \sum_{i=1}^{t-1} \lambda_i \Omega(\theta_t, \theta_i) \right)$
Online learning Efficiently updating models upon real-time data collection	(i) Sequential (ii) Performance gets lower, due to catastrophic forgetting (iii) Memory demand does not change as the number of domains increases (model parameters in the original domain are inherited but training data is not); computational cost is comparatively low	Reversal learning (Wilson et al., 2014) Delayed alternation (Mishkin et al., 1969) Extinction learning (Phelps et al., 2004) Set-shifting (Dias et al., 1996; Konishi et al., 1998; Robbins, 2007)	$\theta^* = \arg\min_{\theta_t} \sum_{t=1}^{T} \lambda_t L_t(\theta; x_t)$

Table 1: A summary of adaptive learning paradigms and their goals, key properties, representative formulations of the loss functions, and the corresponding paradigms in neuroscience/psychology. *Transfer learning:* D_t, data from task T_t. L_t, the loss function for target task T_t (task-specific loss, e.g., cross-entropy or mean squared error for task T_t with data D_t). R, regularization term (e.g., L$_2$ norm, $||\theta - \theta_s||^2$). Parameters θ are initialized with θ_s learned from source task T_s. *Meta-learning:* θ_i are parameters for task T_i, L^{task} represents the loss function for base-model learning. Each task has training dataset D^{train} and validation dataset D^{val}. D_s and D_t represent the data from the source and the target task, respectively. *Multi-task/joint learning:* λ_i are task-specific weights (static or dynamically computed), and L_i is the loss function of task T_i with D_i being the data from the same task. *Incremental learning:* L_t is the loss function of the ongoing task at time step t of the ongoing task T_t with D_t being the data from T_t. The regularization term Ω (e.g., L$_2$ norm, $||\theta - \theta_s||^2$) is implemented to mitigate forgetting by maintaining similarity between the target (current) task parameters θ_t and previous parameters $\theta_i (i < t)$. , the weight for the i-th regularization term, controlling how far in time the old task knowledge is maintained. *Online learning:* L_t is the loss function of the ongoing task at time step t.

where θ_i are parameters for task T_i, L^{meta} refers to the outer objective, L^{task} for the inner objective (i.e., base-model learning). Each task has training dataset D^{train} and validation dataset D^{val}. D_s and D_t represent the data from the source and the target task, respectively.

3. **Multi-task learning:** Multi-task learning aims to jointly learn several related tasks, to benefit from regularization due to parameter sharing and the diversity of the resulting shared representation, as well as compute/memory savings (Hospedales et al., 2021; Sener and Koltun, 2018; Zhang and Yang, 2022). The general goal is to minimize a joint loss function over multiple tasks:

$$\theta^* = \arg\min_\theta \sum_{i=1}^{N} \lambda_i L_i(\theta; D_i), \tag{5}$$

where λ_i are task-specific weights (static or dynamically computed), and L_i is the loss function of task T_i with D_i being the data from the same task. The use of shared parameters θ across tasks enhances learning efficiency and across-task generalization.

4. **Incremental learning:** Incremental learning (sometimes referred to as continual learning, e.g., Hospedales et al. (2021); Wang et al. (2024a)) refers to the ability to learn on a sequence of tasks drawn from a potentially non-stationary distribution, and in particular seek to do so while accelerating learning new tasks and without forgetting old tasks (Hospedales et al., 2021; Wang et al., 2024a). There is a diversity of ideas and algorithms proposed in the field but, generally speaking, they are formulated with some optimizations where the model is designed to balance between minimizing the task-specific loss and avoiding catastrophic forgetting (Chen and Liu, 2018; Hadsell et al., 2020; Kudithipudi et al., 2022; Wang et al., 2024a). A representative formulation is:

$$\theta^* = \arg\min_{\theta_t} \left(L_t(\theta_t; D_t) + \sum_{i=1}^{t-1} \lambda_i \Omega(\theta_t, \theta_i) \right), \tag{6}$$

where L_t is the loss function of the ongoing task at time step t, and L_t is the loss function of the ongoing task T_t with D_t being the data from T_t. The regularization term Ω is designed to mitigate forgetting by maintaining similarity between the target (current) task parameters θ_t and previous parameters θ_i ($i < t$). is the weight for the i-th regularization term, controlling how far in time the old task knowledge is maintained (e.g., temporal discounting).

5. **Online learning:** In online learning, data arrives sequentially, and the model updates with each new data point. The general goal is to make a sequence of accurate predictions by learning from a sequence of data instances one by one at each time (Hoi et al., 2021; Shalev-Shwartz, 2011). Given a data stream x_t, the goal is to minimize the cumulative loss over time:

$$\theta^* = \arg\min_{\theta_t} \sum_{t=1}^{T} \lambda_t L_t(\theta; x_t), \tag{7}$$

where L_t is the loss function of the ongoing task at time step t. The key feature is in updating the models upon real-time data collection which facilitates rapid adaptations to dynamically changing environments or task contexts. λ_i is the weight for the loss, controlling how far in time the old task knowledge is taken account of (e.g., temporal discounting).

Neuro-inspired solutions to various learning settings: The functions of neuromodulators

The brain is confronted with distinct optimization problems in each learning setting, which gives rise to diverse computational demands. The question of how the brain can enable such an extraordinary feat by orchestrating multiple neuromodulators that act in distinct aspects of learning and of how each neuromodulator expresses its functions in each learning setting is addressed by computational and experimental studies:

- **DA:** A seminal study by (Schultz et al., 1997) demonstrated that the phasic responses of dopaminergic neurons during learning closely resemble reward prediction error (RPE) signals in reinforcement learning (RL). This finding led to the prediction error hypothesis of DA signaling, proposing that DA neurons encode the difference between how good the future outcome was expected to be, and how good it turned out to be.

  The prediction error signaling by DA provides valuable information when exploring better task performance in continual learning settings, particularly in transfer learning, incremental learning and online learning, but this is not the whole story: Accumulating evidence indicates that DA neurons encode not only RPE but also movement-related variables and aversive/threatening stimuli, calling for an updated hypothesis of DA signalling (Akam and Walton, 2021; Avery and Krichmar,

2017; Engelhard et al., 2019; Gershman et al., 2024; Kim et al., 2023; Lerner et al., 2021; Matsumoto and Hikosaka, 2009; Menegas et al., 2018). Besides, DA is required for encoding new item memory (Lee et al., 2021). These signals can support various aspects of continual learning such as invigoration for new learning and multitasking (Beierholm et al., 2013; Niv et al., 2007), novelty detection (Avery and Krichmar, 2017), developing schema or model-based strategies in meta-learning (Akam and Walton, 2021; Hattori et al., 2023), overcoming and managing uncertainty during transfer learning, incremental learning or online learning (Avery and Krichmar, 2017).

- **NA:** NA has been linked to vigilance, attention, learning and memory (Aston-Jones and Bloom, 1981; Sara, 1985). More recently, studies have suggested new functional roles of NA in adaptive gain control, network resetting and decision-making in uncertainty (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005; Yu and Dayan, 2005). These studies collectively indicate that NA is essential in continual learning, particularly in transfer learning, incremental learning and online learning where the agent is required to prioritize and integrate new task-relevant information into the existing knowledge, and flexibly update its behaviors upon changes in the environment or task. NA can also facilitate multi-task learning, set-shifting and task-switching by adjusting attention and modulating exploratory behaviors (Shenhav et al., 2013; Tervo et al., 2014).

  Then, how is the NA-locus coeruleus (LC) system involved in balancing the exploitation and exploration in diverse learning settings? A modeling study on LC neuronal network indicates that the phasic mode of LC activity promotes focused or selective attention, whereas the tonic mode can produce a state of high behavioral flexibility (e.g., exploratory behaviors), illustrating the critical importance of dynamical aspects of neuromodulation in learning and cognition (Aston-Jones et al., 1999). With the advent of novel neurogenetic tools such as optogenetics and GRAB sensors, recent studies has started to address circuit-level questions such as how projections from LC to frontal cortex regulates attention, impulsivity and behavioral switching (Bari et al., 2020; Su and Cohen, 2022). It is likely that neuronal circuits in PFC, ACC and striatum differentially and cooperatively process NA signals in continual learning settings (Hassani et al., 2024), but the precise circuit mechanisms remain an open question (see Figure 4 for a case study).

- **5-HT:** Studies have suggested that 5-HT balances exploration and exploitation (Clarke et al., 2004; Dayan and Huys, 2008; Doya, 2008). Given that the capacity to make such balance is a crucial component in transfer-learning, incremental learning or online learning in which the learning agent is required to apply the previously-learned task knowledge to novel situations/tasks, 5-HT is thought to be a crucial ingredient for continual learning. Indeed, Doya (2002) suggested that 5-HT controls the time scale of reward prediction in RL settings. Such a role of 5-HT in controlling how far in time the previously learned knowledge (i.e., reward) is maintained in the brain may be extended beyond RL. In continual learning settings such as incremental learning and online learning, a learning agent needs to determine how far in time the previously-learned knowledge should be taken into account of in learning new task (incremental learning) or in assimilating newly incoming data stream (online learning), which is expressed as the weight parameter λ_i (incremental learning) or λ_t (online learning) in their loss functions and can be regarded as an analog of the reward discounting factor in standard RL models (Schweighofer et al., 2008; Story et al., 2014).

  The activity of 5-HT in particular neuronal circuits in the brain may substantiate computations that correspond to adjusting these weight parameters in continual learning settings. Besides, 5-HT is also associated with mood, emotions and stress responses in various behavioral contexts (Cools et al., 2011; Dayan and Huys, 2008). Given that, in continual learning, which often involves managing conflicting task demands and the stress from handling multiple tasks, 5-HT is likely to contribute to stabilizing task-related parameters (e.g., expected reward) in loss functions that are optimized in continual learning by adjusting affective states and stress responses.

- **ACh:** ACh is critical for encoding new memories, supporting working memory, and modulating attention, likely through the cellular/subcellular mechanisms such as strengthening afferent inputs to specific neuronal circuits, modulating oscillatory circuit dynamics (e.g., theta rhythms) and promoting persistent spiking activities (Hasselmo, 2006). Such effects of ACh on neuronal circuits are derived from ACh's capacity to modulate inhibitory interneurons (Hasselmo and McGaughy, 2004). Since the capacity to integrate, retain and use new memories is a central component of learning and memory, ACh is a crucial ingredient for continual learning settings such as transfer learning, incremental learning and online learning. ACh can also facilitate cognitive flexibility under uncertainty when an agent is required to simultaneously handle uncertainty among multiple tasks (e.g., multi-task learning) by controlling attention and working memory (i.e., focusing on task-relevant stimuli and ignoring distractions) (Parikh et al., 2007; Sarter and Bruno, 1999). Yu and Dayan (2005) suggested that ACh in combination with NA modulates attentional processes, allowing the agent to efficiently allocate cognitive resources to make inference and continuously

learn in uncertain environments. Furthermore, recent studies indicated that the intrinsic dynamics of ACh in combination with DA in the striatal circuits is driven from extra-striatal afferents and facilitates adaptive learning behaviors by linking action and reward-history to decision-making (Chantranupong et al., 2023; Krok et al., 2023).

2   NEUROMODULATORY SYSTEMS IN THE BIOLOGICAL BRAIN

Neuromodulatory systems in the brain play a crucial role in regulating neural activity and behavior through the release of specific chemical substances known as neuromodulators (Mei et al., 2022). Unlike classical neurotransmitters, which act on specific synapses to transmit signals between neurons and convey information between closely adjacent neurons, neuromodulators diffuse widely and exert more generalized effects on neural circuits, modulating the excitability and plasticity of entire networks of neurons. This allows them to influence the overall state and function of the brain rather than just point-to-point signaling (Marder, 2012).

Definition and key properties

Neuromodulatory effects can be diverse, affecting neuronal excitability, synaptic plasticity, network dynamics, and ultimately behavior (Marder, 2012; Nadim and Bucher, 2014; Thiele and Bellgrove, 2018). Importantly, neuromodulation can occur on various timescales, from rapid changes in neuronal activity to longer-lasting alterations in synaptic strength and network connectivity. Therefore, neuromodulatory systems in the brain play a critical role in shaping and regulating neural circuit activity, impacting various cognitive functions, behavior, and emotional states (Cools and Arnsten, 2022; Grossman and Cohen, 2022; Thiele and Bellgrove, 2018). These systems comprise specific sets of neurons that release neuromodulators that influence the activity of widespread brain regions.

Neurons that produce and release neuromodulators are often clustered in small, well-defined regions of the brain, such as the raphe nuclei for 5-HT, the LC for NA, the nucleus basalis of Meynert in the basal forebrain for ACh, the substantia nigra for DA and the tuberomammillary bodies for histamine (Mei et al., 2022). Despite their compact origins, these neuromodulatory neurons project throughout the brain, innervating the cortex, thalamus, hippocampus, and other key areas involved in sensory processing, memory, and executive functions. The release of neuromodulators can adjust the gain, timing, and synchrony of neural circuits, enhancing or dampening the effects of synaptic transmission based on the organism's current physiological state, environment, and behavioral context (Marder, 2012; Nadim and Bucher, 2014; Thiele and Bellgrove, 2018).

One of the most fascinating aspects of neuromodulatory systems is their ability to exert long-lasting effects on brain circuitry. This is achieved through a variety of intracellular mechanisms, including changes in synaptic strength, modulation of receptor activity, and even alterations in gene expression (Marder, 2012; Mei et al., 2022). As a result, neuromodulators do not simply mediate fast, point-to-point communication like classical neurotransmitters but can set the stage for more enduring changes in neural circuits. This capacity to fine-tune brain function makes neuromodulatory systems essential for maintaining cognitive flexibility and resilience in the face of changing environmental demands (Shine, 2019).

