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The Neural Basis of Escape Behavior in Vertebrates

Tiago Branco¹ and Peter Redgrave²

¹UCL Sainsbury Wellcome Centre for Neural Circuits and Behaviour, London W1T 4JG, United Kingdom; email: t.branco@ucl.ac.uk

²Department of Psychology, The University of Sheffield, Sheffield S1 2LT, United Kingdom; email: p.redgrave@sheffield.ac.uk

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Abstract

Escape is one of the most studied animal behaviors, and there is a rich normative theory that links threat properties to evasive actions and their timing. The behavioral principles of escape are evolutionarily conserved and rely on elementary computational steps such as classifying sensory stimuli and executing appropriate movements. These are common building blocks of general adaptive behaviors. Here we consider the computational challenges required for escape behaviors to be implemented, discuss possible algorithmic solutions, and review some of the underlying neural circuits and mechanisms. We outline shared neural principles that can be implemented by evolutionarily ancient neural systems to generate escape behavior, to which cortical encephalization has been added to allow for increased sophistication and flexibility in responding to threat.

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1. INTRODUCTION

Escape behavior has evolved to protect animals from being harmed or killed by threatening events. These events include attacks from predators; other species defending their territories, mates, and young; and aggressive conspecifics. The purpose of escape is to quickly move the animal away from a dangerous situation toward safety. Escape behavior is prevalent in phyla as different as Arthropods and Chordates, which diverged more than 550 million years ago (Kumar & Hedges 1998), and species that occupy an immensely diverse range of habitats. This suggests that various forms of defensive escape have evolved independently many times through their ability to increase an individual's reproductive fitness. Accordingly, there is a wide range of actions across the animal kingdom that implement the goal of evading attack. For example, fish escape with short swimming bursts, rodents run toward nearby refuges, and most spiders drop vertically toward the ground using gravity (Cooper & Blumstein 2015).

Over the last century, escape has been the subject of numerous observations in natural habitats and field work. Behavioral studies have generated immense knowledge about the general properties of escape behavior, including the distance from the predator at which flight is initiated (Ydenberg & Dill 1986, Lima & Dill 1990), the interaction with refuges (Martin & López 1999), and the trajectory of escape actions (Domenici et al. 2011). It has also been revealed how escape can be influenced by a variety of factors, including the type of and strategies of the attacker (Bulbert et al. 2015), the physical abilities of the attacked (Stankowich & Blumstein 2005), social and reproductive variables (Cooper 1999), and predation risk (Møller 2008). From these data, rules and models of escape have been derived to describe economic trade-offs of escape decisions, predict when escape should be initiated, and calculate optimal escape trajectories (Ydenberg & Dill 1986, Lima & Dill 1990, Domenici et al. 2011).

Laboratory research in the past 50 years has, in turn, described key neural circuits and mechanisms of escape. A major advantage for the neural study of escape behavior is that most animal species react innately to threat, often to specific and well-defined sensory stimuli that signal its presence. Because temporally precise stimuli can be used to trigger escape, this behavior has been particularly attractive for neurophysiological studies aiming to link neural activity to ethologically important sensorimotor transformations. For example, neural responses to looming stimuli, which represent objects on a collision course, have been extensively characterized for a variety of vertebrate and invertebrate species (Fotowat & Gabbiani 2011, Herberholz & Marquart 2012, Yilmaz

& Meister 2013, Dunn et al. 2016, Peek & Card 2016). For animals such as the locust, we have a very detailed understanding of how the stimulus causes an escape response (Fotowat & Gabbiani 2011). Recent advances in the study of escape behavior in mice have opened the prospect of reaching a similar depth of understanding for mammals. Particularly exciting is the effort to dissect the role of cortical and subcortical circuits in controlling the many facets of escape behaviors.

Here we review the implementation of escape at the circuit and neuronal levels in vertebrates, with emphasis on mammals and how their circuits compare to lower vertebrates. The same information for invertebrates, where this knowledge is arguably vaster, has been extensively and recently reviewed elsewhere (Fotowat & Gabbiani 2011, Hemmi & Tomsic 2012, Peek & Card 2016). We focus here on locomotor escape: motor actions that move the animal to a new position in space. Although other defensive responses may precede and establish the conditions for locomotor escape to be executed, we mention freezing, fight, and other defensive actions that are alternative means of avoiding harm only in passing. We first discuss the computational challenges of generating escape behavior and then provide an overview of the neural mechanisms that implement different stages of escape.

2. COMPUTATIONS AND ALGORITHMS FOR ESCAPING

Escape behavior can be decomposed into several high-order computational problems that must be solved in order to link sensory threats to motor escape movements (**Figure 1**). It is worth considering what these main problems are and how they can in principle be solved from an algorithmic perspective.

The first challenge in implementing escape behavior is that, among all current sensory stimuli that impinge on the brain, a threat stimulus must be detected and in most cases selected to become the focus of attention and allowed to guide movement. Multimodal sensory input arriving from all regions of space represents a vast array of events that have the potential to guide future movements that are often incompatible—approach and avoidance, or simultaneously focusing attention to more than one spatial location. The fundamental problem is that multiple sensory events cannot simultaneously be allowed to drive incompatible eye, head, or body movements. Therefore, it is imperative that once a threat stimulus has been detected, it must either gain immediate command of the motor system or go into a priority competition with all other current sensory events. This posits the need for systems that solve the sensory selection problem by the stimulus either being so dangerous it gains immediate access to the motor systems generating locomotor escape or somehow achieving the necessary input salience for being chosen by selection circuits.

For escape behavior, investigations using a variety of animal species have shown that sensory stimuli are perceived as imminent threats that require escape actions if, first, they suggest the animal has been detected by the attacker, i.e., they are being directly approached, and second, the attacker moves past a proximity boundary. This is known as the flight initiation distance (FID), which in economic models of escape behavior is the point at which the costs of not escaping outweigh the costs of escaping (Ydenberg & Dill 1986). The FID varies between species and individuals (Cooper & Blumstein 2015) and is modulated by several variables such as alarm calls (Seyfarth et al. 1980, Hollén & Radford 2009), the response of conspecifics (Marras et al. 2012), and the availability of food and mates (Cooper et al. 1999, Killian et al. 2006, Schadeegg & Herberholz 2017). However, when the threat is approaching fast or close to the animal, escape is invariably and immediately initiated without further consideration. This determines that there should be processing within sensory systems that are particularly sensitive to events that approach rapidly. In principle, this is most likely to be achieved through highly conserved innate

