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The zona incerta in control of novelty seeking and investigation across species

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Abstract

Many organisms rely on a capacity to rapidly replicate, disperse, and evolve when faced with uncertainty and novelty. But mammals do not evolve and replicate quickly. They rely on a sophisticated nervous system to generate predictions and select responses when confronted with these challenges. An important component of their behavioral repertoire is the adaptive context-dependent seeking or avoiding of perceptually novel objects, even when their values have not yet been learned. Here, we outline recent cross-species breakthroughs that shed light on how the zona incerta (ZI), a relatively evolutionarily conserved brain area, supports novelty-seeking and novelty-related investigations. We then conjecture how the architecture of the ZI's anatomical connectivity – the wide-ranging top-down cortical inputs to the ZI, and its specifically strong outputs to both the brainstem action controllers and to brain areas involved in action value learning – place the ZI in a unique role at the intersection of cognitive control and learning.

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Introduction

The intersection of neuroscience and machine learning has shed light on the intuition that to perform multiple, statistically heterogenous, and embedded behavioral tasks, the brains of animals evolved multiple mechanisms for learning, planning, and acting – that is, distinct circuits that learn and forget on different time scales, utilizing distinct learning rules [1–11]. These efforts expanded our understanding of neural mechanisms of reflex-like behaviors as well as of the relatively slower mechanisms of value learning and value-based decision-making [12–15]. But to date, little is known about how neural circuits support adaptive behavior in situations in which higher-order cognitive computations must be rapidly linked to ongoing motor control, particularly when the value of ongoing action has yet to be determined.

One example is the experience of and response to perceptually novel objects. Novel objects need to be detected, their values need to be learned, and behavioral selection must occur rapidly even though their behavioral value has yet to be fully determined. But, despite the importance of novelty seeking in the daily lives of humans and animals, the neurobiological mechanism of novelty-driven behaviors, such as novelty seeking, remains poorly understood [16].

The purpose of this review is to discuss emerging evidence for a role of the zona incerta (ZI) in specific components of novelty-related behavior: in the seeking out of future perceptual novelty and subsequent inspection and investigation of perceptually novel objects. We discuss how the ZI links ongoing cognitive processing of objects, including predictions of future novel objects, with online control of action in the brainstem. We show that many ZI neurons' activity incorporates information about action (e.g., location and action timing) and information about the prediction and detection of novel objects.

We then conjecture how the architecture of the ZI anatomical connectivity – particularly, the wide-ranging top-down cortical inputs to the ZI and the specifically strong outputs of the ZI to both the brainstem action

controllers and to brain areas involved in action value learning — could place the ZI in a unique role at the intersection of cognitive control and learning, including learning the values of novel objects and novelty-seeking actions.

ZI anatomy and functions

ZI cytoarchitecture and circuits

The ZI, first described by Forel [17], is a relatively conserved structure found in both mammals and other vertebrates [18–22]. Developmentally, it is part of the prethalamus [23]. It is a long, horizontally oriented structure that lies dorsal to the subthalamic nucleus (STN), and medial to the reticular nucleus (RT), extending from the rostral pole of the thalamus to the rostral subgeniculate nucleus in rodents, nonhuman primates (NHP), and humans [18] (Figure 1a–b). The ZI in both rodents and primates is roughly divided into four components: a rostral portion (ZIr), a central portion that is divided into dorsal and ventral regions (ZId and ZIv), and the caudal portion (ZIc). The ZIr extends from its rostral pole to the emergence of the STN. The central portion lies dorsal to the STN and ventral to the thalamus nucleus. The ZIc sits at the posterior end of the STN and lies between the STN and ventroposterior thalamic nucleus (Figure 1a–b). In rodents, there are differences in connectivity among the medial and lateral parts [24]. Recently, the medial component, ZIm, has been recognized as possibly functionally distinct [25,26].

Cell-types in the ZI

Most generally speaking, in terms of neurotransmitters and neuromodulators, ZI contains at least four groups of cell types: GABAergic (~85% of ZI neurons), glutamatergic, dopaminergic, and melanin-concentrating hormone (MCH) neurons. The ZI includes large projection neurons that make up ~90% of the ZI cells and local interneurons. ZI projection neurons have long extensive dendrites, oriented along the principal axis of the nucleus, and are presumed to be primarily GABAergic [25] (Figure 1b–c) which sets it apart from the thalamus dorsally and STN ventrally. These neurons are involved in a variety of behaviors and states, including sleep [27], fear [28], defensive behavior [29], food eating [30], and hunting [25]. There are also populations of glutamatergic neurons, most prominently in the caudal ZI (Figure 1c). In both rodents and primates, tyrosine hydroxylase (TH) is concentrated in a dopaminergic region called A13 in the ZIrm (Figure 1c). A majority of these TH-positive neurons co-express GABA [31]. While their functions are poorly understood, some studies have implicated them in fear and nociception-related functions [32]. MCH-expressing and dopaminergic neurons are distinct but intermingled in the A13 area [33]. The functional role of the MCH-positive neurons in ZI and whether they are involved in motivational behaviors [34] remains to be understood.

The functional diversity of the ZI neurons is beyond the heterogeneity of neurotransmitters and neuromodulators. Parvalbumin (PV)-expressing neurons are most prominent in the lateral ZIv with almost no overlap with somatostatin (SST) and calretinin (CR)-expressing neurons [35]. The PV-positive neurons are required for fear memory acquisition and recall of remote fear memory [36]. PV-positive neurons are also involved in itch processing [37]. Another subpopulation of inhibitory neurons, located in ZIv, expresses LIM homeodomain factor Lhx6 and bidirectionally regulates sleep time [38]. Yet, another subpopulation of GABAergic neurons, which are distinct from PV- and SST-expressing neurons, is tachykinin precursor 1 (Tac1)-expressing neurons. These neurons are required in investigatory and novelty-seeking behaviors that we discuss in detail subsequently in this article [26].

