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Information integration for motor generation

Chun-feng Shang[1,4], Yu-fan Wang[1,2,4] and Jiu-lin Du[1,2,3]

Animals sense the world and choose the ecological niches suitable for their survival and reproduction. As the environment keeps changing, the brain does not simply receive all streams of information and direct each of them to a corresponding motor output. Instead, highly relevant sensory information is extracted from various sensory sources and modalities, integrated through multiple steps of computation, and updated adaptively according to the assessment of cost and consequence, to generate appropriate motor outputs. Previously, these aspects were studied in different brain areas and animal species. In this review, we provide an overview of how information is integrated to generate appropriate motor outputs and highlight recent progresses in the circuitry mechanisms underlying motor generation.

Addresses
[1] Institute of Neuroscience, State Key Laboratory of Neuroscience, Center for Excellence in Brain Science and Intelligence Technology, Chinese Academy of Sciences, 320 Yue-Yang Road, Shanghai 200031, China
[2] University of Chinese Academy of Sciences, 19A Yu-Quan Road, Beijing 100049, China
[3] School of Life Science and Technology, ShanghaiTech University, 319 Yue-Yang Road, Shanghai 200031, China

Corresponding authors:
Shang, Chun-feng (cfshang@ion.ac.cn),
Du, Jiu-lin (forestdu@ion.ac.cn)
[4] Equal contribution.

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Introduction

In the ever-changing wild, animals need to live with abundant ambient changes and behave appropriately for survival and reproduction. They need to avoid predators, pursue food, choose mates, and find viable habitats. In a classical stimulus-response model, an animal, for example, a toad, receives an external stimulation through a specific sensory pathway. The signal is assessed for its behavioral relevance and relayed to the premotor neurons to trigger a stereotyped motor output [1]. However, sensory signals in the natural environment are usually elusive and embedded in a complex background [2], requiring a predator to gather all relevant cues of the prey, like its edibility, position and moving direction, using vision, audition or other sensation to maximize the information necessary for a successful capture. Furthermore, the predator is more likely to launch the capture when it is hungry, and when the environment is safe to itself. It may stop when any of the motor consequence deviate from its expectation. Thus, the motor output is generated based on the integration of various information and updated continuously. The underlying neural circuit is thus widely distributed beyond a single premotor area. Here, we draw an overview of the functioning of such a global circuit based on several recent works.

A sensory signal is processed through parallel pathways

A sensory signal may contain multiple features which are processed in different pathways [3–5]. Separately extracted information about these features can be exploited differently to generate the appropriate motor output. In larval zebrafish, the Mauthner cells are a pair of single neurons whose activation leads to escape [6]. Their special morphology and molecular composition guarantee fast and effective escape. However, as escape costs a large amount of energy, Mauthner activation should be evoked only upon real danger. In fact, C-startle escape can be evoked by an expanding dark disc, corresponding to an approaching predator, but not by a non-threatening visual stimulus, such as a flash. A dopaminergic-inhibitory circuit has been found to discriminate these two types of stimulation [7••]. The hypothalamic dopaminergic neurons are selectively activated by flash and suppress the tecto-Mauthner projection through the activation of a group of hindbrain glycinergic interneurons [8,9]. As a result, although the Mauthner cell was activated by both types of visual stimuli, its activation was abolished shortly after the onset of the flash but not after that of the expanding dark stimulation. Thus the Mauthner cell integrates the flash information separately extracted by the optic tectum and the hypothalamic dopaminergic neurons to control escape initiation. Besides, it has also been shown that multiple visual pathways may converge on the same sensorimotor output [10]. Such a bi-pathway strategy may enable the animal to flexibly weight different aspects of the visual signal according to their significance so that an appropriate motor output can be generated.

Cross-modal sensory signals are integrated through different mechanisms

While a single signal may contain multiple types of information, the same information, such as object identity or location, can also be coded in signals of different sensory modalities which could be integrated together [11,12••]. The superior colliculus (SC) receives both visual and auditory inputs and sends out motor output. In cat SC, coincident visual and auditory stimuli activate the same neurons and their responses are integrated supralinearly, making the output stronger and more reliable [13]. Similarly, neurons in the monkey dorsal medial superior temporal area integrates visual and vestibular inputs for an optimal estimation of the heading direction [14].

Besides such an integration of congruent signals of different modalities, object detection may also benefit from reduced background noise. In larval zebrafish, the Mauthner cell receives auditory inputs from the VIII cranial nerve. The success rate of this auditory innervation, and the resulted escape, were found to be enhanced by a preceding visual flash [15]. Upon flash stimulation, the spontaneous spiking activity of the auditory nerve was suppressed for around *2* s and the transmission efficacy of the audio-Mauthner synapse was enhanced. Thus, auditory inputs coming in this time window are facilitated, resulting in higher postsynaptic and behavior responses. Interestingly, such a visual modulation of auditory response is also mediated by the hypothalamic dopaminergic neurons.