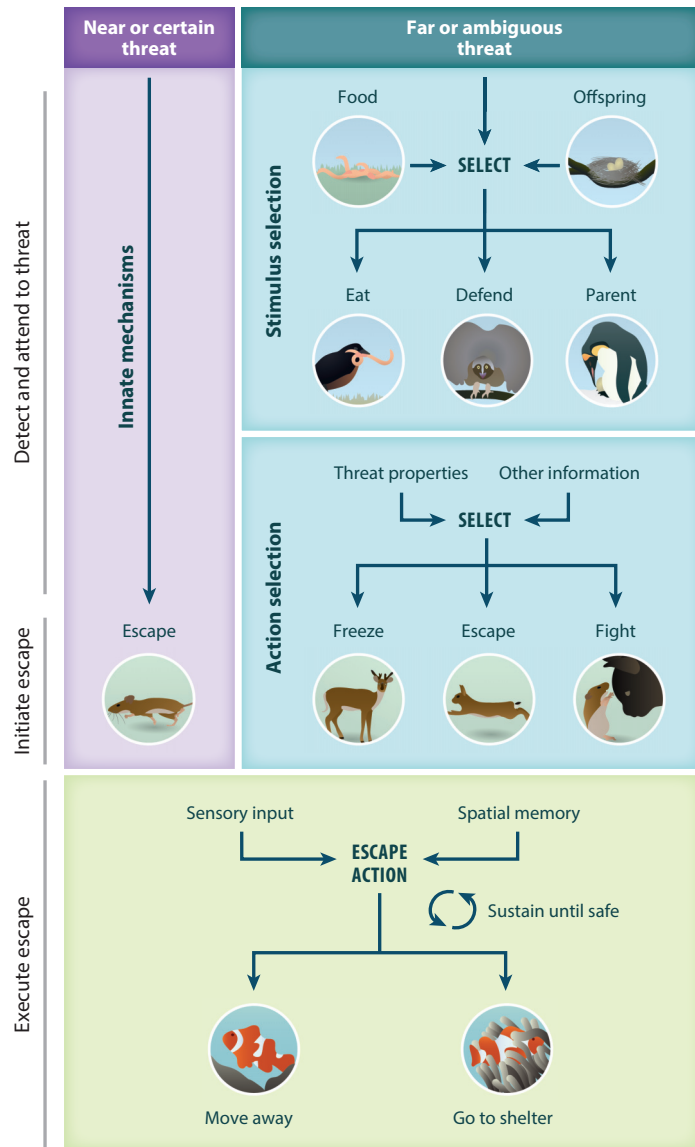


Figure 1

Basic algorithmic steps for escaping from threat. The schematic illustrates three stages of the escape process: detecting threat, initiating escape, and executing the escape actions. For linking detected threats to escape initiation, two different channels are possible: Near or certain threats can directly trigger escape initiation via hardwired, innate mechanisms; if the threat is far or ambiguous, further sensory processing can be used to identify its nature, and a stimulus selection process arbitrates which sensory events should guide future actions. If the highest priority is given to the threat stimulus, information about the threat nature can be used to select the most appropriate defensive action. Once escape is initiated via either processing route, additional sensory information and memory, if available, are used to guide escape execution away from the predator or specifically toward refuge, and the action should be sustained until safety is reached.

mechanisms put in place by evolution. On the other hand, an additional important consideration is that in natural circumstances life and death are often initially signaled by stimuli close to sensory thresholds—the snap of a twig or the slight movement of a blade of grass. This means that the detection system for such threats needs to be able to boost physically weak stimuli such that they become sufficiently salient to win competitions for sensory attention. Perhaps the evolution of multisensory integration, which would boost the signal-to-noise ratio of weak sensory threats by combining multiple sensory modalities, has been forged by this requirement. These mechanisms could be innate, with multisensory processing channels delivering the necessary amplification, or learned, where a reinforcement-based valence system is recruited to increase the salience of weakly presenting threats.

Having detected a threat, a second problem that must be solved in the generation of escape behavior is how to link the various threat stimuli to the motor systems so they can guide appropriate escape movements. From the outset, two solutions appear possible: (a) Link the threat stimulus directly to movement centers that initiate escape behavior or (b) feed the threat stimulus into sensory and action-selection systems that arbitrate between other ongoing stimuli and possible actions. In this regard, time is likely to be of the essence. In the case of immediate and imminent threat (e.g., a large, rapidly looming stimulus), much would be gained by having the selected representation of an attacker directly linked to the motor plan capable of initiating escape. Circuitry with these properties is most likely to be innate but could be modified by various state and contextual information or acquired through learning. In such cases there would be no explicit action selection, rather the selection of escape movements would be embedded in the process of stimulus selection, and competing actions would be inhibited after escape is selected. In the alternative scenario, when the threat is not imminent, it would be advantageous to determine the nature of the threat. This would allow possibly vetoing initiation of escape in favor of behaviors that satisfy more salient competing motivations, such as hunger or defense of territory or young, and also choosing the best possible strategy for defense for that particular threat.

Irrespective of whether escape is triggered directly by an imperative sensory event or it is chosen through action selection processes after the nature of the threat has been identified, a third challenge in escaping from threats is executing actions that maximize safety. In principle, the simplest way of achieving this would be to maximize the physical distance between the animal and the attacker. Implementing this, however, is complicated. First, it requires detecting the vector and speed of the approaching threat and initiating an action that moves the animal away from the impending collision. Thus, a threatening stimulus impinging on the right-hand side should initiate movements toward the left-hand side. Second, an immediate low-level consideration when escaping is to not bump into things or, for terrestrial animals, fall into holes. Here, a solution could involve the extraction of free space paths using the deformation of optic flow patterns caused by objects and holes (Gibson 1974). Third, to sustain an escape response, more sophisticated sensorimotor processing is required. For example, a sequence of movements that takes an animal away from an attacker means that the threat stimulus may no longer be detectable in relevant sensory systems, most likely vision. In this case, a mechanism would be required to maintain escape movements in the absence of the triggering stimulus. Moreover, animals being chased by an attacker must consider not only the dynamically evolving position of their chaser but also the dynamics of their escape path relative to the spatial environment. While running faster and for longer than the attacker might be a viable strategy in some situations, in others, running as fast as possible toward a refuge might be a better option. Reaching the refuge could be done using sensory systems to find one while escaping and steer locomotive actions in that direction; this might have to be done in novel environments, and it might be challenging to achieve while escaping at high speeds. When the spatial surroundings are known, there would be an advantage to using memories of

paths and shelter locations. These representations could be used for guiding escape execution and implementing spatially efficient threat avoidance.