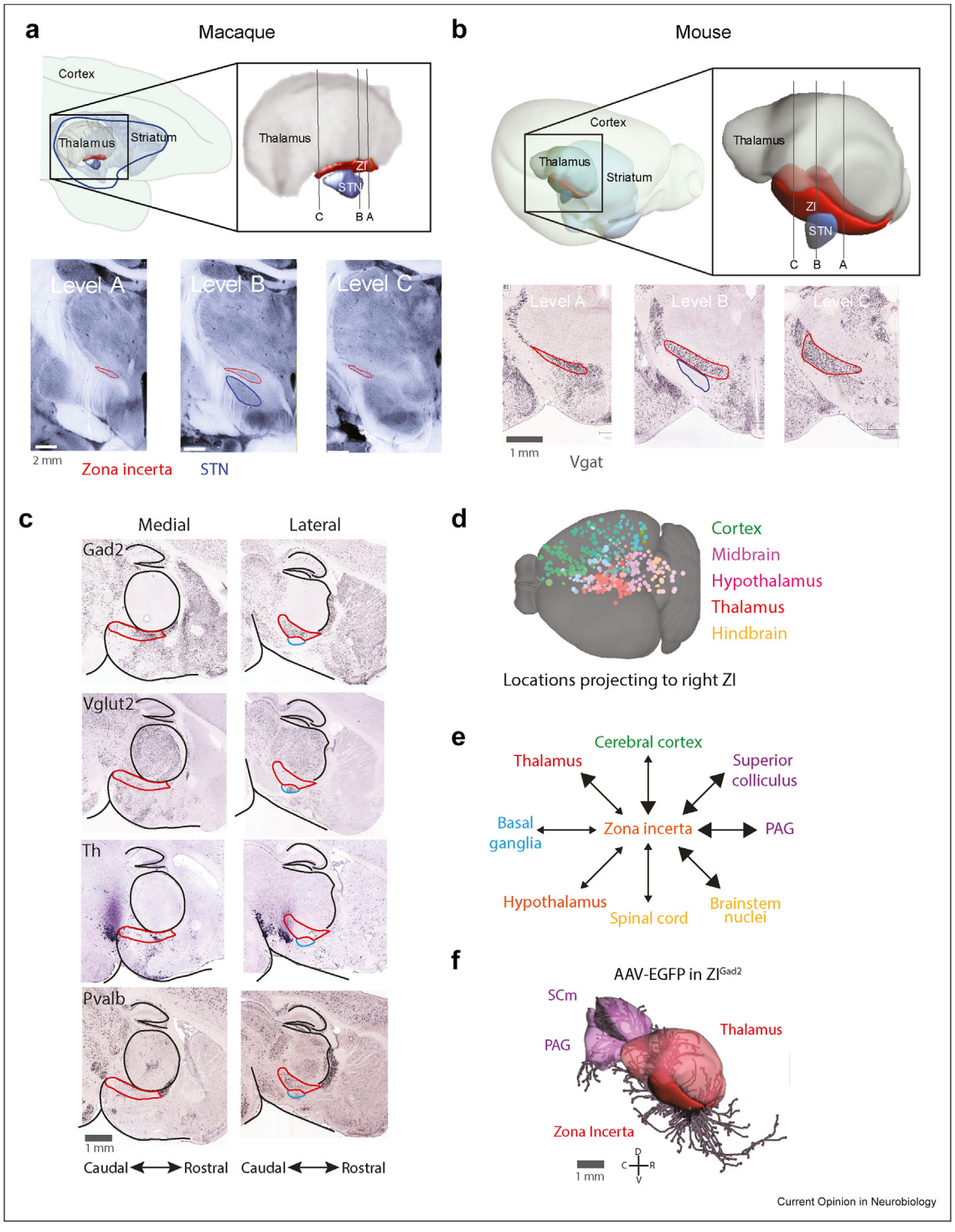
ZI connections in rodents

The ZI receives input from across the brain [24,39] (Figure 1d–e). Most inputs come from the ipsilateral side, but there is also input from the contralateral hemisphere [39,40]. Direct visceral and somatosensory inputs from the spinal cord and trigeminal nucleus arrive in ZIv [24,39,41]. ZId and ZIr receive input from many brainstem nuclei, in particular, the midbrain reticular nucleus, periaqueductal gray (PAG), raphe nuclei, and the substantia nigra (SN) [24,39,42], but also from the pons, medulla, and deep cerebellar nuclei in the hindbrain [39,42]. The ZIrm receives input from the laterodorsal tegmental nucleus in the brain stem and the anterior pole of the superior colliculus (SC) [43]. ZIv receives input from the pretectal nucleus [44] and from the deep layers of SC in rodents and primates [24,39,45]. The lateral SC, responding to the stimuli in the lower visual field projects to the medial ZIv. The medial SC, responding to the upper visual field, projects to the lateral ZIv.

Importantly, most areas of the cerebral cortex project to the ZI (Figure 1d) [46]. There are particularly strong projections from the cingulate, frontal, motor, and parietal areas [46,47] and topographically organized projections from sensorimotor cortex [46,48]. There is also input from temporal cortex [49,50]. The cortical input comes largely from layer 5b neurons [46,51] and terminates non-homogenously in the ZI. The ZId and ZIr receive projections from the cingulate cortex, ZIr from medial prefrontal [29], ZIrm from frontal eye field like area [43], and ZIm from prelimbic and medial prefrontal [26,29].