Advanced neuroimaging techniques like functional magnetic resonance imaging (fMRI) have been instrumental in revealing how neuromodulators impact the brain's functional networks. By measuring changes in blood oxygenation, fMRI allows researchers to map activation patterns and identify functional networks that underpin various cognitive processes (Liu et al., 2017; Zerbi et al., 2019). Studies have shown that the LC, through its widespread projections, influences both local and global brain states, enhancing cognitive flexibility and enabling the brain to adapt to changing environments (Aston-Jones and Waterhouse, 2016; Breton-Provencher et al., 2021). The interactions between neuromodulators and cognitive functions are highly flexible, exhibiting synergistic, complementary, and balancing effects (Avery and Krichmar, 2017). For instance, DA and 5-HT can work together synergistically to regulate mood and reward processing, enhancing the brain's ability to respond to positive and negative stimuli (Cardozo Pinto et al., 2025). ACh and NA may complement each other in modulating attention and arousal, ensuring that cognitive resources are appropriately allocated based on task demands (Slater et al., 2022). Additionally, neuromodulators can balance each other's effects to maintain homeostasis within neural circuits; for example, DA may counterbalance the inhibitory effects of GABA to fine-tune motor control and decision-making processes (Mora et al., 2008). Furthermore, neuromodulators can interact in complex ways, often converging onto the same target areas and cognitive functions, and even interacting at the level of single neurons (Nadim and Bucher, 2014). For instance, 5-HT and DA can have opposing effects on reward processing (Esposito et al., 2008), while histamine and ACh may jointly modulate attentional states in the cortex (Bacciottini, 2001). These interactions can be synergistic, complementary, or balancing, allowing the brain to adaptively manage complex cognitive functions by leveraging the unique and overlapping roles of different neuromodulators, thereby supporting robust and adaptable behavior (Avery and Krichmar, 2017).
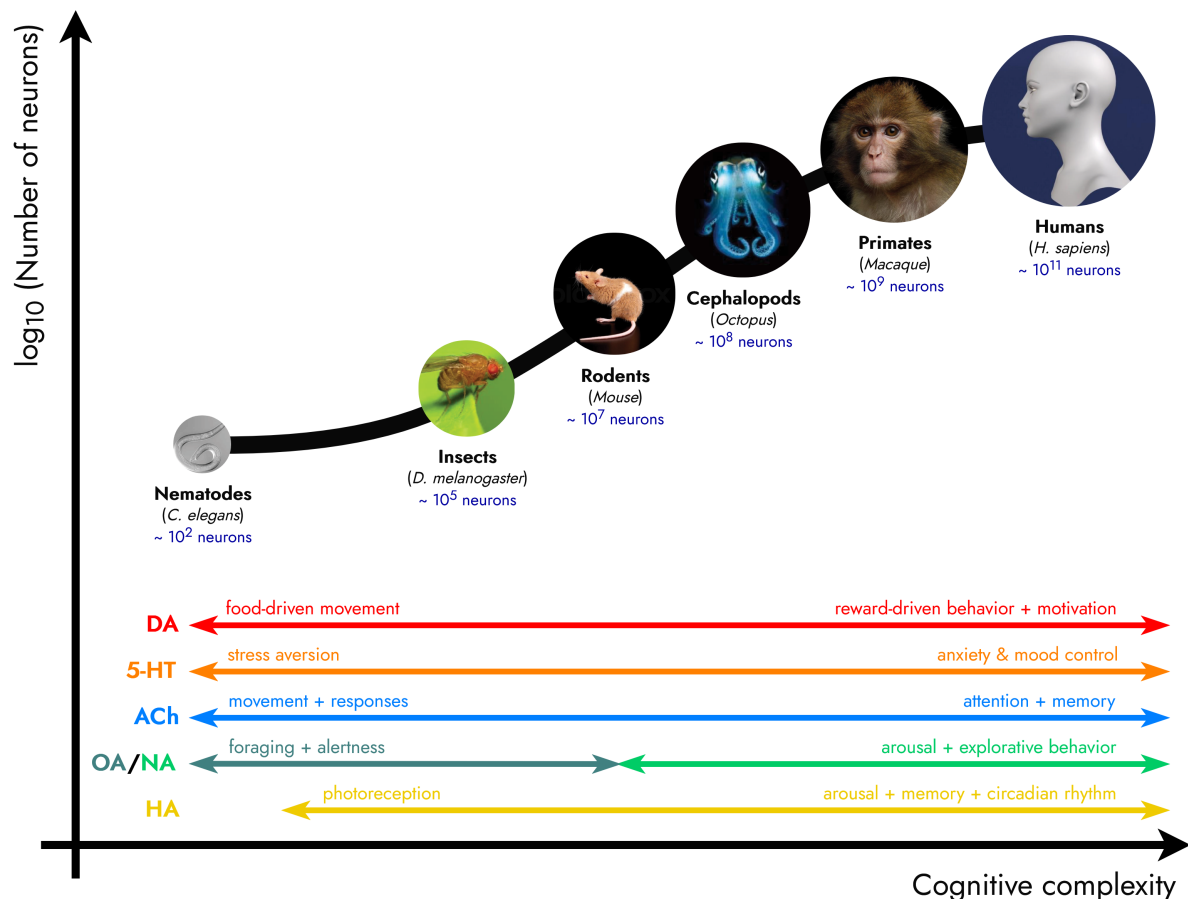
Figure 1: Neuromodulators conservation. Conservation of neuromodulatory systems among species and their roles in supporting a range of cognitive processes, with increasing complexity across evolution. DA: dopamine; 5-HT: serotonin; ACh: acetylcholine; OA: octopamine; NA: noradrenaline; HA: histamine.

Understanding how these neuromodulators interact to shape brain activity and behavior is a major challenge in neuroscience. It requires integrating data across molecular, cellular, and systems levels (Mei et al., 2022; Rodriguez-Garcia et al., 2024). Advances in neurotechnology and computational modeling are now enabling researchers to dissect these complex interactions in unprecedented detail, paving the way for a deeper understanding of how neuromodulatory systems contribute to the flexibility and adaptability of the brain. This intricate interplay is crucial for cognitive functions such as attention, learning, and decision-making, and highlights the importance of neuromodulators in maintaining the brain's dynamic balance between stability and flexibility.

Neuromodulatory systems across species

Conservation of neuromodulators

Neuromodulatory systems are highly conserved across a wide range of species, from simple organisms like C. elegans to complex mammals such as humans, underscoring their fundamental role in biological processes (Figure 1). This conservation is evident in the presence of similar neuromodulatory nuclei and system architectures across diverse taxa, including birds and reptiles. These systems are crucial for enabling organisms to adaptively respond to environmental changes, supporting complex behaviors and cognitive functions. Comparative studies across species also reveal how disruptions in neuromodulation can lead to neurological and psychiatric disorders like depression, anxiety, and schizophrenia.

Throughout evolution, the brain has developed increasingly complex architectures, with neuromodulatory systems playing a key role. The emergence of specialized brain regions, particularly the neocortex in mammals, enhanced sensory processing, cognition, and decision-making (Briscoe and Ragsdale, 2018, 2019; Hamel et al., 2022). Neuromodulatory nuclei in the brainstem, midbrain, and forebrain form the foundational architecture of the mammalian brain, coordinating broad behavioral and cognitive states through extensive projections (O'Callaghan et al., 2021; Shine, 2019; Shine et al., 2018).

The persistence of neuromodulatory systems underscores their importance in regulating behavior and maintaining neurophysiological balance (Figure 1). They enable dynamic adjustments in neural ex-

citability, synaptic plasticity, and network dynamics, which are essential for cognitive flexibility and behavioral adaptability. This adaptability allows organisms to thrive in changing environments by efficiently navigating and responding to challenges.

Higher-order brain functions

Across different species, several higher-order brain functions are supported by neuromodulatory systems, contributing to continuous learning and adaptive behaviors:

1. ***Cognitive flexibility:*** The ability to switch strategies or behaviors in response to changing circumstances or goals. From *C. elegans* adjusting behavior based on environmental cues to primates and humans adapting decision-making strategies based on reward contingencies.

2. ***Developmental plasticity:*** The ability of the brain to change its structure and function in response to experience during development and throughout life. This has been seen in the formation and refinement of neural circuits for sensory processing, motor control, and cognitive functions across species.

3. ***Memory retention and retrieval:*** Processes involved in encoding, storing, and recalling information over time. From basic forms of associative learning in invertebrates like cephalopods to complex declarative and procedural memory systems in mammals and humans.

4. ***Adaptive learning and decision making:*** The ability to learn from experience, predict outcomes, and adjust behavior accordingly. From simple conditioning in *C. elegans* and *Drosophila* to sophisticated decision-making processes involving RPEs and executive functions in primates and humans.

Studying these functions across diverse species provides insights into the evolutionary origins and adaptive significance of neuromodulatory systems. While the complexity and specific mechanisms may vary, the fundamental roles of neuromodulators in shaping neural circuits and behaviors highlight their conservation and adaptive value across evolutionary time scales. This comparative approach not only enhances our understanding of basic neuroscience principles but also informs research into neurological disorders and the development of neuromodulation-based therapies.

Implications for artificial neural networks

The evolutionary conservation and versatile functionality of neuromodulatory systems offer valuable insights for developing ANNs (Hassabis et al., 2017; Kudithipudi et al., 2022; Mei et al., 2022). Emulating the dynamic modulation observed in biological brains can enhance ANNs' adaptability, flexibility, and robustness. Neuromodulatory like mechanisms allow ANNs to adjust learning rates, synaptic weights, and network configurations in response to changing environments and task demands, mirroring the cognitive flexibility of natural neural systems (Mei et al., 2022; Rodriguez-Garcia et al., 2024).

Neuromodulation-inspired architectures can improve learning efficiency by prioritizing pathways and adjusting focus based on contextual cues, similar to biological attention and decision-making processes (Shine et al., 2021). Additionally, integrating neuromodulatory elements may enhance ANNs' resilience to disruptions and noise, ensuring stable performance in dynamic scenarios (Rodriguez-Garcia et al., 2024; Shine, 2019). Understanding the synergistic, complementary, and balancing interactions of neuromodulators in biological systems can inform the design of more sophisticated ANN models that replicate human-like decision-making and problem-solving abilities (Kudithipudi et al., 2022; Mei et al., 2022).

In summary, studying conserved neuromodulatory systems not only deepens our understanding of biological neural networks but also inspires advancements in artificial intelligence. Leveraging neuromodulation principles enables the development of ANNs with greater cognitive flexibility, adaptability, and efficiency, bridging the gap between biological intelligence and artificial systems.

3   MULTI-NEUROMODULATORY DYNAMICS ACROSS SCALES AND ITS EFFECTS ON LEARNING

Mapping neuromodulatory systems to cognitive functions

One task can involve multiple neuromodulatory systems

The anatomical signatures of neuromodulator-releasing neurons (e.g., extensive arborization, high density of release sites, and long-range and wide-spread projections (Doucet et al., 1986; Doya et al., 2021; Matsuda et al., 2009; Poe et al., 2020)) have been linked to systems-level dynamics and signaling of global brain state changes (Aston-Jones and Cohen, 2005; Aston-Jones et al., 1999; Matityahu et al., 2023). This higher-level view, which considered neuromodulation a homogeneous process with spatially-unified activity patterns, may be a result of **(i)** experimental evidence linking neuromodulatory systems

to global and basic brain functions (e.g., arousal and attention), **(ii)** the need to streamline neuromodulatory computations in cognitive and information processing paradigms, and **(iii)** the appeal of developing a unifying theory for individual neuromodulators (Aston-Jones and Cohen, 2005; Fuxe et al., 2010; Poe et al., 2020). Such assumption of neuromodulator functions has partially contributed to one-to-one mappings between individual neuromodulators and pervasive cognitive functions—some prominent examples include NA to arousal/signal-to-noise modulation, 5-HT to cost assessment, DA to reward learning, and ACh to attentional processes.

Although these simplifications may be computationally efficient and conceptually intriguing, in the biological brain, a single neuromodulator frequently influences the release and transmission of other neuromodulators, thereby modulating their activities and functions (Briand et al., 2007). In many cases, such modulation can be reciprocal, further emphasizing the recruitment of multiple neuromodulators even in transient cognitive processes (Box 1). Using technical tools including opto- and chemo-genetics, studies report dense interconnections across neuromodulatory systems. This suggests the involvement of multiple neuromodulators in individual primitive or higher-order cognitive tasks (Box 1), which is consistent with a "many-to-one" pattern. Receptors for the neuromodulators NA, ACh, DA and 5-HT have been identified in multiple functionally defined networks and cognitive processes, ranging from sensory and perceptual behaviors to social and emotional functions (Froudist-Walsh et al., 2023; Hansen et al., 2022). From the perspective of timescales, the signaling of a single neuromodulator can be transient, occurring over a period of milliseconds to seconds, or more sustained and longer-term, spanning minutes to hours. In tasks of greater complexity, there is continuous cooperation between sensory and motor subtasks, and neuromodulators not only help regulate the segregation and integration of local, transient sensorimotor events, but can also exert overarching signals that reflect higher-level end goals of the task (Graybiel, 2008; Shine et al., 2018).
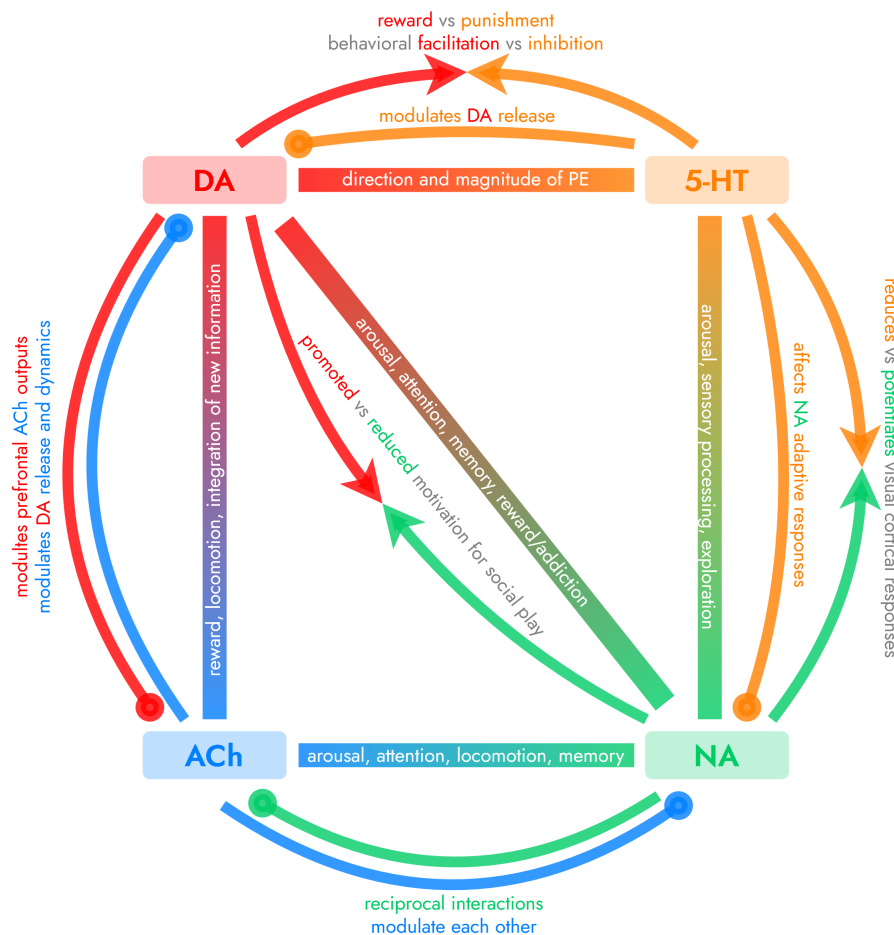

Figure 2: Neuromodulatory relationships diagram. A) Modulatory (●—): One neuromodulator modulates the release, transmission and/or functional output of the other neuromodulator. Convergent (+): Two neuromodulators exhibit overlapping, yet sometimes distinctive functions in shaping sensory and cognitive processes. Opponent (→←): Two neuromodulators exert opposing effects on sensory and cognitive processes, or one suppresses the activity of the other. See Box 1. DA: dopamine; 5-HT: serotonin; ACh: acetylcholine; OA: octopamine; NA: noradrenaline; PE: prediction error

Box 1: The neuromodulatory systems demonstrate complex relationships (Figure 2).