3. DETECTION AND ATTENTION TO THREAT

Depending on species and the ecological niche they inhabit, threats may approach at different speeds and in different shapes and sizes, suggesting that escape responses need to be flexible and responsive to circumstance. An example of this can be seen with the conspecific alarm calls of vervet monkeys. Calls indicating the presence of a leopard cause the monkeys to escape to the trees, eagle calls to scan the skies, and snake calls to search the floor (Seyfarth et al. 1980). This example also serves to illustrate the importance of having sensory systems that can correctly identify the nature of the threat. However, there are extreme circumstances where escape responses are initiated before the nature of the threat is known.

3.1. Escape Before Threat Identification

Some sensory events predict harm so reliably that innate mechanisms have evolved to evoke escape movements before the nature of the threat has been identified. One example is an exponentially expanding looming stimulus (Gibson 1974). Such stimuli evoke escape responses in a wide range of species, including fish (Temizer et al. 2015), birds (Wu et al. 2005), mice (Yilmaz & Meister 2013), monkeys (Schiff et al. 1962), and humans (King et al. 1992, Billington et al. 2011). Original work by the Blanchards (Blanchard & Blanchard 1988) described a distance defense hierarchy for wild rodents. When a human threat was perceived at a distance and was a small point on the retina, the evoked response was for the rats to freeze. However, as the human approached, the expansion of the image on the retina, kept at a stationary center of gravity, would at some point cause the wild rat to flee to a place of safety, if available. A more formal confirming report of these observations was published recently (De Franceschi et al. 2016). The fundamental point, however, is that a rapidly expanding but otherwise stationary dark stimulus on the retina signals an impending collision and, as such, is a universal threat. Under such circumstances, advantage is to be gained by initiating escape before turning to see what it is. Confirmation of this was provided by King et al. (1992) in a study with humans where a defensive head movement away from a looming threat was initiated before a saccadic eye movement toward the stimulus.

Given that a collision-predicting loom is always dangerous, neural mechanisms that could resolve such stimuli (Sanes & Zipursky 2010) and directly trigger effective escape responses (Grillner & Wallen 1985) were present at the outset of vertebrate evolution (**Figure 2**). The optic tectum [or superior colliculus in mammals (OT/SC)] is the primary visual structure responsible for detecting the presence of looming stimuli (Westby et al. 1990, Wu et al. 2005). It is a multilayered region located in the dorsal midbrain, which receives multimodal sensory input (Wallace et al. 1998, Knudsen & Schwarz 2017). Visual input comes directly from retinal ganglion cells to the superficial layers, while auditory and tactile input to the intermediate layers arrives indirectly via primary sensory relay structures in the brain stem. Neurons in the deep OT/SC project directly to premotor structures in the brain stem and spinal cord that control movements of the eyes, head, and body (May 2006). Although the evolution and function of the OT/SC have been primarily linked to visual processing (Knudsen & Schwarz 2017), the increase in number of layers and complexity of its intrinsic circuits from cyclostomes to birds allowed for the detection of multisensory threats.

The OT/SC neurons receive direct input from OFF-channel retinal ganglion cells whose directionally sensitive firing is strongly driven by dark expanding objects (Yilmaz & Meister 2013).

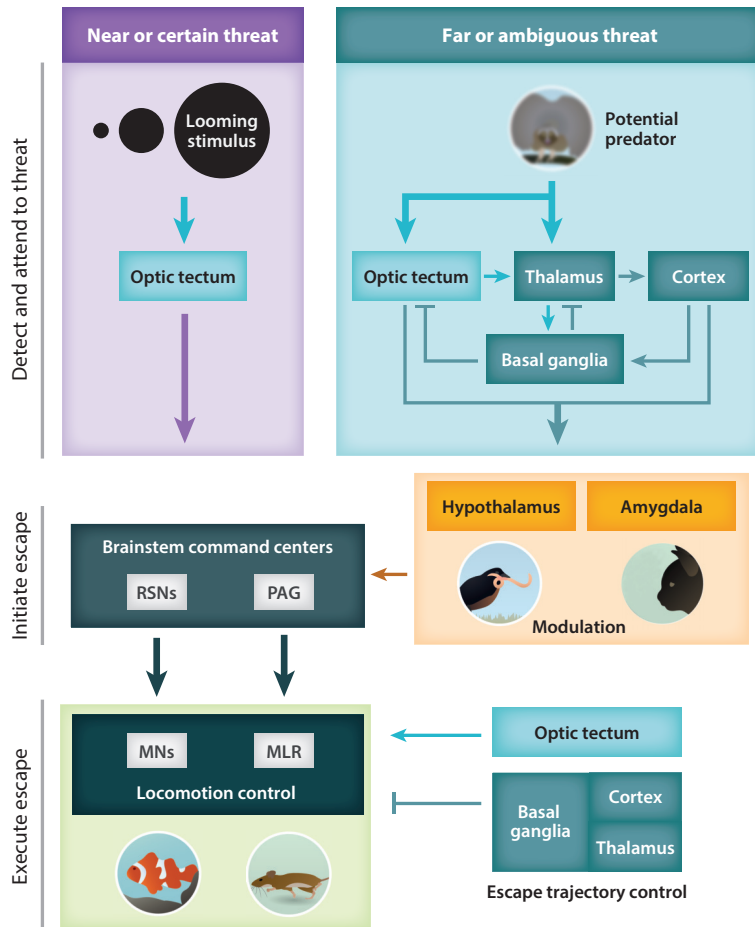


Figure 2

Neural circuit blueprint for computing escape behavior in vertebrates. Schematic illustrating the key neural structures for generating escape locomotive actions in the presence of threat. (*Top row*) Sensory stimuli that represent immediate threats, such as a looming stimulus signaling impending collision, are detected by the optic tectum/superior colliculus and immediately activate escape initiation centers. When the stimulus represents an uncertain or distant threat, additional sensory processing by cortical and thalamic circuits contributes to identifying the nature of the threat, and basal ganglia loops determine the priority of the stimulus and whether escape should be initiated. (*Middle row*) Circuits in the brain stem, including the periaqueductal gray (PAG) or reticulospinal neurons (RSNs) such as Mauthner cells, integrate threat input to initiate escape. These structures also receive information about motivational states from the hypothalamus and the amygdala, which can modulate escape initiation. (*Bottom row*) Escape initiation circuits project to networks that coordinate locomotion, such as the mesencephalic locomotor region (MLR) in mammals, or directly to motor neurons (MNs) in fish. The trajectory of the escape action can be adjusted during escape through additional sensory input from the optic tectum or corticothalamic networks via the basal ganglia.