Many of the connections of the ZI are reciprocal (Figure 1e). The ZI sends output to the spinal cord and many brainstem nuclei [40,42,52]. The ZIv projects to the intermediate and deep layers of the SC [39]. The main projection is GABAergic, but the ZIr TH neurons also

Figure 1



Anatomy of the zona incerta (ZI). **a.** Zona incerta (ZI) is wedged between the subthalamic nucleus (STN) and the thalamus. Bottom panel shows the position of the ZI and the STN in the Macaque (on photos taken from the block before each section is cut). Outlines indicate ZI (red) and STN (blue) **b.** Mouse zona incerta (ZI) is at the same location but relatively larger. Bottom panels show Allen Institute ISH (exp. 72081554) for Vgat. **c.** Sagittal slices with ISH from the Allen Institute showing that Gad2 is dense in ZI, but sparser in the medial ZIc (exp. 79903740); Vglut2 is sparse in ZI, but present in medial ZIc (exp. 71724696); Th is present in the medial Zir (exp. 1058); Pvalb is present in lateral Ziv (exp. 75457579). **d.** Collection of all viral injections in the Allen Institute mouse connectivity database with projections to the right ZI. **e.** Scheme showing the connections of ZI with other areas. Colors match **d**. **f.** Projections from neurons transfected with AAV-GFP from a single injection in ZI (exp. 156315468) with the ZI, thalamus, PAG, and motor parts of the superior colliculus (SCm) overlayed.

project to the dopamine-receptor-expressing layers of the SC [53]. The ZI has strong cell type- and zone-specific projections to the PAG (Figure 1f). The ZIr innervates excitatory neurons across the PAG [29]. The GABAergic ZIm neurons send projections to the GABAergic and glutamatergic neurons in lPAG and vlPAG [25,54]. Neurons positive for TH or SST also project to the PAG [35,55]. The ZIr, Ziv, and ZId have strong and distinct patterns of projection to many nuclei in the thalamus, in particular, the vLGN and high-order association and intralaminar nuclei, such as posterior medial nucleus of the thalamus (POm) and reuniens nucleus (RE) [28,56–59]. Also, ZI sends projections to regions enriched with dopamine neurons, many of which signal reward prediction errors (RPEs) for learning the value of states and actions [60].

ZI connections in non-human primates and humans

There are only a few connectivity studies that focus on the ZI specifically in NHPs [8,45,61,62]. Several tracer studies do mention fiber terminals in the ZI in the overall description of connections. Based on these, it can be surmised that the ZI in primates receives input from a wide range of cortical and subcortical areas, with some significant homology to the rodents. Cortical areas that project to the ZI include motor control and sensory areas (primary somatosensory cortex, temporal regions, premotor and motor cortex [8,45,63–68]; medial prefrontal and posterior medial cortices [69–72] and anterior, ventromedial temporal regions [8]). Subcortical inputs include PAG [73], SC [45], interstitial nucleus of Cajal [74], pontine nuclei [75], and the spinal cord [76–78]. Finally, the descriptions of dopaminergic terminals in the ZI [79] and recent tracer data indicate that the ZI has reciprocal connectivity with the SN and the ventral tegmental area [62].

This recent work in particular corroborated the many observations about the primate ZI and largely extended our knowledge of ZI connectivity [62]. They showed that in monkeys, the rostral ZI (ZIr) receives a wide range of prefrontal inputs, but not sensorimotor inputs (which based on other work likely is sent more caudally). Finally, the same paper also demonstrated a strong projection from the ZIr to the lateral habenula.

Functional diversity of the ZI

While the purpose of this review is to discuss recent findings linking the ZI to novelty seeking, it is worth first mentioning that the ZI has many other functions supported by different ZI regions and cell types. For example, the ZI is thought to be involved in feeding [30,60,80–82], hunting [25,83], sleep [27,38], and processing various emotional and motivational states [28,36,80,84].

This diversity may be supported by the topographical gradients in ZI connectivity and distinct cell types within the ZI. For example, while the stimulation of the ZIr drives mice toward food and not novelty, more caudal stimulation of the ZI makes even a fasted mouse choose novelty over food [26], suggesting some functional distinction among ZI subregions in their processing of novelty and other motivational drives. Rodent ZI has also been implicated in fear and vigilance-related behavioral responses. For example, the activation of GABAergic ZIr^{Gad2} neurons reduces noise-induced flight and conditioned freezing [29], and the stimulation of ZI^{Vgat} terminals in the thalamic reuniens (RE) attenuates fear generalization and reduces fear response after extinction [32]. Again, there are differences between zones or cell types in the ZI, because PV-positive neurons in the ZIv are required for fear memory acquisition [36], and the activation of these neurons enhances, rather than reduces, noise-induced flight [85]. While some results suggest that the ZI is associated with positive valence, as the pairing of activation of GABAergic cells in the ZIr and ZIm with place or nose poking induces place preference and persistent nose poking [25,26,30], other results suggest a relationship of ZI with negative affect, as ZIv^{PV} neurons regulate itch [37], and implicate ZI in pain processing [86].

In contrast to what is known about the functional diversity of the ZI in rodents, we know very little about the functional diversity of the ZI in NHPs and humans. For example, the relatively caudal ZI contains neurons with oculomotor signals that selectively predict gaze shifts to novel objects [8]. But, it is likely that the same neurons could also be involved in other gaze-related behavior beyond novelty seeking [61]. Also, another line of research that further highlights the heterogenous nature of the ZI is on the effects of deep brain stimulation (DBS) of the ZI in humans. For example, the caudal ZI has become a DBS target for a wide number of disorders [87–89], such as various tremor disorders and Parkinson's disease, a disorder known to have motor and non-motor components [90]. It is widely reported that DBS of the ZI has wide-ranging effects, including cognition and mood [91–93]. The rostral ZI on the other hand is a promising target for obsessive-compulsive disorder [62,94] – a complex disease that includes many cognitive and emotional components [95–97].

ZI in novelty-related behaviors

Overall, the pattern of connectivity of the ZI in primate and rodents indicates (1) that ZI neurons integrate a large variety of cortical inputs, but that this cortical input has some topographical and functional organization (2) that ZI neurons have direct access to motor output controllers in the brainstem, and (3) that ZI neurons have direct access to brain areas that mediate reinforcement learning. We next creview emerging data on how the caudal ZI contributes to novelty seeking and

inspection and relate this discussion to previous work on the anatomy and function of the ZI.

