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Zona Incerta: An Integrative Node for Global Behavioral Modulation

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Abstract

Zona incerta (ZI) is a largely inhibitory subthalamic region connecting with many brain areas. Early studies have suggested involvement of ZI in various functions such as visceral activities, arousal, attention and locomotion, but the specific roles of different ZI subdomains or cell-types have not been well examined. Recent studies combining optogenetics, behavioral assays, neural tracing and neural activity recording reveal novel functional roles of ZI depending on specific input-output connectivity patterns. Here, we review these studies and summarize functions of ZI into four categories: sensory integration, behavioral output control, motivational drive and neural plasticity. In view of these new findings, we propose that ZI serves as an integrative node for global modulation of behaviors and physiological states.

Keywords

subthalamic region; inhibitory nucleus; processing node; animal behavior; physiological state; motivation; neural plasticity; input/output pattern; gain modulation

ZI is positioned as an integrative node

The brain is a complicated wiring system which requires integrative nodes for efficient information processing. The zona incerta (ZI) is a subthalamic region with extensive connections throughout the brain[1]. Recent studies have demonstrated diverse functional roles of ZI in processing sensory information, regulating behaviors, conveying motivational states, and participating in neural plasticity[2]–[9]. Together, the structural and functional findings indicate a high likelihood of ZI functioning as one of the brain's integrative nodes.

ZI is a largely inhibitory nucleus comprised of heterogeneous groups of cells. It is known to express multiple molecular markers such as parvalbumin (PV), tyrosine hydroxylase, somatostatin, calbindin and glutamate[10], [11]. In rodents, ZI can be loosely divided into

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four sectors based on cytoarchitecture[1]: rostral, dorsal, ventral, and caudal. However, it might be more practical to divide ZI into subdomains based on input-output connectivity to determine potential functions of this structure, as it forms extensive connections (often reciprocal) with diverse brain regions, such as the cortex, thalamus, hypothalamus, basal forebrain and brainstem[1], [12]–[14].

Previous research has proposed ZI's involvements in visceral activities, arousal, shifts of attention, as well as posture and locomotion[15]–[19]. Clinically, ZI has also been implicated in alleviating essential tremor in treatments of Parkinson's disease using deep brain stimulation (DBS)[20], [21]. These foundational studies provided important clues for potential multi-functionality of ZI, yet they lacked precise dissections of contributions of specific ZI neuronal subpopulations. With the latest advances in neural tracing and activity manipulation techniques, controlling neural circuits with higher levels of specificity has become feasible. More recent studies have begun to dissect ZI's functional roles based on the input-output patterns of different ZI neuronal subpopulations. The emerging evidence suggests that ZI may serve as a processing node for a global modulation of behaviors and physiological states.

Diverse functional roles of ZI

Sensory processing

Previous anatomical studies have shown that ZI receives dense inputs from structures involved in different sensory pathways [14], [22]. As part of the spinothalamic pathway, ZI relays pain information[23]–[26]. According to tracing studies, a substantial part of ZI receives somatosensory information, whereas afferents conveying auditory and visual information are more restricted in the lateral part of ZI [1]. Functionally, *in vivo* multiunit recordings have shown that ZI neurons respond to whisker deflections, auditory stimuli including white noise and pure tones, as well as moving dots and flash-light stimulation[6], [8], [27].

These results lead to an interesting question: how does ZI integrate information from different sensory modalities? Two possibilities are conceivable. One is that inputs of different sensory modalities directly converge onto a single ZI neuron to give rise to its multisensory responses. The other is that there are subpopulations of neurons responding to a specific single modality, and then multimodal information converges through local connections within ZI. A recent study in the mouse has shown that ZI PV⁺ neurons, which are located mainly in the ventral part, and to a lesser degree in the dorsal part, respond to both whisker deflections and noise sound[6]. Another mouse study showed that there are partially overlapping subsets of GABAergic neurons in the medial part of ZI excited by whisker-touch, moving visual dots, or tone stimulation[8]. These results suggest that the two scenarios mentioned above may co-exist. Moreover, for many of these neurons, stimulation of multiple sensory modalities evokes a stronger response than any single modality following a pattern of sublinear integration[6]. Whether this sublinear pattern of sensory integration is universal within ZI, or whether linear and supra-linear integration could occur for specific sensory stimuli remains unclear. It will be of great interest to characterize the algorithms for sensory integration within ZI more quantitatively in future studies.