Signals arising from the same source may vary their strengths coherently and such coherence may provide a useful cue for multisensory integration. It has recently been found on ferrets that time-varying luminance change can boost the auditory cortical response to coherently varying auditory signal but not the incoherent one. Thus in an auditory scene comprising mixed streams, the visual-coherent stream can be selectively boosted, leading to an improved discrimination from the other streams [16].

Internal and external information streams converge

Signals of internal state, such as hunger, thirst and electrolyte imbalance, represent the requirements of the animal. They need to be integrated with the external sensory signals to elicit homeostatic behaviors and keep a stable internal environment. Hypothalamus is known as the center to process internal signals and control such behaviors, based on studies using lesion, optogenetics, and *in vitro* electrophysiology [17–23]. However, it is less known how the control is exerted until recent works monitoring its neural activity during behavior. Recent progress in the regulation of mouse feeding behavior has shown that both internal and external information streams can converge on the same hypothalamic neurons. Feeding behavior was thought to be controlled cooperatively by the agouti-related protein-expressing (AgRP) neurons and proopiomelanocortin-expressing (POMC) neurons in the arcuate nucleus of hypothalamus. These two populations of neurons are oppositely regulated by hormonal signals of nutritional state [17–21], and elicit and inhibit food-seeking, respectively, upon artificial activation [22,23]. Cell-type specific activity monitoring, through both optical imaging and electrophysiology recording, have found that their activities are also regulated by external sensory signal of food [24–26]. The activity of the AgRP neurons gradually increased over the development of energy deficit and was rapidly inhibited by food presentation, even before a single bite. In contrast, POMC neurons were activated by food presentation. Taken together, these neurons sense both slow internal signals and fast external signals relevant to feeding behavior [27,28•]. Interestingly, internal signals may also be transmitted to the brain fast. Direct synaptic connection was found between the gut secretory cells and the gut-innervating vagal sensory neurons [29,30••], resembling the bi-pathway processing of the sensory information of flash mentioned above [7••].

Proprioception provides another type of internal information, which is about the motor state of the animal itself. The view direction is essential for the interpretation of the received visual signals and for the generation of visuomotor behavior. In mapping the motor output of different portions of the optic tectum of larval zebrafish, it was recently found that the activation of the same portion, like the anterior part of the right tectum, can evoke either left or right swim of the fish, depending on whether the fish was viewing left or right [31•]. Interestingly, such an integration was suggested to take place in brain areas downstream to the tectum, while the danger-relevant and prey-relevant visual information was segregated in the tectum and maintained in the tectofugal tracts, indicating that the visuomotor transformation involves multiple stages rather than a single center.

The benefit and the cost are balanced dynamically

Besides various signals about the current situation, the animal also needs to infer the possible consequence of the motor output to balance the benefit with the cost [32]. Furthermore, such a balance may be dynamic so the animal may shift to more impulsive motor outputs under urgent or stressed context [33]. The prefrontal cortex (PFC) is a component of the frontostriatal system, which encodes various costs, such as effort, delay, and possible danger [34], and serves as a candidate target for the chronic stress. Studies on drug abuse suggested the shift is probably mediated by monoaminergic connections [35]. Optogenetic activation of the serotoninergic neurons in the dorsal raphe (DRN) enhanced the choice of rational behavior strategy and suppressed the impulsive ones, and kept the subject rat waiting longer upon omission of expected reward [36]. In contrast, experiments on patients suffering from Parkinson's disease showed that dopaminergic medication increased the choice of impulsive strategy [37]. Both serotoninergic and dopaminergic innervation are found in the PFC. Upon stressful stimulation, dopaminergic and noradrenergic activation weakens synaptic efficacy in the PFC and results in persistent synaptic changes under chronic stress control [38]. In consequence, the PFC gradually loses its control of subcortical regions, namely amygdala and sensorimotor striatum [33], and the sensory information will be routed to stereotyped motor outputs. Correspondingly the animal shifts to impulsive behaviors to avoid costs.

Recently the circuitry mechanism underlying the weakened frontostriatal control was explored on rat, and the feed-forward inhibition mediated by the striatal fast-spiking interneurons (FSI) was found to be involved [39••]. While both the FSI and the striatal projecting neurons (SPN) receive PFC innervation, FSI responds with a shorter latency than SPN and inhibit the latter in turn. After receiving chronic stress including immobilization and foot shock, the functional connection between the striatum-projecting PFC neurons and FSI was decreased while that between the striatum-projecting PFC neurons and SPN was increased. Consistently artificial manipulation of the FSI activity led to habit-relying behavior similar to that after chronic stress. Such a delicate circuit suggests that the shift from rational motor strategy to cost-avoiding impulsive strategy may serve as an adaptation to the ever-changing context.