Novelty related behavioral responses

Before discussing novelty-related behavioral control by the ZI, we will take a few paragraphs to discuss the importance of novelty in behavior more generally and define which aspects of novelty-related behavior is regulated by ZI activity.

The exploration of perceptually novel objects is an important component of learning and curiosity [98,99]. Novel objects motivate behavior, attract attention and inspection-related behaviors, and mediate learning [16,100–108], and these occur even when novel objects have no bearing on obtaining reward or avoiding punishment, that is when novelty seeking is non-instrumental [8,99,108]. Previous studies have shown that neurons in many brain areas respond to novel stimuli more strongly than to familiar stimuli [2,109]; however, how the preference and the search for future novelty are controlled has remained unclear.

Novelty-related behaviors can be separated into at least two components: a motivational component (seeking or avoiding future novelty) and an investigative component (choosing and inspecting novel objects in the environment). To mediate the motivational component of novelty seeking, a neural network must make predictions about the probability or possibility of future novelty. This is akin to the control of reward seeking, where neural circuits, signal reward predictions to invigorate actions that produce more reward and suppress actions that produce less reward or result in punishments. We define the second component – novelty investigation – as behaviors that occur after the novel stimulus is present, particularly the sequences of approach and engagement. In theory, novelty investigation must be supported by detection mechanisms that classify stimuli as novel or familiar (which may take place through at least several related but distinct computations [2]) and a series of dynamic states that process action selection and give rise to novelty-related behavioral variability [26,110].

In the following sections of this article, we provide evidence in primates and rodents for the notion that one of the functions of the ZI is to regulate novelty seeking and investigating, even when novelty has no extrinsic reward value. We then hypothesize how the ZI could also support context-dependent adaptive behavior, including various forms of learning, through its connections to the basal ganglia and to neuromodulators.

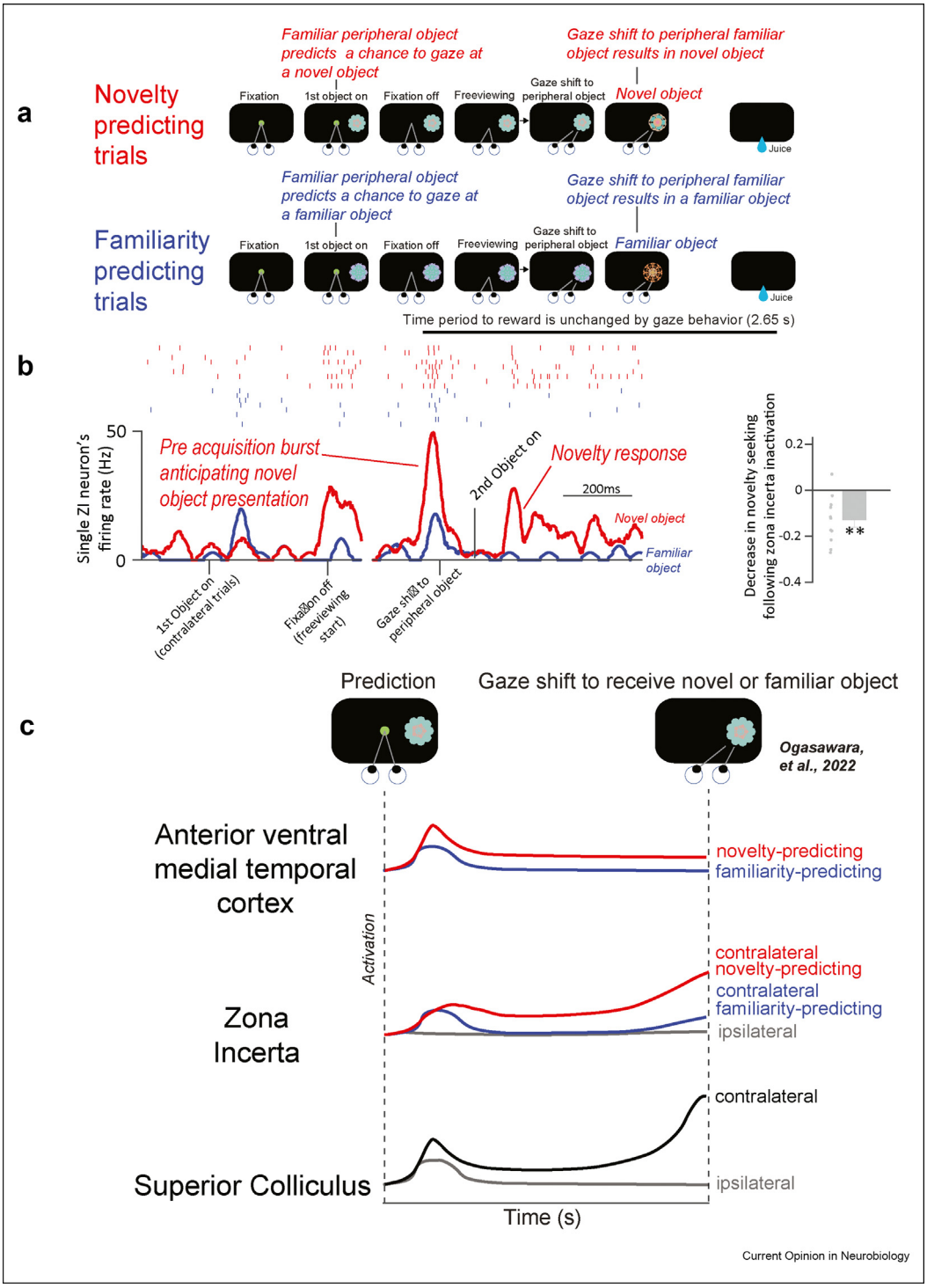
Novelty-seeking and investigation in primates