This property is transferred to the visually sensitive target neurons in the OT/SC, which in lampreys, frogs, fish, birds, and rodents respond intensely to looming spots (Westby et al. 1990, Kang & Li 2010, Liu et al. 2011, Zahar et al. 2012, Zhao et al. 2014, Temizer et al. 2015, Dunn et al. 2016, Evans et al. 2018, Suzuki et al. 2019). In pigeons, for example, tectal neurons signaling an impending collision of looming objects have been reported (Wu et al. 2005), while a study in

rats (Westby et al. 1990) found that medial intermediate-layer neurons in the OT/SC showed no response to small moving dark disks but fired vigorously to looming stimuli. In larval zebrafish, there is a subset of RGC axons within the tectum that respond selectively to features of looming stimuli (Temizer et al. 2015). In these animals, tectal ensemble activity encodes the critical image size determining escape latency (Dunn et al. 2016), and thalamotectal inputs convey luminance information required for loom-evoked escapes (Heap et al. 2018).

One important feature of the OT/SC is that the representation of sensory-motor space is topographically organized; therefore, information in the SC is spatially coded in body-centered coordinates (egocentric) (Masullo et al. 2019). This is important for threat detection, because threats might systematically come from specific egocentric positions, such as the upper sensory field for rodents, whose predators almost always approach from above. In agreement, while direct electrical or chemical stimulation of the OT/SC can evoke escape-like responses in a range of vertebrate species (Redgrave et al. 1981, Cools et al. 1984, Sahibzada et al. 1986, Dean et al. 1988, Northmore et al. 1988, Herrero et al. 1998, DesJardin et al. 2013), OT/SC stimulation in rodents only elicits defensive behavior if it is directed to the medial OT/SC, which represents the upper visual field (Dean et al. 1989). More generally, a role for subcortical visual systems, including the OT/SC, in loom-evoked escape responses is supported by the observations that they can still be observed in cortically damaged preparations (Evans et al. 2018) and that evoked escape in most species occurs with extremely short latencies—e.g., as little as 250 ms in mice (Yilmaz & Meister 2013, Evans et al. 2018) and before orienting eye movements in humans (King et al. 1992). An intact OT/SC is also required for most vertebrate animals to display appropriate escape responses, such as swimming, jumping, or running (Blanchard et al. 1981, Ellard & Goodale 1988, King & Comer 1996, Dunn et al. 2016, Evans et al. 2018, Suzuki et al. 2019).

3.2. Escape After Threat Identification

Thus far, we have focused on the neural circuitry responsible for dealing with extreme threat. In such circumstances the survival imperative is to trigger an escape response without further consideration or computation. Such stimuli must gain immediate priority control over all relevant motor systems. However, when the threat is less immediate, significant advantage would be gained by having the nature of the threat identified (e.g., spider or snake). When considering neural circuits for threat identification, it is interesting to note that in mammals, OT/SC layering has decreased, which has been associated with the first mammals being nocturnal (Striedter 1997, Knudsen & Schwarz 2017). The dramatic expansion of the cerebral cortex in later diurnal mammals, including the development of multiple visual cortical regions, suggests that more sophisticated visual competencies have been developed to supplement the low-level sensorimotor escape responses mediated by the OT/SC (Wang & Burkhalter 2013). Thus, the ability of cortical processing to resolve high spatial frequencies, color, texture, and complex movement (Van Essen et al. 1992) likely plays an important role in determining the threat's identity. In addition to the cortex, an evolutionarily basal structure likely to provide essential contributions to threat identification is the thalamus, which has distinct dorsal and ventral regions that increase in size and complexity across the vertebrate taxa. The primordial role of thalamic circuits is to process and distribute sensory input, predominantly through the dorsal areas, which receive sensory inputs directly from the retina (visual), inferior colliculus (auditory), and lemniscal pathways (somatosensory). The main projection targets of the sensory thalamus are the telencephalic pallium and OT/SC (Butler 2008). An early role of the thalamus in escape behavior might, therefore, be to relay nonvisual and additional visual input to the OT/SC to aid in the identification of threats. Interestingly, the thalamus also receives tectal input, which may be important for higher-order processing of threat stimuli,

particularly in later vertebrates through nuclei such as the nucleus rotundus in birds or the pulvinar in mammals (Butler 2008, Acerbo et al. 2012, Zhou et al. 2016). A subthalamic region called zona incerta, which became predominantly GABAergic throughout evolution, also projects directly to the OT/SC and is thus positioned to exert strong control over threat stimulus processing (Butler 2008, Wang et al. 2019).

Identifying the precise nature of the threat allows for optimal strategies for escape to be deployed. However, before such strategic decisions can be taken, the threat stimulus must become the focus of attention. At this point, a fundamental sensory selection problem must be confronted (Redgrave et al. 1999). Animals with multimodal sensory systems can simultaneously represent a vast array of stimuli, any one of which could potentially be allowed to become the focus of attention. Some mechanism must be in place to select based on priority, which at any point in time should become the focus of attention (**Figure 2**).

The refocusing of overt attention is usually mediated via orienting movements of the eyes, head, and body (Mazer 2011). The circuits most frequently associated with orienting to suddenly appearing novel events are connections between the OT/SC and the basal ganglia (Hikosaka et al. 2000). The basal ganglia, which are already present in the lamprey (Grillner & Wallen 1985, Robertson et al. 2014), have been proposed as a generic selection mechanism that can adjudicate within and between competing sensory, cognitive, and motivational representations (Chevalier & Deniau 1990, Redgrave et al. 1999, Grillner et al. 2013). In the present context, a major output projection of the basal ganglia is from the substantia nigra pars reticulata to the intermediate layers of the OT/SC (Redgrave et al. 1992). This inhibitory projection uses GABA as a neurotransmitter and has a high rate of tonic activity (60–80 Hz), thereby keeping targeted neurons in the OT/SC under tight inhibitory control. These neurons give rise to the OT/SC's crossed descending pathway that terminates in the brain stem premotor nuclei and spinal cord (Bickford & Hall 1992). Orienting movements occur shortly after a subpopulation of topographically coded inhibitory output neurons from substantia nigra temporarily pause. This locally disinhibits a specific location within the OT/SC's spatially distributed motor map (Hikosaka et al. 2000), which in turn activates brain stem and spinal circuitry to produce orienting movements to localize the external event. In the event of an unexpected novel stimulus, the most likely circuit to relay this information to the basal ganglia is the projection from the OT/SC to the striatum via the lateral posterior and intralaminar nuclei of the thalamus (Groenewegen & Berendse 1994, Krout et al. 2001, McHaffie et al. 2005). Here they must compete with all other sensory stimuli associated with ongoing events. Intrinsic circuitry of the basal ganglia is designed to resolve the competition in favor of the unexpected event by inhibiting a restricted population of nigrotectal output neurons (Handel & Glimcher 1999), which, as we have seen, evokes appropriate orienting movements. This tecto-basal-ganglia-tecto circuitry (McHaffie et al. 2005) has been highly conserved throughout vertebrate brain evolution (Northcutt 2002, Grillner et al. 2013). In the lamprey, for example, dopamine neurons in the substantia nigra pars compacta project to the OT/SC and mediate salience coding to visual features, including looming stimuli (Pérez-Fernández et al. 2017).