Given these recent aforementioned findings, it is reasonable to propose that ZI can function as a multisensory integration center. Meanwhile, several important questions remain unanswered. For instance, is there any topographic organization (e.g. tonotopic or retinotopic) for any sensory modalities in ZI? And how do different ZI neuronal subpopulations interact to achieve effective sensory integration? This type of questions may be addressed, in part, by using anterograde transsynaptic techniques[28] and slice recording to map the connectivity between ZI neurons receiving inputs from different sensory pathways.

Behavioral output control

The multisensory convergence may provide ZI with versatile response characteristics. Since ZI projects strongly to many hypothalamic, higher-order thalamic and brainstem regions considered as behavioral commanding centers, is it possible that ZI outputs directly modulate various behaviors? If so, how are the modulations achieved?

Recently, a mouse study has shown that a subset of GABAergic neurons in the ventral part of ZI, which expresses the LIM homeodomain factor (Lhx6), is activated by sleep pressure and promotes sleep, likely via the projection to the lateral hypothalamus[3]. Another mouse study demonstrated that GABAergic neurons in ZI (presumably located in the rostral part based on the reported coordinates) are excited by food deprivation and invoke food intake via their projections to the paraventricular nucleus of thalamus (PVT)[2]. Moreover, GABAergic neurons in the medial part of ZI are required for predatory hunting and activation of these neurons promotes hunting via their projections to the periaqueductal grey (PAG)[8], [9]. More importantly, the activity increase of this ZI subpopulation is correlated with attack epochs during hunting[9]. In the wild, animals routinely follow a “sleep, hunt and eat” schedule. Therefore, it appears that ZI might promote animals’ well-being by facilitating all these activities. Whether ZI is involved in a broad range of behaviors beneficial for animals remains to be tested in the future.

Besides the survival related activities discussed above, a series of studies has shown that ZI can bidirectionally modulate defensive behaviors via its different neuronal subpopulations. Activation of GABAergic neurons in the rostral part of ZI suppresses both noise sound-induced flight and conditioned freezing response through their projections to PAG[4]. Conversely, activation of PV+ neurons in the ventral part of ZI enhances the noise-induced flight via their projections to the posterior medial nucleus of thalamus[6]. Interestingly, the modulation of flight response by the rostral ZI appears to follow a gain control algorithm. More specifically, in an individual animal, the percentage reduction of flight speeds evoked by noise at different intensities when ZI is activated is about the same[4], suggesting that the ZI output adjusts the behavioral gain. It remains to be tested whether such modulatory effect of ZI can be generalized to other types of behavior.

We should note that ZI also sends strong outputs to many other brainstem areas, such as the midbrain reticular nucleus and pontine reticular nucleus, as well as directly to the spinal cord[12], [29], [30]. These projections are likely to be involved in motor control. As previously mentioned, DBS in Parkinson’s disease patients has been shown to alleviate essential tremor[20], [21]. In addition, several reports showed that DBS of ZI and nearby

areas alleviates abnormal muscle activities in orthostatic tremor and dystonic tremor patients, which likely involves downstream targets of ZI[20], [31]–[33]. Through diverse targets, ZI may globally broadcast the integrated multisensory information to modulate a variety of behavioral outcomes.

Motivational drive

In natural environments, sensory stimuli are often associated with either positive or negative valence and drive appetitive or avoidance behaviors respectively. Given that ZI integrates multisensory information and is involved in adaptive behaviors, it seems plausible that ZI may be engaged in conveying motivational states as well.