Modularized organizations in neuromodulatory systems

Neuromodulators can contribute to distinct aspects of individual cognitive processes through modularized processes characterized by connections within and across functionally specialized modules, which promote information processing, adaptive configurations, and robustness (Betzel and Bassett, 2017). These modular organizations have been observed across anatomical and functional domains in various cortical and subcortical regions. At the level of cross-regional projections and connectivities, modularized processing may arise from the emergence of projection site-specific characteristics. For example, the functions of ACh projections originating in the basal forebrain (BF) are contingent upon the site of projection, shaping disparate aspects of emotional learning including cue-based aversive learning (BF to amygdala), spatial learning (BF to dorsal hippocampus), and cue encoding (BF to medial PFC) (Likhtik and Johansen, 2019; Záborszky et al., 2018). This anatomical layout may be considered as a network comprising multiple parallel modules, each of which is responsible for a sub-task in the learning of emotionally relevant scenarios.

The distribution of different biochemical markers and neuron types within a single brain region underlies modularized processing that are anatomically and functionally driven by multiple neuromodulators. One prominent example is the striatum, where the markers for ACh and DA are not uniformly distributed (Brimblecombe and Cragg, 2017; Graybiel and Matsushima, 2023). Rather, their preferential distributions contribute partly to the distinction between two compartments, striosomes and matrisomes, each encompassing distinct neurochemical and developmental profiles, connectivity, functional involvements and computations. As shown in animal studies, on top of different levels of neuromodulators across compartments (e.g., higher DA levels in the matrix of dorsal striatum (Brimblecombe and Cragg, 2017; Salinas et al., 2016)), regulation by other neuromodulators can have compartment-

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dependent effects, adding a layer of complexity to modularized computations.

Multi-neuromodulator dynamics supports and enriches adaptive, continuous learning

An increasing number of studies have reported that different neuromodulatory systems have overlapping innervations and their receptors are co-expressed in the same groups of neurons (Grossman and Cohen, 2022). The spatially-governed interactions between neuromodulators are regarded as a means by which the brain adapts to emerging goals in a non-static environment while maintaining a high cost-efficiency. While the dynamics of single neuromodulators have already been shown to enhance the performance of DNNs (Mei et al., 2022, 2023), incorporating interactions between multiple neuromodulators may further advance their flexibility and efficiency. Recent research underscores the pervasiveness of parallel operations by neuromodulatory systems across spatio-temporal scales, and the diverse computations enabled by localized modulatory processes at the level of neuronal compartments (Sippy and Tritsch, 2023; Yagishita et al., 2014). The highly intricate interplay between neuromodulators is a combinatorial result of structural level complexities at the levels of transmitter dynamics, connectivity properties, and modes of transmission:

1. **Transmitter dynamics:** contrary to Dale's principle, studies have identified neurons that release two or more neurotransmitters (Tritsch et al., 2016; Vaaga et al., 2014). It is also worth noting that regions which are traditionally considered the source of one particular neuromodulator can also release other neuromodulators. A prominent example is the release of DA by neurons in the LC into the dorsal hippocampus (Kempadoo et al., 2016). The interactions between neuromodulators and neurotransmitters, as well as between different neurotransmitters, have led to increasing functional complexity. For example, the spatially non-uniform co-transmission of ACh and GABA in starburst amacrine cells, a type of neuron in the retina, allows for encoding of direction selectivity in downstream retinal ganglion cells (Lee et al., 2010). Such non-uniform neurotransmitter and neuromodulator release has been observed at the level of single neurons, mechanistically contributing to their context-dependent activities, making them more expressive and computationally powerful.

2. **Connectivity properties:** Neuronal connectivity, which encompasses varying degrees of connection density, directionality and weighting, is a mechanism underlyings the encoding of cue dependent alternations in multiple perceptual or behavioral strategies. In one study, NA and ACh projections (Munn et al., 2023) contact the same group of layer V pyramidal neurons in a diffuse (NA → layer V) and targeted (ACh → layer V) manner, endorsing perceptual flexibility and reliability respectively. Such concurrent yet differential effects suggest dual-mode information processing within individual neurons and neuronal microcircuits. Some brain areas, such as the striatum, host multiple neuromodulatory systems thus allowing the co-modulation of DA, ACh and histamine (Cruikshank et al., 2023). Through spatial adjacency as such, neuromodulators not only affect the rate of release of one another to stabilize their concentrations in the extracellular space, but fulfill actions appropriate to contexts. One example is the co-existence of ACh and DA waves in the dorsal striatum and that their phase relationship is potentially modulated by the presence of rewards (Hamid et al., 2021; Matityahu et al., 2023). Such reward-driven modulations can give rise to task-, or cue-specific correlation between neuromodulators, thereby augmenting the representation of task-relevant information by multi-neuromodulatory systems.

   In parallel with region-level correlations between the two neuromodulatory systems, recent studies have also demonstrated the highly localized effects of a single ACh interneuron on striatal DA release. This adds to previous evidence on DA release induced by synchronized ACh neuron activations (Matityahu et al., 2023). In addition to local, fine-tuning effects of neuromodulators that do not necessarily alter functional outcomes, in tasks where optimal decision making requires a reference to past actions and rewards, recruitment of more than one neuromodulatory system is indispensable. In a task that involves updating the action-outcome mapping through behavioral outcomes, without inhibition of DA on ACh, decision making is poorly informed by action and reward, ultimately leading to inefficient action switching (Chantranupong et al., 2023).

3. **Modes of transmission:** The discovery of at least two modes of transmission (wiring/synaptic transmission and volume transmission (Agnati et al., 1995; Colangelo et al., 2019; Özçete et al., 2024) in the study of neuromodulators has challenged our knowledge of intercellular information transfer in the biological brain, and enlightened further studies addressing fundamental questions revolving around the relationship between these two modes, their respective roles, distributions and spatial specificities. A majority of neuro-inspired ANNs take inspiration from wiring transmission, a mode that commonly relies on an identifiable, physically present point of contact between neurons. Given the existence of such channels, and the tight spatial coupling between the zones of receptor release and the receptor sites, classic wiring transmission represents a 1:1 relationship between pre- and post-synaptic sites, minimal transmission delays, and low energy demands. Unlike

wiring transmission, in volume transmission, neurotransmitters diffuse in the extracellular space and reach and act on multiple targets, thus requiring higher energy. In the meantime, given the loose spatial coupling, some target cells may not be reached, thus this 1:many mechanism yields lower signal safety.

The two transmission modes serve varying functional purposes and are dynamically regulated. Accordingly, studies have attempted to address their individual roles in cognitive processing and learning behaviors. In the ACh system, for example, the two transmission modes may complement each other: In conjunction with more refined, spatially precise actions achieved through wired transmission, volume transmission encodes information in a sustained, spatially less specific manner, providing guidance to a sequence of co-occurring actions. The ratio between the two modes is also species- and brain region-specific, suggesting differential developmental processes and functional priorities (Colangelo et al., 2019).

Multi-neuromodulator dynamics across spatio-temporal scales

Neuromodulatory systems regulate neuronal excitability and synaptic plasticity through complex molecular pathways. For example, the LC releases NA that interacts with various G protein-coupled receptors (GPCRs) such as $\alpha 1$, $\alpha 2$, and β subtypes (Benarroch, 2018; McBurney-Lin et al., 2019). These receptors activate distinct intracellular signaling cascades – $\alpha 1$ receptors coupled with Gq proteins activate phospholipase C, leading to calcium release and protein kinase C (PKC) activation, while $\alpha 2$ receptors linked to Gi proteins inhibit adenylyl cyclase, reducing cyclic AMP (cAMP) levels and protein kinase A (PKA) activity. β receptors, primarily coupled with Gs proteins, stimulate adenylyl cyclase, increasing cAMP and activating PKA. These diverse pathways allow neuromodulators to finely tune neuronal excitability, plasticity and synaptic strength, thereby modulating network dynamics and enabling adaptive responses to environmental stimuli.

Incorporating such neuromodulatory mechanisms into DNNs involves creating modulatory layers or signals that can adjust the network's neuronal parameters in real-time based on contextual information. This approach allows artificial networks to dynamically reconfigure their processing strategies, enhancing their ability to learn continuously and adapt to new tasks without extensive retraining (Munn et al., 2023; Rodriguez-Garcia et al., 2024; Williams et al., 2024).

Subcellular dynamics

In neural systems, rapid information transmission is primarily facilitated by ionotropic receptors, which are directly activated by neurotransmitters such as glutamate (Sherman, 2016) and GABA (Staley et al., 1995), as well as neuromodulators like 5-HT (Barnes and Sharp, 1999; Thompson and R. Lummis, 2006) and ACh through nicotinic receptors (Albuquerque et al., 2009). These interactions drive immediate changes in ion flux through channel opening, influencing short-term synaptic plasticity (Hennig, 2013).

On the other hand, metabotropic receptors, which are targeted by most neuromodulators – including muscarinic ACh receptors (Hasselmo, 2006), the majority of 5-HT receptors (Barnes and Sharp, 1999), and all receptors for DA (Missale et al., 1998), HA (Haas et al., 2008), and NA (Aston-Jones et al., 1999) – trigger a cascade of second messengers, initiating intracellular biochemical processes (Destexhe et al., 1994; Hasselmo et al., 2021). These relatively slow-acting processes modulate spiking behaviors and enhance long-term synaptic plasticity, thereby essential for memory consolidation, adaptability, and multi-timescale learning (Hasselmo et al., 2021; Krichmar, 2008; Mei et al., 2022).

Ultimately, the coexistence of fast ionotropic and slow metabotropic synaptic transmissions expands the dimensions of the neural parameter space in biological systems (Hasselmo et al., 2021), thereby enhancing the adaptability of neural networks as they respond to changes over time. Hence, the presence of both receptor types in the neuronal membrane allows neural networks to operate across multiple timescales, facilitating continual learning and ensuring flexibility and resilience in biological systems.

Neuronal dynamics

Neurons present specialized input structures called dendrites, which are organized into complex structures known as dendritic trees (Branco and Häusser, 2010; Chavlis and Poirazi, 2021; Stuart et al., 2016). Affected by ionic mechanisms that depolarize their membranes, these branched structures propagate diverse types of non-linear input signals, known as dendritic spikes (dSpikes), which attenuate as they travel along the dendrite (Acharya et al., 2022; Pagkalos et al., 2024).

Biological neural networks exhibit dendritic-spike-dependent plasticity (DSDP) rules, governed by the timing of synaptic input in relation to postsynaptic dendritic spikes, rather than axonal action potentials (Kampa et al., 2007). These synapses demonstrate scaling as a form of homeostatic plasticity, regulating excitation levels and maintaining the signal-to-noise ratio (Rabinowitch and Segev, 2006; Turrigiano, 2008). Neuromodulators also influence dendritic trees by altering their biophysical characteristics in several ways: **(i)** enhancing and altering ionotropic glutamate or GABA receptors, leading to changes in

EPSPs and IPSPs, **(ii)** releasing Ca2+ to modify the resting potential, and **(iii)** modifying voltage-gated channels, thereby influencing threshold and refractory period adjustments (Shine et al., 2021).

Therefore, the presence of dendrites seems to be responsible for continual learning capabilities in the brain. Specifically, as the location of neuromodulator receptors influences the timing window, impacting behavior and learning, as observed in coordinated adrenergic and cholinergic neuromodulation (Munn et al., 2023), along with DA and 5-HT modulation (Yagishita, 2020; Yagishita et al., 2014).

Circuit-level dynamics

Neuromodulators, such as DA, NA, 5-HT and ACh, play critical roles in transforming fast, trial-by-trial learning to plasticity-based across-session and across-task learning given that neuromodulators are known to subserve multi-timescale learning process; they reshape learning, in part, by gating the time window for the induction of synaptic plasticity (Mei et al., 2022).

Adaptive decision-making   Several neuromodulation-driven mechanisms contribute to learning and decision-making in neural circuits spanning cerebellum, basal ganglia, prefrontal and limbic cortices (Cools and Arnsten, 2022; Doya, 2002; Grace, 2016; Grossman and Cohen, 2022; Lisman and Grace, 2005; Sara, 2009; Schultz et al., 1997). DA plays a crucial role in reinforcing behavior based on RPEs, which are central to adaptive decision-making (Schultz et al., 1997). At the circuit level, midbrain DA neurons project to the striatum and prefrontal cortex and modulates synaptic plasticity in these areas, strengthening connections that predict rewarding outcomes and facilitates learning from experiences by updating expected reward and making decisions based on this information (Doya, 2002; Graybiel, 2008; Hikosaka, 2010; Lisman and Grace, 2005; Watabe-Uchida et al., 2017).