Integration of motor-related signals

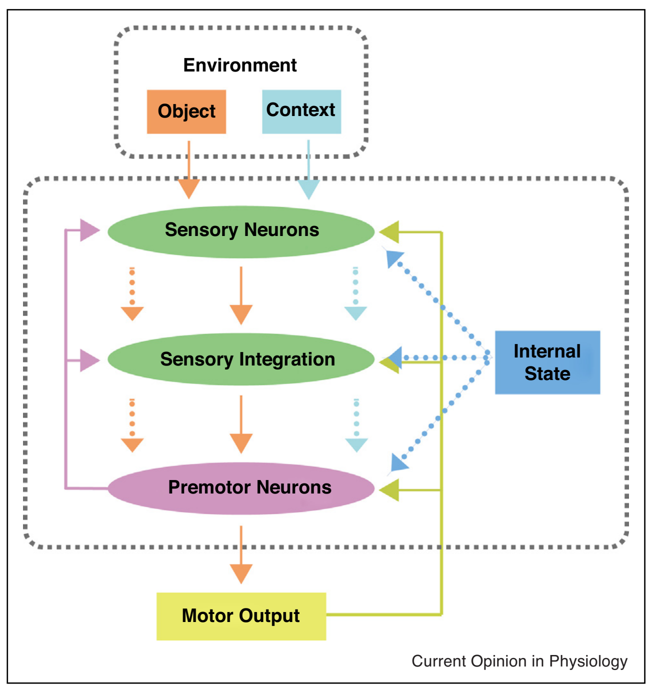
While the forthcoming consequence is inferred for generating motor output, the real consequence modulates subsequent motor generation in turn. Animals integrate the motor consequences with upcoming sensory signals. The integration could often be accounted in a Bayesian model [e.g. Ref. 40]. Recently the neural circuit underlying such Bayesian integration was explored in the monkey frontal eye field (FEF) during planning and executing smooth eye movement [41•]. During consecutive trials of smooth eye pursuit, the target speed was kept constant except for some odd trials. Information about the previous trial was found to affect the current performance in a Bayesian model, with a larger influence in odd trials using less reliable sensory stimulation. Similar tuning was found on the FEF neuronal activity. During preparatory phase, the firing rate of the FEF neurons was modulated by eye speed in the previous trial, representing *a priori* information. The modulation was stronger for the less reliable target, but weaker for the more reliable one. All of these conform to the Bayesian model of integration of information about prior trial and that about current sensory stimulation, and encourages future exploration of the underlying circuitry mechanism, like the brain area origin of the *a priori* information and its cellular and synaptic identity.

The locomotion state can modulate motor generation as early as in the primary sensory cortex. It was found to increase the firing rate of mouse visual cortical neurons without affecting their sensory tuning, suggesting a switch of brain state. This is probably mediated by a neuromodulatory pathway [42,43]. Recently, it was further shown that locomotion increased the mutual information between visual cortical activity and visual stimulation, and improved the discrimination between different visual stimuli. Lomocomotion state also permitted the visual response to be enhanced after prolonged viewing experience [44,45]. All these results suggest that the visual cortex performs better in processing abundant sensory signals during locomotion than during rest.

Perspective

To survive in the wild requires exploiting all accessible signals and generating appropriate motor outputs. The above overview suggests this process involved a widely distributed network (Figure 1). The network contains local circuits which can extract different information coded in the same signal, integrate information about the same object but from different sources, or transform the input activity with dynamic gain. The neural transmission in these circuits can be either fast (glutamatergic, catecholaminergic) or slow (catecholaminergic, peptidergic,

Figure 1



Sensory signals about an interested object, such as prey, predator, or a possible mate, are processed by separate pathways [7••,50•]. Contextual information from the environment, such as danger, and that about internal state, like starvation, stress and focus of attention, is integrated with the sensory information at different stages, in the form of either gain control or well-tuned innervation. Furthermore, information about motor outputs is continuously collected and integrated. Solid lines: sensory information processing and feedback using classic neurotransmitters. Dash lines: contextual modulation using neuromodulators.

hormonal). As these circuits work simultaneously, future exploration of motor generation should be designed considering more about the neural computation and brain areas out of focus. For example, the examination of the significance of visual and auditory information should take into account that the integration may take place in several brain areas with different weights, and that the behavior reports depends on the success rate of previous trials and the difficulty level. The significance of eye movement on vision should also be examined considering both the efference copy and feedback from vision and proprioception. The phylogeny of the examined animal species and brain areas also helps the interpretation of the circuitry mechanism. With such design, the results will be easily compared and integrated across behavior paradigms, brain areas and animal species.

Besides, technical improvements are required to dissect the circuitry mechanism underlying motor generation, including monitoring the neuronal activities globally [46•], recording different activation modes simultaneously [47], and perturbing the circuit functioning precisely [47–49].

Conflict of interest statement

Nothing declared.

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