If this analysis is correct, an immediate problem is how physically weak sensory events that signal potential threats can win sensory selection competitions. Frequently, a subtle movement of a bush or a slight snap of a twig is all that signals the presence of a predator. In natural environments, matters of life and death often begin close to sensory thresholds. One possible answer to this problem is to invoke the processes of multisensory integration known to be present in the OT/SC (Stein et al. 2014). Thus, weak visual and auditory signals originating from the same external location are integrated in the OT/SC to provide a supra-additive response. The probability of a multisensory event being detected and selected to become the focus of attention is thereby increased. Orienting movements that bring an event to the focus of attention allow for a more

detailed sensory examination of the nature of the stimulus. For example, in foveate animals, the more sophisticated visual processing provided by multiple cortical visual areas can be brought to bear (Van Essen et al. 1992). Depending on the determined identity of threat stimuli, competing escape strategies could potentially be resolved by the generic selection circuitry of the basal ganglia (Redgrave et al. 1999).

Finally, when innately neutral sensory stimuli signal impending harm, they themselves become a threat and are sufficient to motivate appropriate escape responses. It is likely that projections from sensory structures such as the OT/SC to the amygdala via the thalamus play an essential role in the association of neutral stimuli with unconditioned aversive stimuli to elicit effective escape responses (Davis 1992, Bruce & Neary 1995, Balleine & Killcross 2006).

4. INITIATION OF ESCAPE

Once an immediate threat has been detected or one has become the focus of attention and selected to guide future actions, how are the escape effector circuits activated? We consider first how these circuits integrate sensory information and then mechanisms for modulating their activity.

4.1. Neural Circuits and Mechanisms for Escape Initiation

The key circuits for initiating escape movements in vertebrates are in the brain stem, and these receive direct input from the OT/SC (Redgrave et al. 1987, May 2006). From cyclostomes to amphibians and teleost fish, the key circuit elements for escape initiation are the Mauthner cells (M cells), a bilateral pair of giant reticulospinal (RS) neurons that command the fast C-start escapes. The physiology of M cells and their role in escape behavior have been reviewed extensively (Eaton et al. 2001, Korn & Faber 2005) and are not covered here in detail. The key aspect we emphasize is that OT/SC neurons project directly to M cells and can cause depolarizations strong enough to drive escape behavior (Dunn et al. 2016). In larval zebrafish, for example, whole-cell recordings have shown that looming stimuli produce larger and longer-lasting synaptic currents in M cells than light flashes (Yao et al. 2016). The visually evoked synaptic input is carried by tectal projections to the M cell, which also activate dopaminergic neurons that control glycinergic inhibition to M cells. Dopamine neurons respond more strongly to flashing stimuli, leading to increased M cell inhibition. These opposing mechanisms provide an elegant means for M cells to respond preferentially to threatening visual stimuli signaled by the tectum.

In mammals, escape is commanded by the dorsal periaqueductal gray (dPAG) (Bandler et al. 1985; Bandler & Carrive 1988; Fanselow et al. 1995; De Oca et al. 1998; Brandão et al. 1999, 2005; Assareh et al. 2016; Deng et al. 2016). Using a mouse model, Evans et al. (2018) showed that excitatory neurons in the dPAG receive excitatory monosynaptic inputs from the dorsomedial OT/SC, which are weak and unreliable and therefore impose a threshold for the OT/SC to activate dPAG neurons (Evans et al. 2018). Only threatening stimuli that are salient enough or presented repeatedly cause enough activation of the deep OT/SC layers to overcome this synaptic threshold mechanism and generate sufficient depolarization to drive dPAG neurons. In agreement with this model, calcium imaging of neural activity in dPAG excitatory neurons reported activation only during threat-evoked escape, whereas activity of OT/SC neurons reflected the threat stimulus strength.

These two examples demonstrate the existence of specialized mechanisms at the level of circuit elements and synapses that regulate the flow of information between the OT/SC and escape initiation centers. Functionally, they could ensure that the dPAG and downstream circuits are activated only when sensory stimuli are immediately threatening, as is the case with rapidly expanding

loom. These mechanisms link threat stimuli directly to locomotor escape actions, and therefore provide a means for innately bypassing action-selection mechanisms that consider the urgency of escape relative to the biological saliency of other competing stimuli and motivations. However, the precise nature of the sensory processing that detects imminent looming stimuli and how such circuitry gains preferential access to escape-related motor circuitry remain to be determined.

In the case of rodents, looming stimuli from the upper visual field activate the dorsomedial OT/SC. In these species, this region may contain loom-detecting circuits that are sufficiently powerful to cause the weak SC-dPAG projection to trip the dPAG's threshold mechanism (Evans et al. 2018). However, both freezing and locomotor escape can be elicited by stimulation of the OT/SC (Redgrave et al. 1981, Sahibzada et al. 1986, Herrero et al. 1998, Bittencourt et al. 2005, DesJardin et al. 2013, Shang et al. 2018). It is likely that separate pathways from the OT/SC are responsible for mediating the two primary responses to threat. In this regard, electrical stimulation studies using rodents are instructive (Sahibzada et al. 1986). Here, when a comparatively small population of neurons in the medial OT/SC (where the upper visual field is represented) was activated by low stimulating currents, animals froze. However, when stimulating currents were increased, a much larger area was stimulated, and explosive escape was evoked. These experimentally induced behavioral responses are reminiscent of the distance-defense hierarchy discussed above (Blanchard & Blanchard 1988). It is interesting to speculate that the internal circuitry of the OT/SC ensures that spatially restricted regional activations (small stimuli) preferentially activate neurons that engage freezing-promoting pathways, such as the OT/SC projection to the amygdala via the lateral posterior thalamus. Selective activation of these neurons in mice has been shown to cause animals to freeze (Wei et al. 2015, Shang et al. 2018), though it is also possible that a more direct route between the OT/SC and ventrolateral PAG (vPAG), within the midbrain, contributes to defensive freezing. However, given that in natural circumstances freezing frequently precedes locomotor escape, there must be mechanisms that accumulate sensory and motivational salience and, at some point in time, typically at the FID, cause a switch from freezing to a locomotor escape response.