There is accumulating evidence that 5-HT plays crucial roles in adaptive decision-making (Cardozo Pinto et al., 2025; Cohen et al., 2015; Cools et al., 2011; Daw et al., 2011). Furthermore, a recent study suggested that 5-HT and ACh play complementary roles in timing decisions and this process involves neural circuits linking the dorsal raphe nucleus (a key source of 5-HT), the basal forebrain (the source of ACh) and the anterior cingulate cortex (ACC) (Khaligh-Razavi and Kriegeskorte, 2014). Glutamate, the primary excitatory neurotransmitter in the brain, plays a significant role in synaptic plasticity and the formation of neural circuits involved in diverse learning and decision-making settings. Recent studies have shown that glutamatergic signaling in the striatum interacts with DA and ACh to regulate learning behaviors in mice (Chantranupong et al., 2023; Krok et al., 2023). These studies demonstrate that a rhythmic regulation occurs in the striatum, where an increase in DA suppresses ACh, facilitating the modulation of reward-based learning. Some studies suggested that DA plays a role in recalibrating the value of actions over time, allowing the brain to adapt to new information and changing environments (Bromberg-Martin et al., 2010; Gardner et al., 2018; Schultz, 2013). Therefore, DA not only reinforces actions based on expected rewards but can also contribute to the brain's ability to "re-evaluate" past decisions which is particularly useful in continual learning, where decisions must be updated based on previous experiences (Langdon et al., 2018).

Attention control   Neuromodulators control attentional states by dynamically adjusting neuronal circuits to be more receptive to new information or to maintain existing knowledge, depending on the current task conditions and the environmental demands (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005; Hasselmo, 2006; Yu and Dayan, 2005). ACh is closely associated with adaptively allocating attention for enhanced sensory processing (Baxter and Chiba, 1999; Hasselmo and McGaughy, 2004; Sarter et al., 2005). At the circuit level, ACh modulates the activity of cortical neurons, particularly in the prefrontal cortex and sensory areas, to enhance signal-to-noise ratios. ACh also increases the responsiveness of neurons to relevant sensory inputs while suppressing responses to irrelevant stimuli (Thiele and Bellgrove, 2018), ensuring that learners can concentrate on task-relevant information.

DA is generally linked to reward-based learning and motivation, playing a critical role in adjusting attentional focus based on reward predictions and outcomes. At the circuit level, DA modulates the activity of dopaminergic neurons in the midbrain, which project to the prefrontal cortex and basal ganglia. These projections influence the allocation of cognitive resources to tasks that are expected to yield high rewards. Dahl et al. highlighted that DA enhances the encoding of reward-related cues, thereby prioritizing actions that lead to positive outcomes (Dahl et al., 2022). This modulation supports the maintenance of motivational states necessary for sustained learning and attention.

In contrast to ACh and DA, NA modulates arousal and stress responses by modulating the LC activity, and facilitates adaptive behavioral control (Aston-Jones and Cohen, 2005; Bouret and Sara, 2005). A recent study investigated how NA increases cortical excitability and enhances the detection of salient stimuli by regulating arousal and stress (Lockhofen and Mulert, 2021). The study suggested that NA helps maintain optimal attentional states that would enable the animals to adapt to new information while preserving existing knowledge. The LC/NA system modulates the neuronal activity in the PFC,

but how attentional control and other cognitive computations such as inhibitory control of behaviors are processed in the LC/NA-PFC circuits remains to be studied (Bari et al., 2020; Robbins and Arnsten, 2009). To sum up, neuromodulators collectively facilitate adaptive control of attention and abate the risk of catastrophic forgetting by enhancing the association of specific task-relevant cues and actions and forming robust task representations that are resistant to interference from new learning.

Memory   Neuromodulators exert their influences on cognitive control and sequential task learning by dynamically regulating synaptic plasticity (e.g., LTP and LTD) in the brain circuits including the midbrain, basal ganglia, PFC, entorhinal cortex and the hippocampus, and enhance the consolidation of memories (Fuchsberger and Paulsen, 2022; Lammel et al., 2014; Lee et al., 2021; Likhtik and Johansen, 2019; Takeuchi et al., 2016), strengthening the neural representations of previously learned skills and preventing their disruption by new learning. For example, DA signaling in the PFC enhances LTP and strengthens connections between contextual cues and task-relevant actions (Puig and Miller, 2015; Seamans and Yang, 2004). In the amygdala, DA suppresses feedforward inhibition and modulates the time window required for long-term changes to enhance synaptic weights (Bissière et al., 2003). In the dorsal striatum, DA governs long-term changes in both strengthening and weakening synaptic connections (Pawlak and Kerr, 2008). NA promotes synaptic changes, such as LTD, which can weaken synapses that are no longer relevant (Tully et al., 2007).

Moreover, neuromodulators can selectively "tag" certain synapses for strengthening or weakening (i.e., synaptic tagging (Frey and Morris, 1997)), ensuring that task-relevant information is preserved while irrelevant connections are pruned, thereby preventing catastrophic forgetting (Clopath, 2010; Moncada and Viola, 2007; Rogerson et al., 2014). Recent studies show that hippocampal engram cell excitability is transiently increased following memory reactivation. This short-term increase of engram excitability enhances the subsequent retrieval of specific memory content in response to cues and is manifest in the animal's ability to recognize contexts more precisely and more effectively (Tonegawa et al., 2015). However, it remains to be studied how neuromodulators can play roles in the formation, maintenance and the rapid control of excitability of the engram cells in the brain circuits underlying continual learning and long-term memory that are resistant to catastrophic forgetting.

4   MULTI-NEUROMODULATORY DYNAMICS ACROSS SCALES AND ITS EFFECTS ON LEARNING

Relevant deep learning architectures

The development of deep learning has significantly advanced machine learning and AI, introducing a range of architectures. Notably, DNNs have improved model performance through fully connected layers and numerous learnable parameters, allowing them to effectively handle complex data patterns (Goodfellow et al., 2016; LeCun et al., 2015). These architectures vary widely in their design, ranging from convolutional networks inspired by visual processing to recurrent networks mimicking sequential information processing in the brain (Cox and Dean, 2014; Khaligh-Razavi and Kriegeskorte, 2014; Kubilius et al., 2019; Rajaei et al., 2019; Yamins and DiCarlo, 2016). While some architectures exhibit parallels to specific brain structures or functions, such as convolutional neural networks resembling the visual cortex, the one-to-one mapping between neural network components and biological counterparts remains elusive.

Autoencoders and transformers represent two distinct architectures within deep learning, each with its unique applications and biological plausibility. Autoencoders, through their ability to learn compact representations of input data, draw inspiration from theories of efficient coding in the brain, where sensory information is compressed to its essential features (Al-Tahan and Mohsenzadeh, 2021; Bagheri and Mohsenzadeh, 2024; Hedayati et al., 2022; Lin et al., 2024; Soulos and Isik, 2024). Recent work by (Al-Tahan and Mohsenzadeh, 2021) has shown that autoencoders can successfully model feedforward and feedback processes in the visual cortex, shedding light on the functional role of brain recurrent processes as reconstructing low level features for improved recognition. Hedayati et al. (2022) proposed a mechanistic explanation of how working memories are built and retrieved from latent visual representations of a variational autoencoder with a structure inspired by the human visual system. This model highlights how compact visual representations allow efficient memory encoding, with familiar patterns efficiently stored in higher visual hierarchies and novel patterns better stored in early layers. More recently, Bagheri and Mohsenzadeh (2024) trained an autoencoder to simulate single-exposure memory conditions. Their work reveals a significant correlation between memorability and reconstruction error, demonstrating that images with unique, challenging features are inherently more memorable for human observers. The autoencoder latent space representations not only capture distinctiveness but also serve as robust predictors of image memorability. Transformers, on the other hand, excel in capturing long-range dependencies and sequential patterns, resembling aspects of information processing in the brain's hierarchical networks (Kozachkov et al., 2023; Muller et al., 2024; Whittington et al., 2021).

Foundation models, encompassing large-scale language and vision models, have revolutionized artificial intelligence by enabling systems to perform a wide array of tasks without extensive task-specific

training (Bommasani et al., 2021). These models are trained on vast, diverse datasets using unsupervised or self-supervised learning techniques, allowing them to capture rich representations of language, images, and other modalities (Brown et al., 2020). Their architectures, often based on transformers, facilitate generalization across various applications, including text generation, translation, and image classification (Vaswani et al., 2017). By leveraging transfer learning, foundation models can rapidly adapt to specific tasks with minimal fine-tuning, thereby reducing the need for extensive task-specific data and computational resources (Howard and Ruder, 2018). Recent advances have demonstrated their exceptional capabilities in multi-task learning (Raffel et al., 2019), few-shot learning (Brown et al., 2020), and zero-shot learning (Radford et al., 2021). However, these models face challenges in continual learning, where the goal is to learn new tasks without forgetting previously acquired knowledge. This phenomenon, known as catastrophic forgetting, remains a significant hurdle (Kirkpatrick et al., 2017).

Emerging research suggests that brain-inspired techniques, such as robust feature distillation and reconsolidation, could enhance continual learning in foundation models (Parisi et al., 2019). These approaches draw inspiration from the brain's ability to consolidate memories through rehearsal of distilled experiences, offering promising avenues for future studies to improve the continual learning capabilities of foundation models.

Nevertheless, while deep learning models have made significant strides, their departure from biological constraints raises questions about their true efficacy, especially in the context of continual learning. Recent endeavors in neuro-inspired architectures, such as SNNs (Eshraghian et al., 2021; Rodriguez-Garcia et al., 2024; Schuman et al., 2022) and memory-augmented models (Santoro et al., 2016), aim to bridge this gap by mimicking the brain's ability to encode and consolidate information over time. SNNs were developed in computational neuroscience to simulate single-cell neuronal activity. Their dynamics rely on accumulating the temporal activity of presynaptic spikes, which trigger a response and transmit information once a threshold is reached (Dayan and Abbott, 2001; Rodriguez-Garcia et al., 2024). This "all-or-none" response enables SNNs to operate in an event-driven manner, resulting in sparse activity where neurons remain dormant until necessary, leading to energy-efficient processing similar to biological systems (Eshraghian et al., 2021; Schuman et al., 2022). SNNs can replicate the same range of architectures as ANNs, from simple models to more complex ones like LLMs (Zhu et al., 2023), but with spiking neurons in place of abstract ones (Eshraghian et al., 2021; Rodriguez-Garcia et al., 2024). Their precise spike timing makes them ideal for real-time tasks involving temporal dynamics and continual learning, while their energy-efficient operation positions them as a promising technology for next-generation parallel processing and neuromorphic computing (Eshraghian et al., 2021; Ivanov et al., 2022; Schuman et al., 2022).

Simulating neuromodulatory effects in DNNs and computational models

Neuromodulatory systems in the brain are fundamental for regulating neural function and enabling behavioral and cognitive flexibility. Essentially, they support adaptive responses to the environment and play a critical role in learning and memory processes (Marder, 2012). Inspired by these systems, recent advances in ANNs have incorporated neuromodulation principles to improve flexible learning, robust performance across diverse tasks, and improved adaptation to changing environments. By mimicking the brain's neuromodulatory systems, these neuromodulation-aware models aim to achieve higher levels of computational efficiency and flexibility, similar to what is observed in biological organisms.

Neuromodulation-aware DNNs

Neuromodulatory-aware components have primarily been integrated into ANNs at two scales: learning rules and hyperparameter adaptation (Figure 3). At the higher, more global level, neuromodulatory signals influence the entire network over slower time scales in response to environmental context. These mechanisms are often implemented through context-driven hyperparameter updates. Some approaches include updating the learning rate and the momentum to optimize performance in response to changing conditions (Mei et al., 2023; Wilson et al., 2018), modifying the slope and bias of the activation functions (Vecoven et al., 2020), or modulating uncertainty to maintain stable learning and prevent catastrophic forgetting (Brna et al., 2020).

Meanwhile, inspired by how neuromodulatory signals shape the synaptic plasticity window in biological neurons (Brzosko et al., 2019; Pedrosa and Clopath, 2017; Zhang et al., 2009), many neuromodulation-aware modes have incorporated neuromodulation at the connectivity level by modulating weight updates through signals such as contextual information (Costacurta et al., 2024; Daram et al., 2020; Hong and Pavlic, 2022; Hwu and Krichmar, 2020; Meshkinnejad et al., 2023; Miconi, 2021; Miconi et al., 2020; Schmidgall and Hays, 2023; Tang et al., 2023; Tsuda et al., 2021). Such top-down reconfigurations of connectivity can be understood as the third factor in the three-factor learning rule framework $w = F(M, \text{pre}, \text{post})$ (Frémaux and Gerstner, 2016; Kuśmierz et al., 2017). Here, represents the extrinsic, global neuromodulatory signal that guides weight changes in response to environmental changes or shifting task demands, complementing the pre- and post-synaptic activity. In some studies, eligibility
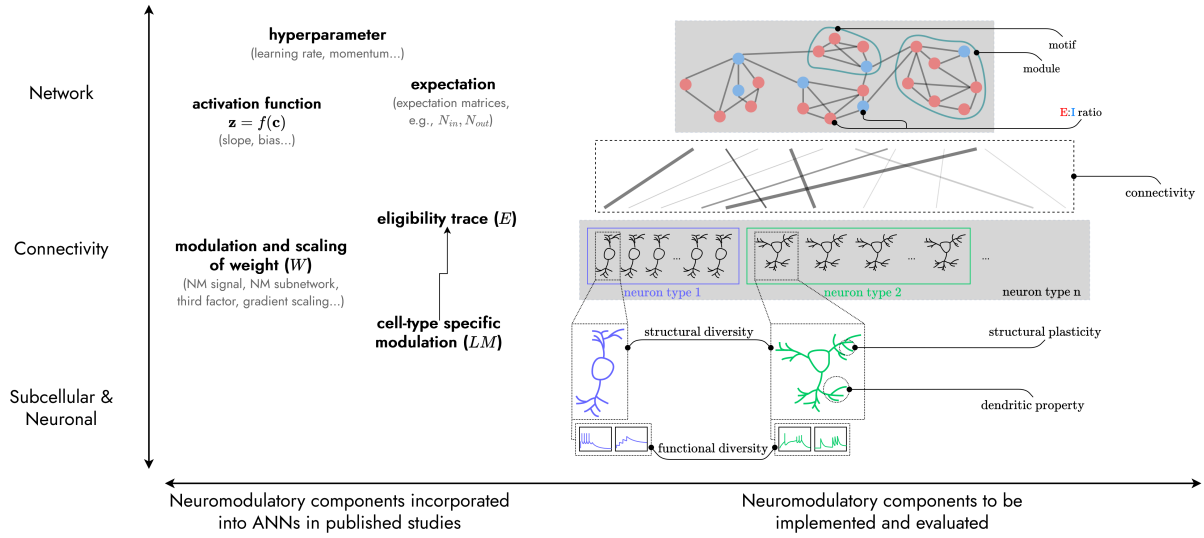
Figure 3: A framework for integrating neuromodulatory components into ANNs. Previous studies have implemented neuromodulation-inspired computation at the network and connectivity levels, enhancing learning through hyperparameter and activation function tuning, context-driven expectation update, and weight modulation. To further advance these approaches, the impact of neuromodulatory components can be explored through network topology, neural population heterogeneity, and dendritic properties, to name a few. NM: neuromodulation; ANNs: artificial neural networks.

traces are used to bridge the temporal gap between fast synaptic events and slower, global neuromodulatory, ensuring that weight updates may only occur when a modulatory signal is present (Barry and Gerstner, 2024; Liu et al., 2021; Miconi et al., 2020; Schmidgall and Hays, 2023). Notably, most modulatory signals considered within this framework are related to reward processing or DA signaling (Bellec et al., 2020; Chung and Kozma, 2020; Liu et al., 2021; Miconi et al., 2020; Schmidgall and Hays, 2023). However, recent approaches have expanded these third-factor rules to include surprise signals (Barry and Gerstner, 2024), which are more closely associated with the biological effects of NA. Furthermore, some studies consider multi-neuromodulatory effects, tuning the plasticity window of neuronal connections through combinations like DA and ACh or DA and 5-HT (Wert-Carvajal et al., 2022; Zannone et al., 2018), examining both opposing and collaborative interactions between neuromodulatory signals. While these top-down learning signals help address the credit assignment problem in ANNs, they remain insufficient, prompting new approaches to incorporate cell-type-specific neuromodulation (Liu et al., 2022a, 2021).