Some supporting evidence for this idea comes from the clinical literature, since DBS of ZI and nearby areas to treat movement disorders is sometimes accompanied by altered pleasure-seeking behaviors such as binge-eating[34], [35]. More direct evidence for the involvement of ZI in valence coding has been observed in mice, in which activation of GABAergic neurons in the rostral ZI drives palatable eating by inhibiting PVT[2], a structure known for conveying valence[36], [37]. Further, direct activation of these neurons or the GABAergic neurons in the medial part of ZI induces place preference[2], [8], suggesting that they encode positive valence. More strikingly, optogenetic activation of GABAergic neurons in the medial part of ZI results in repetitive and persistent nose poking to receive a laser “reward”[8], indicating a strong appetitive and reinforcing motivational drive.

The reported coding of positive valence by ZI suggests that it may be able to regulate motivated behaviors in general. Some of the open questions are whether different ZI neuronal subpopulations can code valence of different signs, and whether valence signals conveyed by different sensory cues or internal states could be integrated within ZI. By conveying motivational drive, ZI could potentially contribute to reinforcement learning, leading to strengthening of behavioral patterns which are overall beneficial for animals given specific environments.

Neural plasticity

Repetitive exposures to aversive or reward events can lead to synaptic plasticity, which is a key cellular mechanism underlying learning and memory. ZI connects with a broad range of structures in meso-cortico-limbic pathways, such as the amygdala, ventral tegmental area and medial prefrontal cortex (mPFC)[12], [14], [38], [39], suggesting that it may play a role in affective learning. Carrying valence signals, ZI may vary its activity in adaptation to complex environments, facilitating experience-dependent plasticity.

Pavlovian fear conditioning involves associating certain initially neutral environmental stimuli with aversive events and can serve as a good model for studying neuroplasticity. Recently, a study has found a negative correlation between ZI activity and fear generalization in fear learning: ZI is less active in animals that generalize fear[7], implying that ZI activity might affect the level of association. Another study showed that blocking synaptic transmission of outputs from ZI PV+ neurons or blocking the input to these neurons from the amygdala impairs fear memory acquisition and retrieval[5]. Apart from acquisition,

fear extinction is another form of learned fear regulation[40], [41]. Activity in the rostral ZI is found to increase during extinction training, which correlates with the gradual reduction of conditioned fear response[4]. This increase is driven by the input from mPFC, and suppressing either mPFC or ZI impairs the extinction of fear response[4].

A natural follow up question is whether ZI is involved in other neuroplasticity processes beyond fear learning. One recent example in that regard is from the pain domain. The study demonstrated that a subregion of the cingulate cortex sends excitatory output to ZI GABAergic neurons, and that after daily activation of either the cingulate-to-ZI projection or ZI, hypersensitivity to pain in a neuropathic pain mouse model is alleviated, and appetitive memory is generated [42].

Taken together, these findings indicate that ZI may be engaged in plastic processes during fear learning and chronic pain regulation. We should note that ZI also connects with brain areas conveying physiological states, such as the hypothalamus and insular cortex[42], suggesting a potential role of ZI in mediating plastic changes induced by interoceptive cues and maintaining homeostasis. Overall, ZI may be able to participate in a variety of sensory and physiological plastic processes, allowing flexible and adaptive behaviors of animals in response to their ever-changing needs and surroundings.

Concluding Remarks and Future Directions

To summarize, we propose that ZI may serve as an information processing node to globally modulate behaviors (Figure 1). After integrating multisensory inputs, ZI broadcasts the integrated information to regulate broad neural circuit functions through diverse downstream structures. This view is supported by the recent findings that ZI, via different neuronal subpopulations, promotes eating, sleep and predatory hunting, as well as bidirectionally regulates defensive behaviors. In addition, ZI is important for widespread decreases in brain activity induced by low-frequency stimulation of a thalamocortical pathway[43], further supporting its role in global modulation of brain functions. Emerging evidence also suggests ZI's involvement in valence coding and neuroplasticity processes. As a whole, ZI seems to promote animals' well-being by integrating multimodal cues from dynamic environmental contexts and internal needs, and regulating behavioral responses to them. As one possible mechanism for its modulation, we propose that ZI output provides a gain signal to adjust the amplitude of behavioral outcome.