In addition to visual input from the tectum, brain stem escape-initiation circuits also receive sensory information from other modalities. M cells in both lampreys and teleost fish are directly activated by acoustic and mechanosensory input carried by spinal afferents and cranial nerves (Korn & Faber 2005), which seem to be very efficiently converted into action potentials. Thus, evoking a single action potential in larval zebrafish somatosensory neurons is sufficient to elicit M cell-dependent C-start responses (Douglass et al. 2008). Moreover, glutamatergic inputs of the same modality in lamprey cause sustained depolarizations in RS neurons by engaging favorable intrinsic excitability mechanisms (Antri et al. 2009). The rodent dorsolateral PAG has a similar organization, with sensory input conveyed via the thalamus, inferior colliculi, and sensory cortices (Marchand & Hagino 1983, Vianna & Brandão 2003, Benarroch 2012).

Given that multisensory information is also integrated in the OT/SC (Stein et al. 2014), and that in most species the OT/SC circuit seems to be necessary for escape, why do escape effector circuits receive sensory information from so many additional sources? One possibility is that different afferents for the same sensory modality carry functionally different types of information. For example, a critical consequence of routing sensory inputs through the OT/SC is that they become associated with a spatial dimension, which as discussed above, is important for the sensory selection process and subsequently guiding the trajectory of escape movements (see below). Thus, inputs that reach the dPAG via the OT/SC in one sense have already been selected by virtue of their location in space. For example, the ecological niche of rodents has ensured that a looming stimulus is only threatening if it expands in the upper visual field (Yilmaz & Meister 2013). Additional descending input from higher structures that target different regions of the PAG could be used to modulate the OT/SC-dPAG circuit. An example would be a threatening sound that

activates the OT/SC and would signal the presence of a threat that needs to be dealt with through a variety of possible defensive actions (Evans et al. 2018). Parallel routing of the same stimulus directly to the dPAG (via the inferior colliculus, for example) (Xiong et al. 2015) could convey an additional signal to cause a locomotor escape action to be selected directly in favor of alternative defensive actions. This model places emphasis in the computation of coincident input arising from different streams, and future work on the integrative properties of dPAG neurons will be required to test such ideas.

4.2. Modulation of Escape Initiation

Less pressing threats, i.e., those not necessarily associated with rapidly expanding loom, do not always elicit immediate escape behavior in a deterministic and stereotypical manner. The link between sensory evidence of threat and escape initiation can be modulated by several variables (Cooper & Blumstein 2015). Such flexibility allows animals to change the FID in an adaptive manner to satisfy competing needs and to incorporate experience into escape decisions. As discussed above, a key means of achieving this flexibility is through the competition for attention in the OT/SC–basal ganglia loops (Redgrave et al. 1999), which can be used to prioritize competing stimuli and motivations. For example, an input to the basal ganglia signaling extreme hunger would be expected to raise the threshold for foraging to be interrupted by threat. In addition, the circuits that command the initiation of escape receive a vast array of information from a variety of different sources. This anatomical architecture could provide for sophisticated patterns of integration that could contribute to flexibility in escape behavior or, alternatively, reflect that escape is a possible output response that can be triggered by a variety of different functional systems. These possibilities are not mutually exclusive.

A further important system that projects to brain stem escape centers is the hypothalamus, which is a hub for regulating motivated behaviors (Hahn et al. 2019). In mice, multiple hypothalamic nuclei that integrate information about aversive and stress states modulate active defensive behaviors via glutamatergic projections to the PAG, such as the paraventricular hypothalamus (Mangieri et al. 2019) and the lateral hypothalamus (Li et al. 2018). Also, the anterior hypothalamic nuclei, ventromedial hypothalamus, and dorsal premammillary nucleus constitute a hypothalamic defensive circuit that projects directly to the dPAG (Motta et al. 2009, Gross & Canteras 2012, Silva et al. 2013, Wang et al. 2015). These nuclei are predominantly involved in processing olfactory predator cues, which reach them via the medial amygdala. Consequently, they are involved mainly in the initiation of defensive behaviors toward the top of the defensive hierarchy (Blanchard et al. 2009). That is, smell does not necessarily indicate that a predator is dangerously close, and the best strategy is often to cautiously explore then avoid the source of the odor (Blanchard et al. 2009). However, predator odors should modulate the likelihood of escape, which could be mediated via projections of the hypothalamic nuclei to the dPAG. Evidence that hypothalamic-PAG inputs are modulatory and do not directly drive escape comes from the optogenetic stimulation of the ventromedial hypothalamus. Such stimulation can evoke active defensive behaviors, but with prolonged latencies of several seconds (Kunwar et al. 2015, Wang et al. 2015).

Information about hunger states, which can powerfully modulate escape responses (Barker & Baier 2015, Burnett et al. 2016, Filosa et al. 2016, Jikomes et al. 2016), are also encoded in hypothalamic nuclei (Sternson et al. 2013, Betley et al. 2015). For example, AGRP⁺ neurons in the arcuate nucleus project directly to the PAG (Atasoy et al. 2012), and their activation can inhibit defensive behavior (Burnett et al. 2016). In fish, M cells also receive direct hypothalamic input, which has been shown to enhance escape behavior from auditory stimuli (Mu et al. 2012). A tentative summary view of the role of hypothalamic systems in escape is that they act to change the

threshold for escape initiation, presumably by providing additional synaptic input that is integrated with threat-related sensory signals at different levels within the nervous system. A contrary view can be advanced from a recent study in larval zebrafish that identified multiple hypothalamic populations that are engaged during fast avoidance. These neurons were shown to project directly to spinal-projecting premotor neurons that regulate escape (Lovett-Barron et al. 2019). In addition to releasing neuropeptides and neuromodulators, these neurons also release glutamate and are recruited in a fast timescale. This study suggests, at least in larval fish, that the hypothalamus could have a role in driving fast active-avoidance behaviors, in addition to the better-established slower modulatory effects.