Computational models of neuromodulation

To the best of our knowledge, neuromodulation has yet to be implemented at the subcellular and neuronal scale in ANNs. However, an abundance of studies have attempted to study the neuromodulatory processes through a theoretical framework, investigating the functional roles of neuromodulators in single cell and network models (for a review, see Fellous and Linster (1998)). Fellous and Linster's earlier work investigated the activity of neuromodulators through five computational models of progressively increasing biological fidelity: the Markovian kinetics model, the Hodgkin-Huxley model, the FitzHugh-Nagumo model, the leaky integrator model, and the connectionist model. While the biological realism represented in the majority of these models is incompatible with traditional DNNs due to the associated computational costs (Rodriguez-Garcia et al., 2024), the models presented in this review exemplify how neuromodulator dynamics can be flexibly parameterized across various levels of abstraction. Importantly, the study underscores two significant challenges that still persist today: the absence of direct biological analogs for some neural network parameters and the inability to fully represent all neuromodulation-related processes through parameter changes alone.

Following this biophysical approach, neuromorphic spiking control systems use fewer neurons with complex dynamics, such as FitzHugh-Nagumo models, to perform motor control tasks in robotics (Schmetterling et al., 2024; Sepulchre, 2021). These tasks leverage network motifs and neuromodulatory signals to regulate movement through stable and unstable network states (Ribar and Sepulchre, 2021). However, scaling these systems to large-scale ANNs remains limited by computational costs, posing another challenge in single-cell neuromodulation modeling.

Neuromodulation-inspired components across scales

By introducing multi-scale, neuromodulation-aware components, DNNs can achieve a level of adaptability and flexibility akin to biological neural systems. Emulating the intricate interplay of morphol-

ogy, neuronal dynamics, and neuromodulatory influences enables artificial networks to better navigate complex and changing environments, potentially advancing the capabilities of artificial intelligence. Our proposed framework leverages multiple network scales to enhance continual learning in ANNs given neuromodulatory signals impact different spatio-temporal scales (Figure 3). The framework generalizability supports learnable synapses across supervised, unsupervised, and reinforcement learning schemes. It accommodates gradient-based backpropagation (Neftci and Averbeck, 2019), Hebbian and STDP-like learning rules (Zenke et al., 2017), and even evolutionary approaches for complex optimization tasks (Habashy et al., 2024). Furthermore, meta-learning approaches (Miconi et al., 2020; Schmidgall and Hays, 2023) can be further integrated into the framework through third factor plasticity rules, evolutionary algorithms or global learning signals.

Subcellular and neuronal level

The structural complexity of neurons plays a crucial role in information processing. Dendritic heterogeneity, which refers to the variation in dendritic branching and spine density, allows neurons to integrate diverse inputs more effectively. Mimicking this in DNNs involves designing architectures that can adaptively modify their connectivity patterns, enabling more nuanced feature extraction and representation learning.

Neuronal dynamics, including spiking behavior and receptor modeling, are essential for temporal information processing and synaptic plasticity. Incorporating spiking mechanisms into DNNs can enhance their ability to handle sequential and time-dependent data. Additionally, modeling neuronal heterogeneity, where neurons exhibit diverse response patterns, can lead to more robust and versatile network behaviors.

At the subcellular and neuronal level, structural and functional complexity can be incorporated through dendritic compartments and learnable biases in ANNs, as well as different spiking behaviors in SNNs.

Structural diversity   Incorporating dendritic architectures enables resilient continual learning (Acharya et al., 2022; Pagkalos et al., 2024) and offers a plausible explanation for backpropagation signals (Greedy et al., 2022; Payeur et al., 2021; Sacramento et al., 2018). An architecture featuring context-driven dendritic layers has been proposed and shown to learn multiple tasks with minimal forgetting (Iyer et al., 2022). Similarly, multi-task learning can be achieved through NMDA-driven dendritic modulation in a self-supervised biophysical model, where task-dependent modulations are applied to individual neurons (Wybo et al., 2023). Incorporating temporal diversity also enables dendrites to function as temporal gates, leading to multi-timescale learning (Zheng et al., 2024).

Leveraging multi-compartmental morphology combined with neuromodulation brings a new dimension for tuning neuronal responses. Neuromodulation-inspired mechanisms enable contextual cues to shape dendritic processing, and compartmental models can help highlight the role of neuromodulators in promoting dendritic and spine structural plasticity, where modifications in dendritic properties may be introduced through parameters including dendrite length, diameter, and branching.

Functional diversity   Heterogeneous neuronal dynamics is fundamental to biological systems (Fan et al., 2025; Izhikevich, 2004; Kanari et al., 2019; Markram et al., 2004; Rich et al., 2022) and is frequently overlooked in DNNs. A study on ANNs leverages neuronal bias for multi-task learning through backward transfer, underscoring the importance of functional heterogeneity (Williams et al., 2024). In SNNs, neuronal time-scale heterogeneity in LIF neurons enhances robustness (Perez-Nieves et al., 2021), while introducing a temporal hierarchy within the network improves performance (Moro et al., 2024). Another study employed evolutionary algorithms to investigate bursting parameter heterogeneity, allowing the network to solve spatio-temporal tasks (Habashy et al., 2024). Theoretical work with heterogeneous SNNs of Izhikevich neurons demonstrated that this diversity adapted network computations at the spiking level (Gast et al., 2024), offering a potential mechanism by which neuromodulatory influences on neuronal dynamics could be implemented.

Neuronal heterogeneity expands the parameter space, thereby giving a way to robust optimizations in complex tasks. Given the computational costs associated with simulating subcellular and neuronal-level neuromodulatory processes (e.g., modifying on ion channel parameters), higher-level abstraction is possible using a process similar to simplifying biophysical models and representing the overall properties, such as adaptive firing threshold, which can shift the gain function at the population level (Shine et al., 2021). Furthermore, axonal and dendritic propagation delays, a mechanism that is often overlooked in computational studies, can contribute to the emergence of connectivity patterns. Neuromodulators such as DA can alter the excitability of axons, and therefore, the temporal fidelity. Introducing neuronal level heterogeneity can help link these neuron-level mechanisms with network-level dynamics.

Receptor dynamics   ANN architectures primarily emulate the rapid feedforward flow of information, effectively capturing the short-term plasticity mediated by ionotropic receptors. However, they largely overlook the slower, more complex dynamics governed by metabotropic receptors, which play a critical role in higher-order cognitive representations (Hasselmo et al., 2021). In DNN models that capture the dimension of metaplasticity driven by metabotropic receptors through neuromodulated learning rules (Frémaux and Gerstner, 2016), many other dimensions of effects by these receptors remain unexplored.

Neuromodulatory signals primarily act through metabotropic receptors, modulating internal neuronal properties and influencing behavior over longer temporal scales. These receptors regulate a wide range of physiological functions, including spiking behaviors, gating, and metaplasticity (Hasselmo et al., 2021). However, modeling the dynamics of metabotropic receptors remains a challenge, as these processes depend on intracellular signaling pathways often resulting in high computational costs, which limits their practicality and scalability in artificial systems.

Recurrent architectures such as gated recurrent units (GRUs) and long short-term memory networks (LSTMs) can represent long-term dynamics, making them promising candidates for modeling the role of neuromodulators in regulating neuronal activity through gating mechanisms. For example, neuromodulatory signals could be functionally approximated by the forget gate in LSTM cells (Costacurta et al., 2024). Furthermore, a recent study explored ANN learning by independently training weights and biases, opening up the possibility for studying how neuromodulators might dynamically adjust biases to enable rapid, adaptive learning (Williams et al., 2024).

Nevertheless, to achieve precise control over single-neuron dynamics, SNN models are essential, as they accurately represent the spike-driven behavior of biological neurons. Neuronal models such as the Izhikevich model, which captures a range of spiking behaviors through voltage-gated and calcium-dependent conductances (Izhikevich, 2003, 2004), and generalized integrate-and-fire (GLIF) models, which have been shown to replicate the activity of multiple cell types (Teeter et al., 2018), provide effective solutions for modeling the dynamics of metabotropic receptors (Hasselmo et al., 2021; Rodriguez-Garcia et al., 2024). These models offer a computationally efficient approach for controlling the neuronal spiking behavior through neuromodulatory signals triggered by contextual adaptations.

Circuitry level

The circuitry level takes into account both the structural elements such as neuronal connectivity and population-level diversity of neurons (micro-circuitry), as well as the emergence of neuronal populations into functionally specific groups and the interconnections across these groups (meso-circuitry). In the biological brain, unlike ANNs, connectivity between neurons features a sparse pattern and is determined by multiple factors. Such distinct connectivity facilitates energy efficiency, evolves over development, and underlies learning and plasticity.

Connectivity   The microcircuit structure of biological neural networks varies across brain regions. Bio-inspired DNNs attempt to mimic this complexity by imposing constraints on synaptic weight plasticity, adjusting connectivity features like sparsity and connection probability (Lachi et al., 2024; Perez-Nieves et al., 2021; Yang and Molano-Mazón, 2021). In comparison with DNN architectures with fully connected layers, the connection probability between neurons in the brain is low (Song et al., 2005), exhibiting sparse topological connectivity (Mocanu et al., 2018). Neuronal connectivity is shaped by factors such as the genetic type of neurons involved in the connection, and the distance between them (Billeh et al., 2020; Markram et al., 2015; Stoeckl et al., 2021). However, this sparse connectivity can be introduced in DNNs by adding a non-trainable sparse matrix to define the connectivity of the network (Yang and Molano-Mazón, 2021). Additionally, a recent approach explored stochastic wiring by incorporating connection probabilities, highlighting that neuronal randomness in connectivity might be an evolutionarily developed feature in biological organisms (Lachi et al., 2024; Perez-Nieves et al., 2021).

Neuromodulation can regulate the global connection profile of neural networks, allowing dynamic reconfiguration of their connectivity. Meanwhile, network connectivity affects the changes of network dynamics caused by changing the neuromodulatory tone (Rich et al., 2020). Given the multitude of pre- and post-synaptic processes neuromodulators affect, they not only participate in regulating the probability of connection, but its strength. Neuromodulation plays an important role in modifying circuit level connectivity through both direct and indirect mechanisms. For example, they contribute to the formation or elimination of synapses (direct mechanism), and in the meantime, alter the excitability of neurons (indirect mechanism) (Nadim and Bucher, 2014). Moreover, one synapse may be under the influence of multiple neuromodulators, and the combined effects may not be additive, and depend on the network state (Koh et al., 2003; Nadim and Bucher, 2014).

Excitation and inhibition   Dale's principle (Dale, 1935), later formalized by Eccles as the 'one neuron, one transmitter' hypothesis which suggests neurons consistently excite or inhibit (Eccles et al., 1954),

led to the introduction of excitatory and inhibitory neuronal populations into ANNs and has recently been challenged by the finding that neurons can release more than one neurotransmitter (Tritsch et al., 2016; Vaaga et al., 2014). In practice, this imposes a constraint on the sign of the synaptic weight connectivity in the network, meaning that excitatory neurons are restricted to facilitating positive signal transmission, while inhibitory neurons are limited to negative signal transmission (Yang and Molano-Mazón, 2021). A few DNN and recurrent neural network (RNN) architectures have incorporated these features, often adopting the biological brain's experimental 80:20 excitation:inhibition ratio (Cornford et al., 2020; Kao, 2019; Li et al., 2023; Song et al., 2016). A study on SNNs highlighted the significance of this specific ratio, showing that it leads networks to reliably train at low activity levels and in noisy environments, underscoring the robustness of this balance (Kilgore et al., 2024). However, while this constraint adds bio-inspiration, it often limits the learning and performance of DNNs by reducing the available parameter space (Cornford et al., 2020; Kao, 2019; Li et al., 2023). The addition of neuromodulatory signals at this level could enable switching between excitatory and inhibitory weights, allowing networks to better adapt to specific tasks and support multi-task learning by preserving weight signs across sequential tasks.

Topology   Network neuroscience provides tools for unveiling the functional implications of brain structures and their emerging properties, and potentially a powerful analytical framework for the study of the neuromodulatory systems. Network neuroscience research employs graph theory and treats the brain as an interconnected network of nodes (brain regions) and edges (functional connections). Key measures such as modularity, integration, and participation coefficient offer insights into the organization and efficiency of these networks. Neuromodulatory systems interact with these properties by dynamically adjusting connections and promoting efficient communication across and within brain regions, and play a vital role in maintaining the balance between network segregation and integration, which is essential for robustness, efficiency and adaptability.