To study circuits of novelty seeking and inspection/investigation, a recent study designed a paradigm that presents novel or familiar objects as outcomes, contingent on gaze shifts. This behavioral procedure included novelty-seeking trials and novelty-inspecting trials. In novelty-seeking trials, monkeys could shift their gaze to a familiar peripheral fractal object to gain the opportunity to view a novel fractal object (Figure 2a). The task is akin to studies of reward seeking in which monkeys shift their gaze to obtain reward; however, here they made gaze shifts to obtain the opportunity to gaze at novel or familiar objects. The reward amount, timing, or overall rate were not contingent on these gaze shifts. Monkeys displayed a strong preference to receive the chance to view novel objects versus familiar objects. They were faster to shift their gaze onto familiar objects that delivered the opportunities to view novel objects versus those that delivered other familiar objects. When given an option to choose among the opportunity to gaze at a novel object in the future versus a familiar one, monkeys displayed a significant preference for future novelty, indicating that novelty had an intrinsic value [8].

Many ZI neurons, particularly in the caudal lateral regions above the STN, conveyed information that is necessary and sufficient to control novelty seeking. One example of a neuron's activity is shown in Figure 2b. This neuron selectively increased its activity in anticipation of gaze shifts to obtain novel objects. This selective novelty predicting activation was spatially selective. It was only observed before gaze shifts to objects appearing on the contralateral side of the visual field (see Figure 1 of Ogasawara et al., 2022). And, during trials in which novel objects appeared in the periphery, the neuron responded selectively to novel objects versus familiar objects and anticipated gaze shifts to inspect these novel objects (Figure 1 of Ogasawara et al., 2022). Like this ZI neuron, many neurons recorded in the ZI signaled information that was well suited to guide novelty seeking and investigating gaze shifts. And, accordingly, pharmacological disruption of the ZI areas enriched with such novelty-related neurons disrupted novelty-seeking behavior (Figure 2b, right panel).

In contrast to what we observed in the ZI, many value prediction errors-related dopamine neurons did not signal novelty predictions or respond to novel objects. We propose that this is the case because novel objects have no reward value in this task and do not predict opportunities to learn about upcoming reward. Also, the basal forebrain, a region that signals surprises about rewards and punishments [101,111,112], contains phasic bursting neurons that do differentiate novel versus familiar objects with very short latency [101]. These neurons may play important roles in the rapid deployment of novelty-investigating behaviors or attention more generally. However, like dopamine neurons, they did not convey predictions about future novelty that is required to guide novelty seeking behavior [8].

Figure 2



ZI mediates novelty-related behavior in primates. **a.** Behavioral conditions to measure the motivation to obtain the opportunity to gaze upon future novel objects. Two trial types are shown based on Ogasawara et al., 2022. In one, termed novelty-predicting trials, a familiar object predicts the opportunity to gaze at a novel object, contingent on a gaze shift. In the second one, termed familiarity-predicting trials, distinct familiar object predicts the opportunity to gaze at another familiar object. **b.** Single ZI neuron's activity shown for novelty-seeking trials. Because the ZI is spatially selective (e.g., it did not respond selectively when stimuli appeared on the ipsilateral side), here, we show trials in which the objects appeared on the contralateral side relative to the recording electrode. **B-right panel**. Inactivation of the ZI reduces novelty-seeking. Each dot is a session. Error bar is SEM. **c.** Schematic of novelty seeking in primate brain based on Ogasawara et al., 2022. Anterior ventral temporal cortex signals novelty predictions and detects novel objects (detection not depicted here). The ZI processes novelty prediction and novelty detection related information, and integrates it with action control variables (e.g., displaying spatial selectivity for object location and anticipating the time of the gaze shift to the object) to modulate the superior colliculus (SC) which controls gaze behavior and spatial attention.

Because of the lack of novelty prediction signals among reward prediciton error signalling dopamine neurons and phasic basal forebrain neurons, Ogasawara and colleagues sought to identify the sources of novelty predictions in the primate brain. High-channel count recordings revealed that the anterior ventral medial temporal cortex (AVMTC) was a prominent source of novelty predictions. AVMTC includes the anterior medial inferotemporal cortex and the perirhinal cortex [106], which have established roles in detecting novel objects, in several forms of object memory, and in object-to-object associations [106,113–117]. The new data expanded the role of AVMTC beyond the detection of novel objects: AVMTC neurons signaled novelty predictions, and this signal was observable earlier in AVMTC than in the ZI. Moreover, the AVMTC did not have motor preparation-related signals as observed in the ZI, consistent with the idea that the novelty-prediction signals from AVMTC are integrated with motor plans elsewhere, including prominently in the ZI.

How does AVMTC generate or learn novelty predictions? While the answer is currently unknown, we propose that this signal can be generated due to the association of familiar objects with abstract categories of novelty and familiarity. That is, in our task, distinct familiar objects predicted subsequent novel or familiar objects, and novelty predictions in AVMTC may reflect this learned object-to-category association.

A final point worth noting is that the caudal ZI receives diverse inputs from many premotor cortical regions [62]. Indeed, Ogasawara and colleagues found that during novelty-seeking actions, other regions known to be involved in attention and gaze control [118–121] were recruited, for example, 45b/8v, globus pallidus, and some neurons in the anterior caudate nucleus. These regions may form a functional network with the ZI in support of novelty-seeking gaze behavior.

Novelty-seeking and investigation in mice

A recent study also linked the ZI to novelty seeking in rodents [26]. Ahmadlou and colleagues studied novelty seeking while mice displayed innate investigatory behaviors. In mice, hunting, foraging, and object investigation overlap in their action sequences (approaching, sniffing, grabbing, and biting), and most novelty-seeking studies in mice summarize the investigatory behavior as the duration of time spent nearby or in interaction with novel objects (or conspecifics) compared with familiar objects (or conspecifics), regardless of what actions are taken. To gain insight into brain mechanisms underlying novelty seeking in mice, it was essential to study the precise actions or sequence of actions mice take to investigate novel objects.