Modulation of escape initiation can also be a substrate for experience-dependent changes to escape behavior. C-start escapes can be both habituated and enhanced through repeated stimulus presentations, with the underlying mechanisms including calcium-dependent long-term potentiation of the inhibitory or excitatory synapses onto M cells (Roberts et al. 2016). In mammals, the amygdala plays a central role in aversive conditioning. This is where a neutral conditioned stimulus acquires the ability to evoke a conditioned defensive response after having been paired with unconditioned aversion. This process is perhaps best understood in the context of freezing behavior, a topic that has been reviewed extensively (Paré et al. 2004, Balleine & Killcross 2006, Johansen et al. 2011, McNally et al. 2011, Tovote et al. 2015). While comparatively little is known about plasticity within the mechanisms of locomotor escape, the amygdala in mammals has been shown to mediate active and passive conditioned defensive response through different neuron populations in the central amygdala (CeA) (Fadok et al. 2017). Long-range inhibitory neurons project from the CeA to the vIPAG. This could provide a possible mechanism for regulating the expression of escape by shifting the excitation-inhibition balance between the vIPAG and dPAG through local inhibitory connections between these two PAG columns (Tovote et al. 2016). A further PAG-projecting circuit for incorporating learning into the control of escape is the lateral habenula, which is known to participate in learning aversive outcomes and has been shown to mediate escape behavior in mice (Lecca et al. 2017). Finally, brain stem escape circuits in most vertebrate species express receptors for a large range of neuromodulators, such as serotonin and dopamine. These can regulate the excitability of specific circuit elements. For example, serotonin inhibits goldfish M cells by increasing synaptic inhibition onto these neurons (Mintz et al. 1989), and dorsal raphe serotonin neurons in mice facilitate escape under high threat conditions (Seo et al. 2019).

In summary, it is clear that while the OT/SC and the PAG represent a conduit through which the initiation of locomotor escape is triggered, there are numerous mechanisms throughout the neuraxis that enable the thresholds for escape actions to be triggered by some or adjusted and modified by others.

5. ESCAPE EXECUTION

In this section, we consider neural circuits and mechanisms responsible for the execution of fast locomotive escape movements. The principle issue to be addressed here is the control of locomotor escape so that distance from the attacker is quickly increased, obstacles avoided, and safety reached.

5.1. Implementation of Escape Actions

A defining quality of escape actions is that they are fast and sometimes require motor coordination programs that are different from the ones used during exploratory behavior, to drive different

locomotion gaits, for example. These different motor programs are often controlled by specialized neural circuits. In mammals, a key area for locomotor control is the mesencephalic locomotor region (MLR), which comprises a series of nuclei that, in mammals, include the cuneiform (CnF) and the pedunculopontine nucleus (PPN) (Ferreira-Pinto et al. 2018). Neurons in the MLR provide the excitatory drive for locomotion via glutamatergic RS projections to central pattern generators in the spinal cord (Ryczko & Dubuc 2013). Different MLR nuclei specialize in either slow or fast locomotion (Grillner et al. 1997), and the CnF appears to have a unique role for supporting high-speed locomotion, in contrast with its neighboring MLR nucleus, the PPN (Jordan 1998). Thus, experimental stimulation of the mammalian CnF has been shown to elicit not only high-speed locomotion but also escape-like explosive running and jumping (Depoortere et al. 1990). The MLR receives direct afferent inputs from the dPAG, and during escape, the activity of excitatory neurons in the dPAG can control locomotion speed (Evans et al. 2018), most likely through CnF projections (Zemlan & Behbehani 1984, Ryczko & Dubuc 2013, Ferreira-Pinto et al. 2018). Interestingly, the OT/SC also projects directly to the MLR (Redgrave et al. 1987, Mitchell et al. 1988, Shehab et al. 1995), indicating that sensory stimuli detected by the OT/SC can simultaneously activate the dPAG and MLR. Additional studies are required to understand the necessity for these parallel pathways in controlling escape behavior. In teleost fish, the M cell drives fast, vigorous escapes through action potentials propagated at high conduction velocities to monosynaptic connections onto motor neurons. Pufferfish species that do not have M cells escape with longer latencies and less vigor (Greenwood et al. 2010), and the escapes of zebrafish with M cell lesions are also slower (Liu & Fetcho 1999, Kohashi & Oda 2008). Slower escapes are mediated by additional RSNs (Gahtan et al. 2002, Liao & Fetcho 2008), which, in intact animals, can be recruited together with M cells to control the amplitude of the C-start bend (Shimazaki et al. 2019), a process coordinated by specialized hindbrain interneurons (Bhatt et al. 2007).

One important aspect in executing escape actions is to ensure that the circuits that drive the desired movements are activated while the circuits that elicit competing incompatible movements are suppressed. For example, in bilaterally symmetric animals, a key choice is whether to escape left or right. In fish that perform C-start escapes, the direction of the turn is determined by which M cell is activated. M cells receive ipsilateral sensory input and project to contralateral motor neurons; thus, activating one M cell causes the fish to turn away from the stimulus (Korn & Faber 2005). Escape in a straight line resulting from simultaneous activation of the two M cells is prevented by a network of reciprocal and feed-forward interneurons, which implement a winner-takes-all mechanism (Lacoste et al. 2015, Koyama et al. 2016). After one M cell is recruited, additional mechanisms prevent repetitive activation of downstream cranial relay neurons (CRNs), which would lead to the initiation of multiple C-start bouts and prevent the fish from swimming away from the threat (Gelman et al. 2011). These mechanisms include short-term synaptic depression at the M cell–CRN synaptic connection due to a decrease in release probability, which decreases synaptic strength during repeated M cell action potentials. In mammals, steering during locomotor escape is largely unstudied, although after having turned away from the threat, the computational imperative is to not bump into obstructions or fall into holes or off edges. The lateral paragigantocellular nucleus (LPGi) in the brain stem plays an important role during forward exploratory locomotion (Capelli et al. 2017), and it is possible that it could be recruited with more vigor for the purposes of escape. This is a genuine possibility, as the LPGi receives extensive bilateral input from the escape networks in the midbrain, including the OT/SC (Kaneshige et al. 2018), and is thus well positioned to control left-right movements during escape (Cregg et al. 2019).