The emergence of open source brain atlas and data sharing has allowed a close examination of network properties of the brain, offering a data-intensive view of brain network topology and correspondingly, its specialized structural and functional modules responsible for perceptual, cognitive and motivational tasks (Hansen et al., 2022). Recently, network topology found in the biological neural networks have been used to construct ANNs that feature reduced numbers of parameters without performance decline (Goulas et al., 2021; Mocanu et al., 2018). Moreover, brain topologies derived from the connectome data have been shown to promote efficient reinforcement learning when incorporated into SNNs (Wang et al., 2024b).

Determining the modularity from brain networks and superimposing it with the spatial domains of neuromodulation, then probing its convergence and divergence across functions and brain states, may serve as a guide to create specialized network topologies for different tasks. In the meantime, identifying shared nodes and clusters across tasks may shed light on a unifying view of central processing across task domains.

- *Motif and modularity:* In the analysis of complex systems, motifs are defined as smaller structural organizations of few nodes or links (Papo et al., 2022). When comparing brain networks with randomized networks, motifs featuring specific patterns of interactions occur at high frequencies (Milo et al., 2004; Mittal and Narayanan, 2024). With individual motifs assuming specialized functions, the occurrence of such motifs represent characterized processing mechanisms at a local level, and serve as the building block of functions emerging from cross-motif interactions. Thus, motifs in brain networks have been linked to enhanced local processing, as well as the manifestation of different forms of degeneracy (Mittal and Narayanan, 2024; Sporns et al., 2007).

  Modularized architectures can serve as a middle ground between a unifying network for all tasks an agent encounters, and a collection of networks, each solving one individual task. Modular organizations exploit sub-modules to address task-specific needs, and are biologically-intuitive given its architectural alignments with the brain, as well as its potential to accommodate developmental needs, and cognitive demands over evolution (Hadsell et al., 2020; Meunier et al., 2010). Inspired by neurogenesis, novel architectures facilitate multi-task learning by incorporating progressive network modularity (Parisi et al., 2019; Rusu et al., 2016).

  High modularity allows for specialized processing within sub-networks, while high integration ensures cohesive interactions across the entire network. Context-based modulation of modules promotes an optimized positioning across tasks through task information and inter-task relationships: A contextual signal may give rise to altered network dynamics, enabling progressive adaptation. In neuromodulation-inspired models (Beaulieu et al., 2020; Vecoven et al., 2020; Wilson et al., 2018), a specialized network processes contextual information, and plays a role similar to biological neuromodulatory networks by signaling when and how to adapt the learning process.

Under a modularized design, some submodules can be used in certain tasks while others compute hidden variables through predictive processes such as error prediction or task contingency changes, thereby signaling neuromodulators to be released in the task-relevant modules at different spatio-temporal scales. Moreover, the innervation of submodules by neuromodulatory inputs can be determined through properties of submodules such as cell types, hierarchical level and functional demands, simulating site-specific projections and preferential distribution of neuromodulatory systems.

Integration and segregation: The brain's flexibility and robustness could be partly attributed to a balance between integration and segregation, realized by the coexistence of and cooperation between global, unified and local, specialized processes. A shift in this coordination may be induced to address a change in context, and in a more extreme case, such shift is a sign of pathological conditions and maladaptive behavior (Papo et al., 2022).

Depending on the nature and demands of a task, functional networks in the brain can move toward a higher degree of segregation or integration (Coronel-Oliveros et al., 2023). Nevertheless, structural networks stay relatively unchanged in this process, and can give rise to both pre- and post-transition functional networks. In (Shine, 2019), neuromodulation is considered a mechanism driving the generation of multiple functional connectivity patterns. For instance, ACh can increase segregation depending on contextual information (Coronel-Oliveros et al., 2023), while NA promotes integration in arousal states, potentially repurposing cognitive resources (Shine et al., 2018). In addition to the integration of neuromodulatory drives into specialized network modules, these results also lead to novel methods for evaluating neuromodulation-aware models based on their contribution to network topology changes across cognitive and behavioral states, adding to existing model evaluation metrics.

Network level

Neuromodulatory systems play a crucial role in shaping large-scale brain network dynamics. These systems extend their influence beyond localized circuits, modulating brain-wide activity patterns and facilitating the coordination of diverse cognitive functions (Marder, 2012; Mei et al., 2023). At this broader systems level, understanding the impact of global neuromodulatory signals on large-scale networks offers valuable insights for the design of ANNs.

Hyperparameters and activation functions Incorporating neuromodulatory-like mechanisms enables ANNs to adjust hyperparameters and activation functions, thus network dynamics in response to changing environments, task demands and cognitive/behavioral states (Brna et al., 2020; Mei et al., 2023; Vecoven et al., 2020; Wilson et al., 2018). This capacity for adaptive reconfiguration at the whole network scale is critical for improving the resilience of ANNs, enhancing their ability to withstand disruptions or noise while maintaining stable performance. This adaptability is crucial for developing intelligent systems capable of operating autonomously in real-world environments where conditions and requirements frequently shift.

Global multi-neuromodulatory interactions Inspired by Doya (2002), deep reinforcement learning (DRL) offers a structured way to incorporate multiple neuromodulators with biological inspiration. In this framework, neuromodulatory interactions can be easily mapped to certain hyperparameters in DRL: DA is crucial for reward prediction through temporal difference learning, 5-HT controls the influence of short- and long-term rewards, NA modulates the randomness of the action selection through a Softmax policy, and ACh controls the learning rate of the weight updates (Doya, 2002; Krichmar, 2008; Mei et al., 2022). These analogies have been widely used to support lifelong RL in artificial agents (Ben-Iwhiwhu et al., 2022; Lee et al., 2024; Mei et al., 2022). However, as shown by recent studies, this one-to-one mapping between neuromodulatory signals and their functional role through single hyperparameters may be an oversimplification.

Hence, understanding the synergistic and balancing interactions among neuromodulators is crucial for informing the design of more sophisticated ANN models that replicate human-like decision-making and problem-solving abilities. In biological systems, neuromodulatory systems do not operate in isolation; they interact continuously in a state- and context-dependent manner. This interaction modulates various neurobiological processes essential for adaptive behavior (Avery and Krichmar, 2017; Brzosko et al., 2019) and for integrating new information with existing knowledge (Bradfield et al., 2013; Matityahu et al., 2023). This dynamic interplay allows the brain to fine-tune its responses to ever-changing environments, ensuring that cognitive functions such as attention, learning, and memory are modulated appropriately based on current demands (Mei et al., 2022; Shine et al., 2021).

Overall, the biological plausibility of multi-neuromodulatory interactions can be enhanced by introducing **(i)** regulation and refinement of neuromodulatory drives through other neuromodulators, **(ii)** spatial

and temporal correlations of neuromodulatory drives, and **(iii)** task-specific behavior of global neuro-modulation. Such an approach has the potential to naturally explain emergent behaviors in ANNs and lead to continual learning AI systems.

5   INCORPORATING NEUROMODULATION-INSPIRED COMPUTATION INTO ANNS: A CASE STUDY

To demonstrate how to determine which neuromodulatory components to work with and the ways to incorporate them into ANNs based on requirements of the task(s), in the case study, we use a reward-driven task with set-shifting as an example. Here, we investigate the interplay of predictive coding and biologically inspired learning rules and if computations inspired by NA enhance network adaptation in dynamic environments. Through this experiment, our goal is to reveal how neuromodulation-aware ANNs achieve robust learning and cognitive flexibility, leveraging DA for reward-driven plasticity and NA for flexibility and dimensionality shifting, mirroring the adaptive capabilities of biological systems.
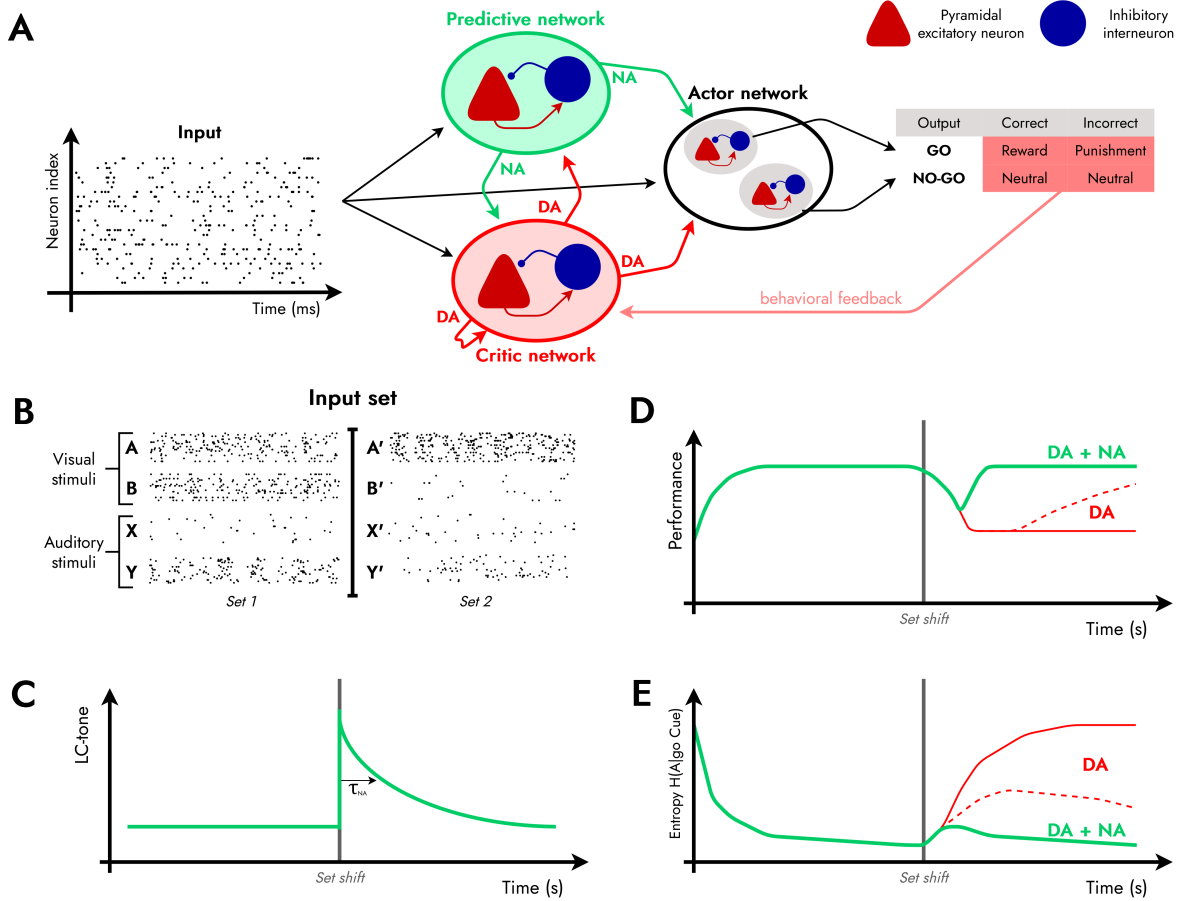

Figure 4: Contingency adaptation in spiking neural networks (SNNs) in the Go No-Go task. A) Diagram illustrating the proposed neural network and its inputs. **B)** The two input sets, utilizing set-shifting to present a random combination of stimuli from both Set 1 (visual stimuli) and Set 2 (auditory stimuli). **C)** Dynamics of the LC and the release of NA-like signals during set-shifting. **D)** Hypothesized systems-level performance with (green) or without (red) NA-like signals, before and after set-shifting, representing NA ablation. **E)** Exploratory behavior of the system following set-shifting with (red) or without (green) NA ablation. As shown in (D) and (E), after the set shift, DA alone may be insufficient to drive exploration of new actions and states, thereby limiting the ability to update weights necessary for learning a new policy. DA: dopamine; NA: noradrenaline; LC: locus coeruleus.

The task

This case study explores how SNNs can adapt to changing environmental contingencies in an extradimensional / intradimensional set-shifting Go/No-Go task (Dias et al., 1996; Konishi et al., 1998; Robbins, 2007). In this task, the agent must respond to pairings of two sets of input patterns representing distinct sensory modalities—such as visual and auditory stimuli (Figure 4B). In this example, Set 1 consists of visual stimuli patterns A and B, while Set 2 contains auditory patterns X and Y.

A key aspect of the task is that there is no fixed "Go" cue. Instead, the contingency – that is, which specific stimulus signals the correct response – changes over time. The agent must learn through trial and error which stimulus currently requires a "Go" response. After the agent learns a specific contingency, the

task changes its set of stimuli and the contingency, requiring continual adaptation. Each trial presents a random combination of stimuli from both sets, resulting in various compound stimuli (Figure 4B). The agent must decide whether to respond based on the current contingency, which could be associated with any of the stimuli. A correct response when the appropriate stimulus is present results in a reward, an incorrect response leads to punishment, and responses during trials without the current "Go" stimulus result in neutral feedback (Figure 4A).

The neural network

We consider a modular SNN architecture with three subnetworks: an actor network, a critic network, and a predictive network (Figure 4A). This design is motivated by DA-driven strategies, which commonly employ actor-critic architectures in RL and deep RL frameworks, where one module makes decisions and another determines the strategy (Chung and Kozma, 2020; Dayan and Abbott, 2001; Sutton and Barto, 2020). Similarly, we extend this idea to include a submodule inspired by the role of NA, which is theorized to detect "surprises" in the environment (Barry and Gerstner, 2024), necessitating predictive coding capabilities to release a neuromodulatory signal modeled after NA, mediating high arousal states (Munn et al., 2023).

Actor network.   The actor network will be responsible for the agent's decision making. We consider two clusters of neurons (one for each action: 'Go' or 'No-Go'), each containing excitatory and inhibitory neurons. The network selects the action depending on the cluster that has the higher net firing rate, i.e., the average firing rate of the excitatory neurons minus that of the inhibitory neurons.