Ahmadlou and colleagues uncovered that mice display distinct sequences of actions when they interact with novel objects (or novel conspecifics) compared to the familiar ones. Mice often leave familiar objects after sniffing, but when novel objects are presented, they often continue interacting with them, through biting, carrying, and grabbing actions (Figure 3a). Therefore, the level of motivational drive and interest to investigate novel objects can be characterized by the sequence of actions taken by the mice: lower motivation leads to only approaching and sniffing the objects, or *shallow investigation*, and higher motivation results in the continuation of the interaction by means of other actions (i.e., biting, carrying, and grabbing), or *deep investigation*. These behavioral differences were then used to link ZI activity and novelty-related behavioral responses.

Ahmadlou et al. (2021) found that optogenetically activating ZIm GABAergic neurons in the presence of novel and familiar objects resulted in a dramatic increase of behavioral interaction with novel objects. Free-access rodent choice paradigms were then used to examine the motivational drive underlying the novel object interaction and dissociate novelty-related interaction from other types of interactions, for example, hunting (Figure 3b). ZIm activation caused a preference for interaction with novel objects over food or prey. Moreover, the activation of ZIm increased the depth of investigation and the inactivation of ZIm decreased the investigation depth (Figure 3c). Therefore, the ZI directly modulates the depth of novelty investigation.

A major input to the ZIm, the mPFC, was similarly activated during shallow and deep investigation, suggesting the unique role of ZIm in novelty investigation. Ahmadlou et al. (2021) also found that when ZIm is activated, its inhibitory inputs are transmitted to PAG during deep investigation (Figure 3d) suggesting that the ZIm to PAG circuitry is important for investigatory behaviors in rodents (Figure 3e).

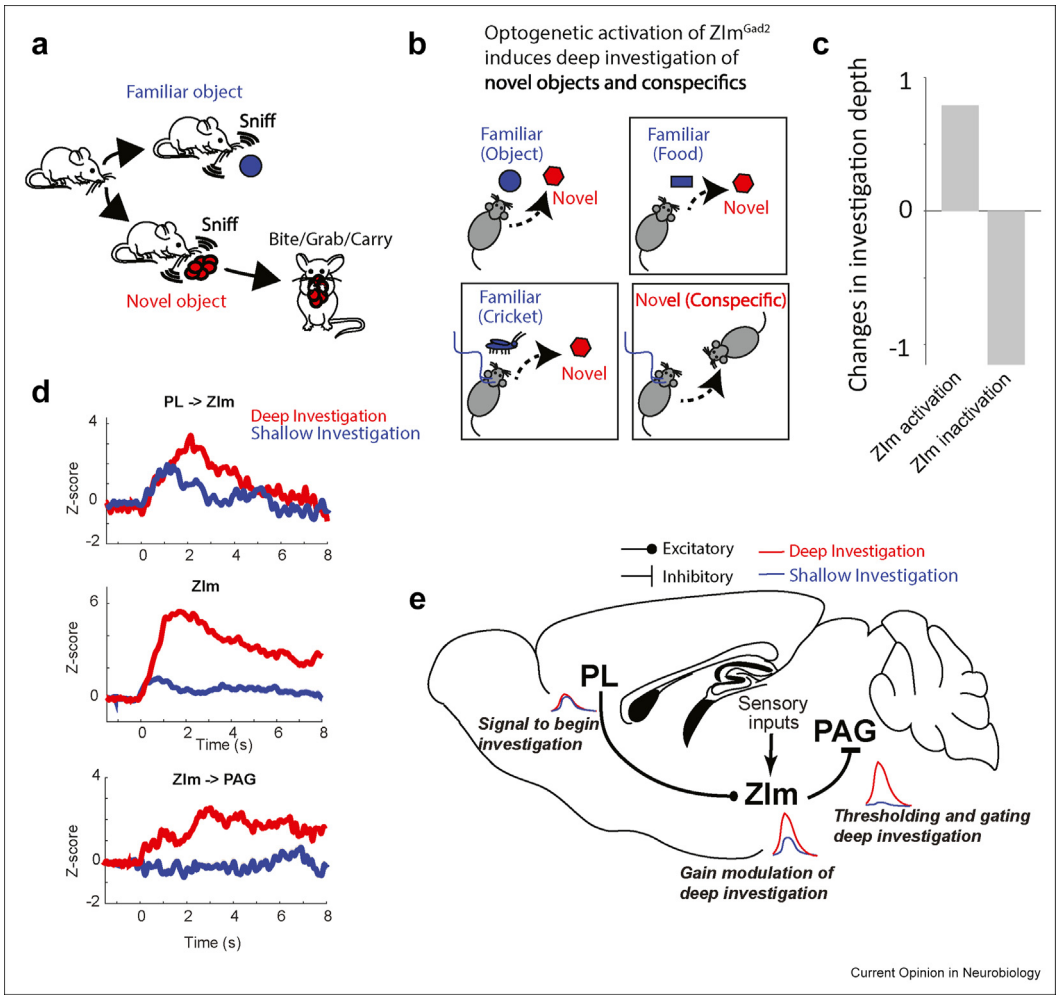
Novelty and reward

Circuits supporting the interaction of novelty-seeking and reward

We propose that the ZI can play an important role in behaviors that require the integration of higher order cortical computation to rapidly control action responses and new learning (Figure 4). Novelty seeking and investigation are crucial examples of such behaviors. We next discuss how this system can interact with neural circuits involved in reward-driven behavior and reward value learning.