The research findings discussed here have primarily been conducted in mice, but the overall organization of the reported neural circuits and pathways is shared by many mammalian species. The results in mice may explain some non-motor effects in patients with DBS of ZI and nearby areas, such as increase of appetite and improvement of sleep[33], [44]. One may also speculate that the growing understanding of ZI may point at additional patient categories that could possibly benefit from DBS of ZI[33].

Our understanding of ZI functions is advancing rapidly, but some important questions remain to be further addressed (see Outstanding Questions). New investigations of ZI can benefit from advances in genetic tools, single-cell gene profiling and large-scale recording

methods[45], [46], which offer excellent opportunities to reveal how different ZI neuronal subpopulations respond, in behaving animals, to diverse sensory stimuli and to signals conveying internal states. In addition, it is fundamental to elucidate how different ZI neuronal subpopulations interact with each other to achieve the most appropriate functional output. This can be achieved for instance by applying large-scale *in vivo* recordings and computational modelling to infer the connectivity within ZI. Although ZI is generally thought of as an inhibitory nucleus, a small proportion of ZI neurons is excitatory[11], [47], and this neural population might be particularly relevant in the context of Parkinson's disease, through the projection of these neurons to the substantia nigra[47]–[49]. The exact functional roles of these excitatory ZI neurons remain to be investigated more carefully. Furthermore, studying the cellular mechanisms underlying ZI-mediated neuroplasticity, including through traditional brain-slice recording methods, would provide a more thorough understanding of ZI functioning as an integrative node for dynamic modulations of behaviors and physiological states.

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Highlights

- ZI can integrate multisensory inputs. Convergence of multimodal information occurs at the level of single ZI neurons.
- Via different neuronal subpopulations, ZI can promote eating, hunting and sleep, as well as bidirectionally modulate defensive behaviors.
- ZI encodes positive valence and promotes reinforcement of appetitive behaviors, suggesting its role in conveying motivational drive.
- ZI is also involved in various types of neuroplasticity, including fear learning and extinction as well as chronic pain regulation.
- In view of these findings, we propose that ZI may serve as an integrative node for global modulation of behaviors and physiological states.

Outstanding questions

- Do different ZI neuronal types have different functional roles? For example, what are the functions of glutamatergic ZI neurons?
- The basis of multisensory responses of ZI neurons remains to be further studied. How do different ZI neuronal subpopulations process multisensory information? What are the algorithms for the integration?
- What are responses of ZI neuronal subpopulations in behaving animals? For instance, what is the activity of ZI PV+ neurons during fear memory acquisition?
- How do different subdomains or neuronal types of ZI interact with each other to achieve the most appropriate functional output?
- The valence ZI codes is currently reported as positive. Can ZI neurons also code negative valence? How are the valence signals passed into ZI, integrated within it, and communicated from ZI to other brain regions?
- ZI has been shown to be involved in neural plasticity in the context of fear learning and pain signaling. Is ZI involved in other types of plastic processes, e.g. reward learning? The answer to this question will indicate whether ZI has a more general role in neural plasticity.

Figure 1.

A Conceptual Model for the General Functional Role of Zona Incerta

ZI may serve as an integrative node for global modulation of a variety of behaviors. Sensory information from multiple modalities first converges in ZI, and then ZI feeds the integrated signal to various downstream targets, including the thalamus, hypothalamus, midbrain and spinal cord, to regulate behavioral outcome. ZI may also convey a valence signal, which can drive reinforcement learning. On longer timescales, neural plasticity may occur in ZI or its downstream structures, modulating behavioral patterns to promote adaptive behavior.