Critic network.   The critic network, composed of excitatory and inhibitory neurons, estimates the value of the expected reward at the current state by its net firing rate. By comparing the estimated value with the actual reward received during the trial, the TD error is computed (Schultz et al., 1997). The RPE represents the DA activity of the network and acts as a third factor that modifies synaptic plasticity, following the R-STDP learning rule (Chung and Kozma, 2020). Specifically, DA activity adjusts the reward expectancy based on the current contingency. Mathematically, for the set of contingencies $C_1, C_2, C_3, ...C_n$ within the task, it will minimize the loss function LC_i for each contingency through the RPE.

Predictive network.   The predictive network is responsible for detecting changes in task contingencies by using principles inspired by predictive coding. It continuously compares incoming stimuli with predictions based on previous experiences to identify any discrepancies or unexpected changes (Barry and Gerstner, 2024). When the network detects such a change in contingency—that is, when the expected relationship between stimuli and outcomes alters – it responds by releasing a neuromodulatory signal modeled after the role of NA. By emulating the LC's dynamics, the signal is timed appropriately to influence the network's processing during the periods of set-shifting (Figure 4C). The released NA-like signal targets the excitatory neurons in both the actor and critic networks, enhancing synaptic plasticity by inducing correlated bursting activity among these neurons. As demonstrated by Munn et al. (2023), such correlated bursting elevates the system's arousal state, flattening the energy landscape and enhancing network flexibility (Aston-Jones and Cohen, 2005). Hence, this heightened arousal facilitates the reconfiguration of the network, allowing it to adapt more effectively to new contingencies by promoting the exploration of alternative actions (Bouret and Sara, 2005; Doya, 2002; Usher et al., 1999). Mathematically, this modulatory NA-inspired component will be dynamically allocating attention across contingencies C_i within the task, helping the agent minimize loss when adapting to new contingencies by influencing the gradient of the loss function, $\nabla_\theta L_{C_i}$.

Evaluating the neural network

To evaluate the proposed model, we can outline several key aspects essential to its functionality and performance in the task. Initially, the model's performance can be assessed before the contingency change, focusing on how well the R-STDP mechanism tunes the actor and critic networks to learn and predict rewards. This includes evaluating the effectiveness of the DA signal by examining how the TD error (δ_t) modulates synaptic weights, thereby improving value estimation in the critic network. Additionally, the performance (Figure 4D) of this mechanism can be compared to similar studies employing R-STDP to benchmark its efficiency and alignment with established results (Chung and Kozma, 2020; Florian, 2007; Frémaux and Gerstner, 2016).

The introduction of NA signaling necessitates additional evaluation criteria: First, it is crucial to analyze the predictive network's ability to detect deviations in stimuli patterns, which is fundamental for identifying contingency shifts (Barry and Gerstner, 2024). Once a shift is detected, the evaluation should focus on whether NA activity promotes flexibility in the actor and critic networks (Munn et al., 2023).

This can be tested by assessing the model's ability to balance exploring new responses versus exploiting known ones after a contingency change and can be measured by the entropy of actions (Figure 4E). A comparative analysis can be performed by shutting down the NA component activity entirely to determine its specific role in facilitating rapid adaptation and robust learning.

Measuring the enhanced exploration driven by NA

We consider an agent that selects actions based on its SNN activity. After completing the experiment, we obtain a set of actions $A = \{a_i\}_{i=1}^{N}$, representing the agent's responses to external stimuli. Our goal is to quantify the randomness in the agent's selection of correct actions $(A|C)$. This randomness reflects the uncertainty in action selection: Greater exploration leads to higher randomness and lower certainty, whereas greater exploitation results in lower randomness and higher certainty. To measure this, we use the Shannon entropy, which in this context captures the uncertainty in the agent's action distribution.

In our case, the conditional entropy of the actions given correct responses is defined as:

$$H(A|C) = -\sum_{i=1}^{N} P(a_i|C) \log_2 \left(P(a_i|C) \right) \tag{8}$$

where $P(a_i|C)$ represents the probability of selecting a correct action a_i.

At the beginning of the task, the system does not yet know the correct responses. Therefore, we can assume a uniform distribution over N possible actions, such that $P(a_i|C) \approx 1/N$. Substituting this into the entropy formula:

$$H(A|C) \approx -\sum_{i=1}^{N} (1/N) \log_2(1/N) = -N(1/N) \log_2(N) = \log_2 N > 0 \tag{9}$$

which represents the maximum entropy, as all actions are equally likely due to the lack of learned information.

As the agent learns, driven by DA activity and reward signals, the probability of selecting the correct action increases and eventually approaches unity, i.e., $P(a_i|C) \to 1$. Hence, the entropy gradually decreases and approaches zero:

$$H(A|C) \to -\sum_{i=1}^{N} (1) \log_2(1) = -N(1) \log_2(1) = 0 \tag{10}$$

Thus, the entropy of the correct actions decreases over time as the agent progressively learns the correct responses. It demonstrates decreased exploration and increased exploitation.

When a set-shift occurs (i.e., a change in contingency), the system no longer knows the correct responses for the new task. Therefore, the probability $P(a_i|C) \to 1$ no longer holds, and the entropy increases again as the agent explores the new contingency (Figure 4E). However, since the network's weights were optimized for the previous contingency, the time scale for adapting to the new one depends on how quickly the system can reconfigure its weights. This can result in prolonged optimization times or, in some cases, failure to optimize altogether (red lines, Figure 4D and E). Introducing NA into the system facilitates weight reconfiguration: NA promotes exploration by increasing the entropy temporarily, enabling the system to rapidly sample and evaluate new actions. This accelerates the discovery of the new contingency, leading to faster adaptation compared to relying solely on RL mechanisms (green lines, Figure 4D and E).

Interpretation

In essence, this case study illustrates how to design a modular, neuromodulation-aware SNN according to task demands, and how it can be trained to adapt to contingency changes in an extradimensional/intradimensional set-shifting Go/No-Go task using predictive coding and neuromodulatory mechanisms, with a particular emphasis on dimensionality shifting. Initially, learning is guided by DA activity through a third-factor rule, taking into account the global, top-down effects of reward signals (Chung and Kozma, 2020; Florian, 2007; Frémaux and Gerstner, 2016; Izhikevich, 2007). Additionally, the predictive network releases a NA component, which has a dual-mode of action: It influences neuronal activity by promoting bursting behavior, thereby enhancing plasticity during heightened arousal states. It also facilitates dimensionality shifting.

Furthermore, the network potentially offers a micro-scale explanation for the emergence of behaviors such as the balance between exploration and exploitation. During periods of high NA release, the increased flexibility promotes exploration of new strategies, while during stable phases, the network exploits learned contingencies to optimize performance. This dynamic interplay ensures that the SNN can efficiently navigate complex and changing environments, mirroring cognitive flexibility observed in biological neural systems.

Despite the potential neuroscience interest of this model, several limitations remain. The simplification of neuromodulatory interactions may fail to capture the intricate dynamics between different neuromodulators, while the modular architecture of the subnetworks (actor, critic, and predictive) does not fully reflect the integrated nature of information processing observed in the brain. Additionally, the predictive network's performance could be unstable in the presence of noise, affecting its ability to reliably detect contingency shifts. Furthermore, the presence of multiple neuron populations increases the complexity of the optimization process, making adaptation challenging even in relatively simple tasks. Addressing these aspects will be essential to enhance the biological plausibility and robustness of the model.

6 DISCUSSIONS AND OUTLOOK

Understanding how humans learn, developing machines that emulate human learning, and identifying the additional features beyond current DNNs required for such systems involve multifaceted research (Kemp et al., 2010; Lake et al., 2017). This article proposes new avenues for introducing multi-neuromodulatory dynamics to ANNs and addresses specificities across scales from the subcellular to the network level. Nevertheless, the integration of neuroscience-inspired mechanisms into AI models requires a deeper exploration of the underlying neural mechanisms that facilitate adaptive learning and memory. Additionally, replicating the complexity of neuromodulatory systems presents significant challenges, such as modeling the nonlinear, context-dependent interactions between neuromodulators and their individual and collective impacts on network dynamics.

Exploring multi-neuromodulatory mechanisms

Amit (1989) offer a powerful conceptual and analytical framework for analyzing how neuromodulators influence learning processes in bio-inspired ANNs, as well as for exploring synergies and opposing mechanisms of neuromodulatory actions. By describing ANNs in terms of attractor dynamics, this approach allows for the application of dynamical systems theory to examine how neuromodulation shapes network behavior, stability, and adaptability. Neuromodulatory release is associated with various behavioral states, where specific cognitive functions are enhanced to address task demands. Moreover, they may act cooperatively to stabilize specific network states or antagonistically to induce transitions between attractors, enabling adaptation to shifting task demands and environmental contexts.

In theoretical neuroscience, different types of attractor dynamics have been associated with distinct cognitive functions, such as memory, motor behavior, and classification (Freedman and Assad, 2006; Li et al., 2016; Mante et al., 2013; Romo et al., 1999). Neuromodulators alter neural dynamics and mediate different modes of activity, allowing the network to respond flexibly to external stimuli (Munn et al., 2023; Shine, 2023). For example, hypothetically, DA-like signals generate attractors for reward-predictive behaviors, while NA-like signals facilitate transitions and ACh-like mechanisms adjust stability, working together to balance exploration, plasticity, and stability in continual learning. Overall, neuromodulatory mechanisms can result in on-the-fly changes to the network's attractor properties, such as their location, type, or stability. As such, neuromodulators play a crucial role in rapid transitions between attractor states, potentially enhancing the robustness of these states against noise.

Multi-neuromodulator dynamics flexibly promote multiple learning paradigms such as transfer-learning, meta-learning, and incremental learning, depending on the particular constraints imposed on the learning agents. However, there are a number of challenges in the study of neuromodulation and in neuromodulation aware ANNs. A prominent example is neuromodulatory projections to specific subtypes of neurons and their region-dependent, projection-specific effects (Box 2). Accordingly, incorporation of modular architectures into neuromodulation-aware ANNs may help implement modulatory projections to specific subsets of units. Nevertheless, it remains to be studied how such modular architectures in ANN could be designed in a principled manner (Rodriguez-Garcia et al., 2024; Yang and Molano-Mazón, 2021). More importantly, the complexity of neuromodulatory systems and neural circuitry in the biological brain (e.g., neuronal heterogeneity, tonic and phasic firing, and multi-neuromodulatory interactions) serves as a foundation of the distinct dynamics of neuromodulation, and the complex interplay between neuromodulators and their receptors (Box 1 and Box 2). Despite recent developments in experimental neurosciences approaches to neuromodulatory systems, several challenges persist (Box 3). The multi-scale effects of neuromodulators, the limited resolution of pharmacological and neurogenetic tools, and the prevalent co-release of neuromodulators and neurotransmitters complicate the study of neuromodulatory mechanisms, highlighting the need for the development of new technical tools.

Computational models enable bridging the gap across multiple levels in space and time, making them crucial for understanding how the brain computes. For example, biophysical modeling of a neuron connects biochemical events at synapses and the spikings of a neuron. Similarly, neural network modelings connect the population behaviors of spiking neurons with adaptive learning, cognition and behavioral outputs of individual animals and humans. Introducing multi-scale neuromodulatory dynamics to computational models allows investigations of neuromodulatory effects at the levels of single

Source- or target-dependent effects of neuromodulators:

1. *Input/source diversity:* Watabe-Uchida et al. (2012) and colleagues reported that there exist more diverse inputs to dopaminergic neurons in the midbrain than previously expected.

2. *Output/target diversity:* The brain exhibits a heterogeneous distribution of neuromodulator receptors across different regions and cell types. This diversity means that the same neuromodulator can have varying effects depending on the receptor subtypes present in a particular area. For example, the midbrain DA neurons send projections to the striatum, prefrontal cortex (PFC), limbic cortices including amygdala and entorhinal cortex, each of which playing distinct functional roles such as signaling the reward prediction error (RPE), associative learning between action and rewarding/aversive events, and between presented items (e.g., odors) and outcomes (Adrover et al., 2020; Chantranupong et al., 2023; Krok et al., 2023; Lee et al., 2021) via particular types of DA receptors (e.g., D1R and D2R) expressed in specific cell types.

Neuronal heterogeneity: Neuromodulators exert type-dependent influences on the dynamics of different neuronal groups, e.g., PV-positive, SOM-positive, VIP-positive interneurons (Hattori et al., 2017; Wester and McBain, 2014) and D1R-/D2R- medium spiny neurons (MSNs) in the striatum (Gerfen, 2023). However, most ANNs do not take into account such functional and morphological diversity of neurons, potentially hindering their computational capabilities (see Rodriguez-Garcia et al. (2024) for SNN models that incorporate both neuronal heterogeneity and neuromodulation).

Distinct dynamical modes: it is suggested that two distinct modes of firing patterns, i.e., phasic and tonic firings of dopaminergic neurons and locus coeruleus (LC) neurons have differential roles in learning and cognition (Aston-Jones et al., 1999; Floresco et al., 2003; Grossman and Cohen, 2022; Schultz, 2007). But it remains to be clarified how these modes are activated and switched depending on the task condition. Biophysical characteristics of neurons embedded in the local circuits of the neuromodulatory systems, e.g., persistent firing in absence of synaptic drive (Major et al., 2013), can be key to bridging across faster and slower time scales. It remains to be studied how these characteristics can be exploited in the design of new ANNs (Rodriguez-Garcia et al., 2024).

Interactions between multiple neuromodulators: Studies provide significant insights into the complex interactions between multiple neuromodulators. For instance, Chantranupong et al. (2023) demonstrated that DA and ACh exhibit multi-phasic and anticorrelated activity patterns during decision-making tasks, with DA suppressing ACh release through D2 receptor-mediated inhibition. This dynamic relationship enables flexible behavioral adjustments based on reward history and task contexts. Similarly, Krok et al. (2023) revealed that DA and ACh maintain rhythmic, periodic fluctuations in the striatum and are driven by separate upstream afferents, to regulate motivation and learning processes. These findings underline the importance of multi-neuromodulator systems in ensuring the adaptability, robustness, and efficiency of neural computations. Incorporating such dynamics into ANNs may enrich their computational capabilities, particularly by enhancing attractor dynamics, stability, and contextual modulation. It remains an open question how such characteristics of multi-neuromodulator circuits in the brain can be assimilated in designing novel ANNs.