Available data suggest that many brain areas contain neurons that are involved in processing both novelty and reward or value [101,122,123]. Furthermore, many brain areas linked to reward circuitry in rodents and primates [2,8,101,113,124–130] are believed to contribute to different forms of novelty detection and investigation. Here, we opted to concentrate on one of these brain

Figure 3

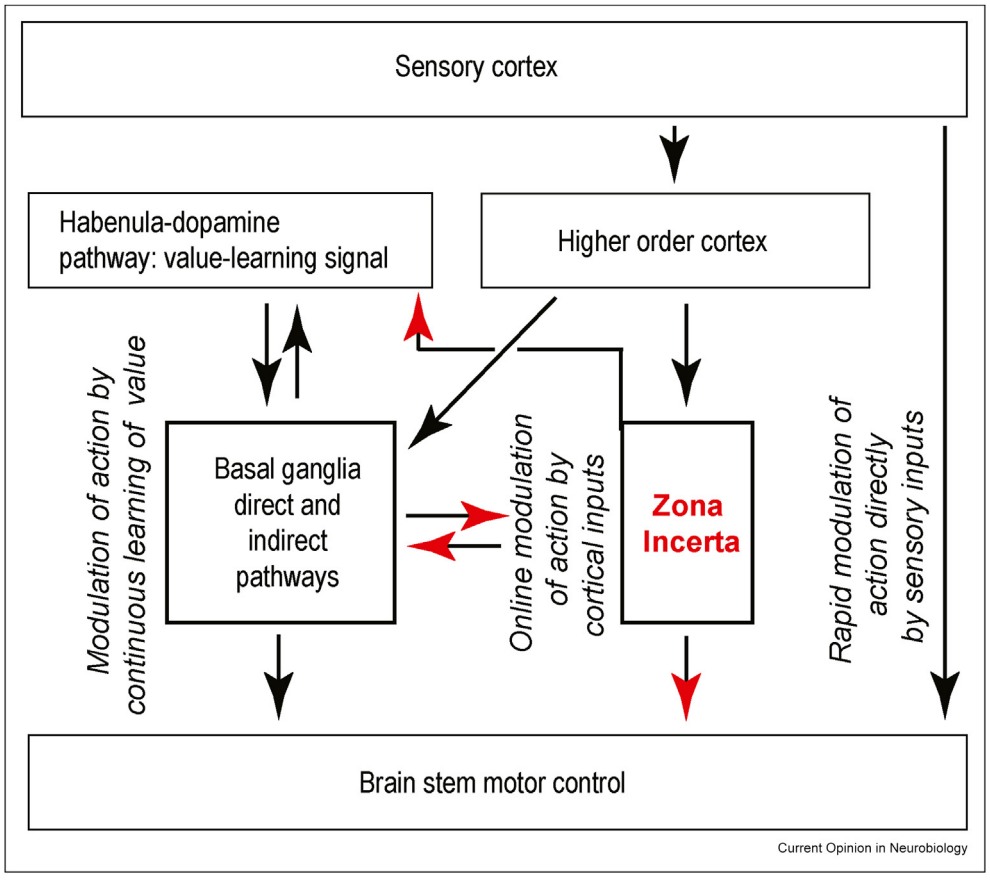


ZIm mediates novelty-related behavior in mice. **a.** Mice investigate novel objects by biting, grabbing, and carrying. **b.** Optogenetic activation of GABAergic neurons in the ZIm induces deep investigation of novel objects and conspecifics. **c.** Activation of GABAergic neurons in ZIm increases the investigation depth, while inactivation decreases the investigation depth. **d.** Calcium levels in axons from prelimbic cortex (PL) to ZIm increase when mice start investigating (top). Calcium levels in GABAergic neurons in ZIm increase much more for deep investigation (middle). Calcium levels in axons from ZIm to PAG increase only for deep investigation (bottom). **e.** Scheme showing the transformation of the motivation to investigate to deep investigation. Panels adapted from Ahmadlou et al. (Science, 2021).

areas — the basal ganglia because it has been widely investigated in the context of reinforcement learning theory, linked to object-based action selection and object-value learning, is involved in processing object novelty, and is regulated by dopamine — a modulator with a demonstrable role in action value learning and motivation [13,110,131–138].

The primate basal ganglia guide eye movements toward learned or familiar valuable objects and repel eye movements from behaviorally unimportant objects in at least several different ways [139], such as, for example, based on fast and slow timescales of learning within different regions of the striatum [3]. The ventral posterior striatal neurons could be well suited to mediate investigational behavior in response to novel and other motivationally salient or important objects. They receive inputs from the AVMTC and other temporal cortical areas [2,136], and robustly discriminate novel versus familiar objects present in the environment [8,126] — a signal which can be readily sent to the superior colliculus through the SN pars reticulata [139] to control gaze shifts and spatial attention [140] to novel objects.

Figure 4



Hypothetical structure of behavioral control over multiple timescales. Sensory systems (**top**) detect and process ongoing events. These are used to control fast reflex-like behavior (**right**) or slower value learning (**left**). Also, ongoing cortical computations in higher-order areas that process sensory inputs and internal states can access behavioral control directly and rapidly through the ZI, which acts as a relay and integrator (**middle**). The organization of ZI connectivity allows it to provide temporally precise signals, such as about novelty, conveying the timing and location of novelty-seeking actions (Figure 2). These signals could be simultaneously sent to the brainstem to trigger actions or behavioral states, to dopamine neurons that transmit teaching signals for reinforcement learning, and to basal ganglia neurons that learn action values from those teaching signals. We propose that this architecture places ZI in a unique role in action selection and in learning and credit assignment (red arrows).

The posterior ventral striatal regions learn the importance of visual objects relatively slowly, but stably and encode their importance in a manner that is resistant to many forms of devaluation or interference, over long time scales without continuous training [139]. One hypothesis worth addressing is that the facilitation of behavioral responses to novel objects through these striatal areas could take place via a learned stable representation of object categories and their importance, which in principle could be triggered by the AVMTC. This type of representation could be learned through salience or surprise-driven learning for example during childhood and stably implemented throughout life.