An additional challenge for executing successful escape actions is to sustain them until safety is reached. In situations where the threat remains within the animal's sensory field, the OT/SC circuit could in principle maintain attention to the stimulus and continuously drive escape through

activation of downstream brain stem circuits. A circuit that is likely to be important in this process is the nucleus isthmi and its mammalian homolog, the parabigeminal nucleus (NI/PBG) (Knudsen & Schwarz 2017). Cholinergic NI/PBN neurons form a topographically aligned positive feedback loop with the ipsilateral OT/SC that amplifies stimulus responses (Knudsen & Schwarz 2017). This property could be used to sustain selective attention to the threat. A similar mechanism has recently been shown to be important for sustaining hunting responses in larval zebrafish (Henriques et al. 2019), and inactivation of the PBN reduces escape behavior in mice (Shang et al. 2018).

However, the mechanisms for sustaining escape when the threat stimulus can no longer be detected are much more mysterious. One possibility is that positive feedback loops within the midbrain, such as the OT/SC-NI/PBN or OT/SC-CnF, have internal reverberation dynamics that allow enough self-sustaining activity to keep the animal locomoting for some distance, after which a further sensory trigger would be needed. Alternatively, the dynamics of the system could be such that they will self-sustain until actively terminated by a stop signal, such as reaching shelter. In addition to reverberations implemented at the circuit level, biophysical mechanisms could also contribute to this process. For example, RS cells in the lamprey have intrinsic membrane properties that transform a short-duration sensory input into a long-lasting excitatory command that activates the spinal locomotor networks (Antri et al. 2009). Future studies are needed to address how escape actions are sustained when turning and running cause the initiating threat to no longer to be represented in vision. In this regard, it might be helpful to consider the concept of the emotion, fear. This is a motivational concept frequently used to explain how defensive behavior might be invoked and sustained in the absence of the original triggering threat. Given that the amygdala is a structure regularly associated with this state (Paré et al. 2004, Balleine & Killcross 2006, Johansen et al. 2011, Tovote et al. 2015), it is perhaps to be expected that projections from the cortical and subcortical sensory structures responsible for detecting threat provide prolific afferent connections to the amygdala (Herzog & Van Hoesen 1976, Mehler 1980, Swanson 2006), which is in turn directly connected to the PAG and can therefore promote escape (Tovote et al. 2015, Fadok et al. 2017).

5.2. Navigation During Escape

After the FID is reached and escape actions are triggered, the final problem to solve is where to go and how to get to a place of safety. Animals across the vertebrate phyla employ different escape strategies, which depend not only on the species but also on the local environment in which they find themselves (Cooper & Blumstein 2015). In open spaces, for example, a good solution is to move away from the threat source, which can be implemented in a stereotyped manner by relatively simple neural circuits, e.g., C-start escapes and M cells. But during the sustained phase of escape that follows the fast escape onset, animals might have to deal with challenges such as avoiding obstacles before reaching safety, and thus a prolonged execution of escape movements should be flexible. While systems such as mechanosensory lateral line input to M cells can already direct escape away from walls during the initiation phase (Mirjany et al. 2011), sustained escape actions will benefit from using additional information from the environment. This process will likely benefit from computations to extract variables such as distance, depth, or any other sensory metric that facilitates reaching safety. These computations are likely to be implemented in cortical (Beltramo & Scanziani 2019) and subcortical circuits (Boehnke & Munoz 2008) that are sensitive to the luminance changes associated with distortions in optic flow patterns during locomotion. These systems could provide the necessary controlling input to the brain stem MLR (Redgrave et al. 1987) to provide the sophisticated guidance necessary to avoid objects or holes during rapid locomotor escape.

When the goal of escape is a refuge, the animal needs to navigate to its location as fast as possible. Lizards and mammals use this strategy often (Cooper & Blumstein 2015), and in rodents, the initial escape action is to orient in the direction of a known shelter location, even when the shelter cannot be seen (Vale et al. 2017). This suggests that escape effector circuits can access information from spatial memory systems to instruct movements toward appropriate locations in space. A key question is whether escape relies on some primitive spatial navigation system, or whether it uses the standard hippocampal formation-dependent circuits (O’Keefe & Nadel 1978). From a behavioral point of view, escape can be implemented simply by using path integration to continuously update a homing vector (Etienne & Jeffery 2004). This requires integration of self-motion cues, which could in principle be done entirely within the brain stem by continuously feeding vestibular and proprioceptive input directly into escape execution circuits to instruct movements in the correct direction. Such a mechanism would seem optimal for fast execution of locomotive actions along the homing vector. However, mechanisms such as path integration rapidly accumulate error over time (Mittelstaedt & Mittelstaedt 1980), and alternatives are required for making the system robust so that shelter is reached, even after long periods of exploratory behavior. These could be based on the use of landmarks (Maaswinkel & Whishaw 1999) or even on a cognitive map of the spatial environment (O’Keefe & Nadel 1978). The latter would incur higher computational costs for deriving the appropriate motor commands, such as transforming allocentric into egocentric coordinates (Burgess 2006), but it would achieve the most flexibility. For example, it would allow animals to compute detours and adapt to abrupt changes in the spatial environment in a more efficient and adaptive way than relying on sensory systems alone during escape. However, currently very little is known about the navigational strategies used by animals while escaping and how they can be modified by circumstance. Obtaining this information will lead to a better understanding of how spatial representations such as head-direction, grid, or place cells might contribute to reaching a shelter as the culmination of successful escape.

6. CONCLUDING REMARKS

The vertebrate brain has evolutionarily ancient neural circuits that implement the basic building blocks of escape behavior. Immediate escape actions can be relatively simple, but extended escape often relies on processes such as predicting the motion of a predator or performing memory-based navigation. Such computational abilities are afforded by the expansion of the cerebral cortex associated with the evolution of mammals, which provided for a more sophisticated, flexible, and adaptive interface to the basic low-level escape system. While theoretical work has extensively modelled escape behavior and formalized its main processes, precise mechanistic descriptions of how they are implemented are largely missing. In addition, the neural mechanisms of escape have so far only been studied in a handful of animal species. Future comparative mechanistic studies across the vertebrate phyla would be important for testing the generality of algorithmic principles of the escape processes and determining whether there are shared designs of implementation between species. While this has traditionally been a challenging goal, new genetic, anatomical, and neural recording techniques should lower the barrier for investigating new model species. Such new techniques, grounded in solid theoretical foundations, should also facilitate obtaining a complete mechanistic understanding of escape behavior in traditional model species such as larval zebrafish and mice. Escape behavior at its simplest is sufficiently tractable to make this a realistic goal. The additional layers of complexity that escape offers would then provide an entry point for understanding general mechanisms of advanced cognitive processes and how brains generate natural adaptive behaviors.

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