Neuromodulators across spatio-temporal scales and their convergence: Neuromodulators play vital roles in coordinating neural computations across spatio-temporal scales by regulating local synaptic plasticity and global network dynamics (Grossman and Cohen, 2022). For instance, DA adjusts RPEs at the synaptic level while simultaneously influencing large-scale cortical-striatal circuits during decision-making and learning. ACh, on the other hand, modulates sensory processing and attentional shifts, dynamically switching between "focused" and "global" processing states.
Neuromodulators enable convergence by coordinating fine-grained neural activity (e.g., spike timing) and broader patterns (e.g., oscillations in large-scale brain networks). This ability to integrate information efficiently across spatio-temporal domains provides robust adaptability in complex environments. Such capacities of neuromodulation to modulate synaptic plasticity, neural gain, and network dynamics can potentially provide computational advantages. By mimicking ACh's role in attention control, computational models dynamically allocate computational resources to critical input features, improving performance in adaptive learning. This approach reflects the biological modulation of "focused" versus "global" processing.

Redundancy and complementarity: Neuromodulators play a critical role in orchestrating neural activity across circuits, with functional overlaps that are sometimes described as "redundant," yet they fulfill complementary purposes depending on context and task demands. These mechanisms are particularly evident in adaptive learning processes, where different neuromodulatory systems contribute to distinct aspects of learning and decision-making. It remains to be investigated how neuromodulators function in a seemingly redundant manner in various adaptive learning paradigms. One recent study on movement encoding highlighted how dopaminergic and cholinergic systems interact in movement encoding within the basal ganglia. While the two systems appear to act redundantly at first glance—both influencing movement selection and initiation—closer examination reveals complementary roles (Graybiel and Matsushima, 2023). In decision-making and reinforcement learning, the dichotomy between model-based (goal-directed) and model-free (habitual) learning provides a compelling example of redundancy and complementarity. Daw et al. (2011) described how dopaminergic modulation in the striatum supports parallel model-based/model-free learning in the striatum and cortex, suggesting that the apparent redundancy between multiple learning systems (i.e., the striatum and PFC) ensures that when one strategy is computationally expensive or fails (e.g., under time pressure), the other can take over (see also Akam and Walton (2021); Dolan and Dayan (2013) for discussions on neuromodulation in model-based and model-free learning). Given the biological evidence for redundancy and complementarity in neuromodulation circuits, ANNs could potentially benefit from incorporating such multiple neuromodulatory-like mechanisms by implementing modular architectures, where specific ANN components mimic specialized circuits in the brain to realize both redundant and complementary functions, enhancing robustness and adaptability (Yang and Molano-Mazón, 2021).

Box 2: Dynamics and interactions within the neuromodulatory systems of the brain.

units, network topology and behavioral outcomes, thus helping generate and test new hypotheses and predictions for experimental results. Important example of modeling-inspired hypothesis testing is the works by David Marr on learning mechanisms in the cerebellum (Albus, 1971; Ito and Kano, 1982; Marr, 1969), and the theoretical and experimental studies in the RL domain (Schultz et al., 1997; Sutton and Barto, 2020). Nevertheless, the explanation of brain dynamics offered by computational models is still limited. Given the advances in ANN in recent years, it is likely that the computational models inspired by the brain will enable not only experimental hypotheses but also predictions of the biological brain dynamics (Avery and Krichmar, 2017; Lee et al., 2024; Ma et al., 2024).

Importantly, computational models can also be used to explore the mechanisms of brain disorders and how they may induce physiological and cognitive changes (Carannante et al., 2024; Lanillos et al., 2020; Lindroos et al., 2018; Pavlides et al., 2015; Verzelli et al., 2024), thus accelerating the search for therapies for neurological and psychiatric diseases (Montague et al., 2012). Biophysical modelings of synapses and neurons may reveal drug action mechanisms and guide the development of effective pharmacological agents. Similarly, modeling the complex relationships of multiple neuromodulators in neural circuits in areas such the midbrain, basal ganglia and PFC/ACC may deepen the understanding of major neurological and psychiatric diseases such as Parkinson's disease and schizophrenia, among others (Frank et al., 2004).

The use of pharmacological tools: Many studies on neuromodulator interactions rely on pharmacological manipulations of individual receptor subtypes and are performed at a systems level. Therefore, it can limit insights into the local, endogenous release and interaction of neuromodulators, especially when experiment are conducted during awake states given the limited spatial and temporal resolutions of drug effects, possible off-target effects, variability in dose-response relationships across subjects, compensatory mechanisms, and imperfect receptor specificity (Grossman and Cohen, 2022).
Importantly, neuromodulatory effects are context-dependent, varying across behavioral states, environmental conditions, and task demands. For instance, ACh release during attention-demanding tasks differs from its role in baseline cortical activity. Pharmacological studies conducted in controlled environments often fail to account for these changes.

The use of neurogenetic tools: Recently developed G-protein-coupled receptor activation-based (GRAB) sensors for neuromodulators such as DA and NA have overcome the limitations of pharmacological manipulations (Feng et al., 2019; Sun et al., 2020). While these sensors significantly advanced the ability to detect and measure the actions of neuromodulators in real-time (Doya et al., 2021), there are still fundamental limitations to their use in the spatial and the temporal resolutions. Similarly, various transgenic animal models (e.g., Cre-driver lines) offer powerful tools for targeting specific neuronal populations. However, this approach has several limitations that can affect the interpretation and reliability of experimental results such as the off-target expression of the marker genes in unintended cell types or brain regions. For instance, in some transgenic mouse lines, the Cre protein expression, which is supposed to target only 5-HT-producing neurons, is not restricted to serotonergic neurons, leading to recombination in non-serotonergic neurons which may confound interpretations of 5-HT-related functions (Ren et al., 2018).

Manipulation of neuromodulators in the brain: Given the diverse and neuron-type specific connections to and from neuromodulator-releasing cells (Watabe-Uchida et al., 2012), it is important to examine the physiological and behavioral effects of manipulating neuromodulatory systems in projection- and neuron-type specific manners. However, there are a few technical challenges to consider:

- *Measurement:* Quantifying neuromodulator levels and their receptor activities in specific brain regions is technically challenging due to their low concentrations and the rapid release and uptake.

- *Selective manipulation:* Developing tools to selectively manipulate specific neuromodulatory pathways without affecting others is difficult, given the extensive and overlapping projection patterns of neuromodulatory systems.

- *Temporal dynamics:* Neuromodulator effects can vary over different time scales, from rapid changes in neuronal excitability to long-term alterations in gene expression. Capturing these dynamics requires sophisticated experimental designs and analytical methods.

Disentangling the co-release of multiple neuromodulators: One major challenge in studying neuromodulation lies in the complexity of neurotransmitter co-release. For instance, cholinergic interneurons (CINs) in the striatum, which are central to ACh signaling, are known to co-release neurotransmitters such as glutamate (Glu) and gamma-aminobutyric acid (GABA). This co-release complicates the interpretation of experimental results, as it becomes difficult to attribute observed effects to ACh alone without accounting for the potential influence of Glu or GABA. For instance, Matityahu et al. (2023) investigated the local effects of CIN activity on DA release in the striatum. Their study revealed nuanced findings, suggesting that CINs can enhance or suppress DA release depending on the specific context and experimental conditions. Similarly, midbrain dopaminergic neurons have been shown to co-release DA and Glu from their axonal terminals with VGLUT2 playing a crucial role in this process (Dal Bo et al., 2004; Stuber et al., 2008; Sulzer et al., 1998). To disentangle the effects of co-release, future studies will require the use of enhanced neurogenetic tools, advanced imaging techniques, and computational models.

Box 3: Methodological limitations in experimental studies of neuromodulation and their implications in the development of neuro-inspired ANNs.

Implementing and interpreting multi-neuromodulatory mechanisms in ANNs

Challenges and avenues

Modeling multi-scale neuromodulatory mechanisms present a significant challenge in both the implementation and evaluation of models. The vast parameter space generated can become particularly problematic, as parameter values derived from experimental evidence do not directly align with those used in DNNs. This misalignment can lead to difficulties in model convergence, overfitting, or failure to generalize to unseen conditions due to a lack of sufficient or well-labeled data for training. Furthermore, variations across deep learning frameworks can yield inconsistent outcomes, even when identical model architectures, hyperparameters and training procedures are used (Mei et al., 2023). This framework dependency can hinder reproducibility and transferability of results across platforms. Additionally, multi-scale, biologically detailed models can suffer from computational bottlenecks, as integrating fine-grained spatial and temporal information requires significant computational resources, potentially leading to high training times and memory constraints, particularly for large-scale simulations.

The complexity of DNNs exacerbates the challenge of understanding how neuromodulatory effects contribute to observed outcomes. The black-box nature of DNNs limits the ability to identify causal relationships between inputs (e.g., neuromodulatory parameters) and outputs (e.g., activity patterns and learning outcomes), making the analysis and validation of results less intuitive. Furthermore, different modulatory effects and hyperparameters can result in the emergence of same activity patterns, a phenomenon commonly referred to as degeneracy (Tononi et al., 1999). This degeneracy complicates the mapping of structural organizations to functional operations and increases ambiguity in evaluating model reliability and interpretability. Lastly, the dynamic nature of neuromodulatory processes introduces challenges in achieving temporal coherence in predictions, as current models may struggle to effectively capture long-range temporal dependencies across scales without significant fine-tuning or architectural adjustments.

Evaluating neuromodulation-aware ANNs requires a focus on explainability to ensure that the dynamic and adaptive mechanisms introduced by neuromodulation are interpretable and align with biological or functional goals. For example, hybrid modeling techniques, which integrate mechanistic models grounded in experimental neuroscience (i.e., parametric models) with data-driven deep learning models (i.e., non-parametric models), can help align biological parameter values with those used in DNNs (Schweidtmann et al., 2024). This approach reduces the misalignment between experimental evidence and computational parameter spaces while considerably preserving biological plausibility. For computational bottlenecks, techniques like model pruning, quantization, and low-rank approximations can reduce model complexity and training time while maintaining performance. Alternatively, distributed computing and GPU/TPU-accelerated training can scale up simulations efficiently.

To address interpretability issues and the black-box nature of DNNs, explainable AI (XAI) techniques can be extended to assess the contributions of neuromodulatory signals to the model's outputs. Attention mechanisms and graph-based approaches may help identify which neuromodulatory inputs (e.g., contextual signals or gain control) influence network activations, learning processes and decisions. Additionally, causal analysis can be used to explore the role of specific neuromodulatory mechanisms by perturbing them and observing changes in the network's behavior or output. From a structural perspective, explainability methods like GNNExplainer (Ying et al., 2019) for graph-based networks or Grad-CAM (Selvaraju et al., 2016) for spatio-temporal models may help reveal how neuromodulatory effects influence node relationships, temporal dependencies, or feature importance. Finally, benchmarking neuromodulation-aware ANNs on biologically inspired tasks and comparing their decision pathways to known neuromodulatory functions in neuroscience can provide additional interpretability and biological grounding, ensuring these models are both transparent and functionally meaningful.

Ensemble learning methods can be employed to compare multiple model outputs and identify consistent activity patterns across different hyperparameter settings. The development of uncertainty quantification techniques can further help assess confidence in predictions, making models more reliable for downstream applications (Abdar et al., 2021). Combining these approaches will facilitate the creation of scalable, interpretable, and biologically meaningful multi-scale models that effectively capture the complexity of neuromodulatory mechanisms.

Some candidate architectures and methods for neuromodulation-inspired computations include neuromodulated RNNs, transformers, and graph neural networks (GNNs), given their ability to handle temporal, spatial, and network-level complexities. SNNs and hybrid mechanistic-deep learning models provide biologically inspired alternatives that bridge neuroscience and AI. RL and dynamic neural fields offer additional frameworks for exploring adaptive, reward-driven, and contextual neuromodulatory behaviors. These methods enable the dynamic modulation of weights, activations, and attention, closely mirroring biological processes and enhancing both interpretability and adaptability of computational models.

Towards neuromodulation-aware AI: interdisciplinary collaborations and community-driven efforts

The computational cost and scalability of such biologically detailed implementations may hinder their implementation in large-scale, real-world AI systems. While neuromodulatory systems have been proposed as a means to enhance adaptability in AI (Mei et al., 2022), the current gaps in our understanding of these systems impede the effective application of neuromodulation-aware models. Thus, advancing continual learning in AI necessitates a collaborative effort between neuroscience and AI research to bridge these gaps and develop more robust models that can emulate the dynamic learning capabilities observed in biological systems (Kudithipudi et al., 2022).

A community-driven knowledge and data base for neuromodulation-aware ANNs could serve as a centralized resource for sharing datasets, benchmarks, models and tools to advance research in both neuroscience and AI. This platform can host experimental and simulated multi-scale data, ranging from neural recordings, synaptic plasticity measurements, and neuromodulatory signals, alongside pretrained models and reproducible implementations of neuromodulation-aware architectures. Benchmark tasks grounded in biologically inspired learning and behavior, such as adaptive memory or contextual modulation, would enable rigorous comparison and validation of methods, fostering interdisciplinary collaborations.

Community-driven efforts that pool data across multiple laboratories to characterize heterogeneous factors—such as species, age, sex and brain states and activities—are crucial for understanding their impact on neuromodulatory neurons (Kelberman et al., 2024). Collaborative resources dedicated to the development of theoretical and computational models provide a solid foundation for integrating biological first principles into ANN architectures (Ramaswamy et al., 2015; Wheeler et al., 2015, 2024). These efforts lay the groundwork for a community-driven knowledge base centered on neuromodulation-aware ANNs and their parameterization for diverse learning settings. Additionally, interdisciplinary workshops focused on the neuromodulation of adaptive learning, organized at the Okinawa Institute of Science and Technology (OIST; *Neuromodulation of Adaptive Learning: Theoretical Lessons Learned From Invertebrate and Vertebrate Brains (TP24NM), 2024*) facilitate the exchange of experimental and computational methodologies on the neuromodulatory principles underlying learning in biological neural networks and their artificial counterparts.

Collectively, these proposed approaches can catalyze the creation and development of a community driven knowledge base that synthesizes experimental and simulation data, models, and theoretical insights into neuromodulatory dynamics, fostering the design of ANNs that mimic adaptive processes in biological systems. Furthermore, the platform can serve as an open-access resource for storing, retrieving and sharing experimental results across various species, brain regions and tasks, along with their associated computational models. This will lead to thorough and systematic evaluations of both published and ongoing research on neuromodulatory systems, promoting innovative experimental designs and model architectures in the field of biologically inspired AI.

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