The posterior ventral basal ganglia in rodents are also part of a novelty response circuit [138,141]. The tail of the striatum in rodents receives a unique dopaminergic teaching signal, transmitting physical salience [138,141]. Dopamine release in this area suppresses engagement with novel objects and predicts responses to novel objects on a mouse-by-mouse basis [110]. The fact that the primate posterior ventral basal ganglia may orient the eyes to novel objects while the rodent posterior ventral basal ganglia may repel mice from them, does not mean the inherent computations differ. Rather, a likely explanation is that the two species are optimized to respond to novelty with different motor programs for different objectives.

Also, some neurons in relatively anterior regions of the basal ganglia, in areas involved in predicting future rewards and in fast and flexible trial-by-trial reward value learning, were engaged during actions that resulted in the availability of future novel objects [8]. This more anterior area of the basal ganglia may also be involved in

novelty seeking and could be a site of the interaction between trial-by-trial reward value reinforcement learning and novelty-based behavioral control.

We propose that to reveal how novelty seeking and value-based motivation interact, the next experiments must assess the interactions between the ZI and the distinct regions or compartments of the striatum, as well as the interaction of the ZI with different groups of dopamine neurons that send teaching signals to posterior ventral and to anterior striatum, for example, such as those signaling physical or motivational salience versus value-based prediction errors [11,138,141,142]. We discuss this issue further in the following section.

Novelty and value learning

Learning theory describes how agents learn extrinsic reward values of actions and states to select future actions to gain more or better rewards and proposes that agents update action value from RPEs — a comparison between predicted and received reward. RPEs are signaled by many medial SN dopamine neurons which are regulated by the lateral habenula [143]. Recent work proposed that novelty could increase RPEs when novelty and reward co-occur [144] to boost the exploration of novel objects. But how this takes place at the level of algorithm or neural circuit remains unknown. Also, how to make algorithms that adaptively explore many contexts that contain differential and variable levels of reward and novelty remains a major challenge.

When animals have not yet learned the meaning or value of novel stimuli, encounters with these stimuli evoke strong dopaminergic responses in many contexts [145,146], but a detailed understanding of this novelty-driven modulation is lacking. For example, it is uncertain if it is additive or gain-like, and the circuit and computational principles that underlie it are unknown.

Understanding these computations could be fundamental for systems neuroscience, artificial intelligence, and may shed light on broader questions regarding the architectures of flexible behavior and value learning. As an example, novelty can be aversive or rewarding or have no extrinsic value at all, depending on the external and internal state of the agent. Knowing how the interaction among novelty computations and valuation occurs to facilitate adaptive action selection may shed light on the architectures and algorithms of behavioral flexibility.

We believe an important insight into this question comes from the observation that many RPE coding dopamine neurons do not signal novelty prediction errors when novelty has no extrinsic reward value and does not predict potential opportunities to learn about future rewards [8,141]. Together with other data we have reviewed here, it suggests that the brain has a capacity to signal signed reward value prediction errors and information about novelty through different neurons. And, this may be critical for context-dependent adaptive learning in novel environments. In particular, the interactions among functionally distinct but anatomically connected circuitry signalling novelty and reward predictions may underlie the amazing capacity of mammals to negotiate many different and variable novel and rewarding environments, for example, by flexibly increasing or decreasing the magnitude of RPEs in response to rewards and novelty in a context-dependent or internal-state-dependent manner (e.g., during exploration versus exploitation).

Beyond the possibility that novelty prediction and detection signals in the ZI can boost or decrease RPEs, there may be at least one more crucial aspect to the interaction between dopaminergic basal ganglia systems and the ZI. To assign credit to actions that result in future novelty or that investigate novel objects, it would be convenient for the brain to contain a temporally precise signal to trigger novelty-driven actions such as observed in single ZI neurons (Figure 2) and to convey this signal simultaneously or in some structured manner to reward prediction and learning circuitry that mediates action value learning to reinforce future behavior (Figure 4). To assess whether the ZI can support a hypothetical credit assignment mechanism, it will be important to understand whether the neurons in the ZI that signal novelty predictions project to both the brainstem action controllers as well as to the basal ganglia and dopamine neurons.

Remarks on future investigations of the relationship of novelty seeking and other curiosity-related behaviors

Perceptual novelty seeking is one component, or dimension, of curiosity which also includes instrumental and non-instrumental information-seeking behaviors that aim to reduce uncertainty about future outcomes [5,147]. Thus far, the relationship of perceptual novelty seeking/investigation and uncertainty-reducing information-seeking remains highly underexplored at the level of behavior or neural circuits. For this reason, in this review, we concentrated on novelty seeking but not on other behaviors that together form curiosity-related traits.

ZI receives topographically organized, but overlapping, input from the neocortex along its rostral-caudal extent. While the caudal ZI has been linked to novelty seeking and receives relatively strong inputs from motor and sensory-processing areas of the neocortex, the anterior parts of the ZI receive relatively more inputs from the anterior cingulate cortex — a region that plays a key role in deliberative or cognitive behavior and regulates uncertainty-reducing

information seeking [148]. Therefore, it maybe that novelty seeking and other forms of curiosity are mediated through a gradient in cortical connectivity to different regions in the ZI via a common architecture that facilitates the linkage between high-level cognitive computations and action value learning and behavioral output (Figure 4). Notably, reward uncertainty selectivity — a key signal for information seeking [5,147] — was observed in relatively more caudal ZI (Figure S8 in Ref. [8]). One possibility is that this tendency would increase in more anterior regions of the ZI which receive more inputs from the anterior cingulate.

In general, to better understand how neural circuits in the ZI support different forms of curiosity-related behavior, the next experiments will need to clarify the functional properties of the inputs to the ZI across a variety of tasks with circuit and cell-type specificity.

Declaration of competing interest

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

Authors' contributions

All authors contributed equally to this manuscript.

Data availability

No data was used for the research described in the article.

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