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Differences in the Neurological Pathways of Innate and Learned Fear

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Abstract

Fear is a fundamental emotion for survival. However, not all fears are the same, leading to a necessary distinction between the two main subsections of fear; innate and learned. This research paper investigates whether the neural pathways underlying innate and learned fear are independent of each other. Using optogenetics and pharmacology, researchers have manipulated specific brain regions and circuits involved in fear processing, such as the amygdala, hypothalamus, and PAG (periaqueductal gray). By measuring the behavioral and physiological indicators of fear in rodents exposed to different types of stimuli, research suggests that there may be partial overlap between the neural pathways of innate and learned fear, with some distinct differences. Lastly, the implications of these findings are discussed for understanding the mechanisms and functions of fear.

Introduction

The subject of emotions has been a long-standing debate in the scientific community. While in the past, it was primarily supported with psychological and philosophical evidence, advancement in neuroimaging technology has led to a more in-depth view of the brain and its pathways, supporting a neurological opinion. However, the brain's complete processing mechanism of emotion is still a mystery, including the neurological circuit of fear. Where some meta-analyses have found distinct patterns of brain activation corresponding to different basic emotions, other studies support a more abstract dimensional framework to supply a better description of the data or that our emotions do not have corresponding distinct patterns of activation (Adolphs, Ralph 80). Therefore, there is a debate about whether fear follows a generalized pathway or if it has specific segregated neural pathways. Furthermore, some opinions denounce emotions' neurological aspects and consider fear a psychological construct. With all the conflicting opinions, the study of fear is shrouded in much debate and contradictions.

Fear is an emotional response to a perceived threat or danger that can help us avoid harm or prepare for action. However, fear can also be excessive or irrational, causing distress or impairment such as post-traumatic stress disorder (PTSD), anxiety, and phobias. Fear can be classified into two main categories: innate and learned. Innate fear is naturally encoded in the brain and is activated without any prior exposure to the stimuli. It is the fear of universally or biologically threatening stimuli, such as predators, aggressive members of the same species (conspecific fear), pain, and dangerous environmental features like heights. These stimuli vigorously and systematically induce defensive behaviors without requiring direct harm or a learning process.

A second type of fear that humans can experience is learned fear, which results from the formation of a memory of an innate fear-inducing event through long-lasting changes in the brain. This memory aims to decrease the likelihood of reencountering the same threat and to better cope with similar future events. One component of this memory is the association between the innate fear-inducing stimulus and a neutral stimulus, such as the context in which it was encountered. This associative form of memory, where a neutral stimulus acquires the ability to induce defensive responses, is known as conditioned or learned fear (Silva et al. 544).

By studying the neuropathways of innate and learned fear, scientists can gain insights into the neural mechanisms that underlie fear and anxiety disorders, such as PTSD, phobias, and panic disorder. These disorders are characterized by excessive or inappropriate fear responses that impair everyday functioning and well-being. By identifying the specific dysregulated brain circuits in these disorders, pharmacologists can develop a more effective treatments that target the root cause of the problem.

Fear is a primal, complex emotion that can be innate and learned. While the two sets of fear seem dependent on each other, needing the innate fear to form associative memory for the learned fear, both categories also appear independent of each other, with how innate fear is established due to genetic code. This raises the question, what are their respective neural pathways? This paper aims to investigate whether innate and learned fears involve separate or integrated neurological pathways.

Methods

The research acquired for this paper was compiled from the databases of Touro Universityonline libraries, PubMed, and the Cleveland Clinic.

Gathering Research and Testing Criteria

A potential concern regarding the study of fear is the emotions of other species are similar to those of humans. If fear is defined as the feeling of being afraid, then can the term 'fear' be applied to animals who cannot verbalize when they feel afraid. Despite this train of reasoning, most consider there to be phylogenetic continuity among non-human primates, rodents, and even invertebrates. Selected species show strong parallels to several human emotions, both functionally and behaviorally, especially in expressing aggression, fear, and disgust (Adolphs, Ralph 80). By understanding the neurobiological basis in animal models, scientists can build on the accumulated data to use as a

reference study of the human brain. Despite the accepted experimentation format, the discovered data leads to more debate and conjecture. For example, some studies in rodents show that there are particular brain circuits for fear, whereas some findings from human neuroimaging seem to make the opposite claim (Adolphs, Ralph 83).

Testing Innate Fear

Several experiments can be utilized to determine levels of innate fear in rodents. One test is the elevated plus maze test, which evaluates the conflict animals experience between their instinct to explore a new environment and their desire to avoid an unprotected open space. A rodent is placed into a plus-shaped container, and its movements are observed. The levels of innate fear are indicated based on the duration spent and distance moved in the open arm area. Animals with high levels of innate anxiety tend to spend less time in unprotected territories (Klarer et al. 7069).

Another widely used experiment to test innate fear is the open-field test. Like the elevated plus maze test, the open field test works based on conflicting animal instincts: exploring or remaining protected. A rodent is dropped into a walled arena corner and is allowed free reign for an allotted amount of time. The area is cataloged into two main zones, the center/middle zone, and the remaining peripheral space. Animals with higher innate fear typically avoid the center zones and stick to the more protected bordering areas. In addition, the number of entries into the middle and the total distance moved in the arena are cataloged to determine the intensity of innate fear surveyed in the specimen (Klarer et al. 7069).

Another method of testing innate fear in rodents is the food neophobia test. The animals inherently avoid the consumption of unusual foods. Therefore, researchers can monitor the time it takes for the rodent to eat and correlate the time with the degree of fear. The greater level of innate fear experienced would be indicated by a longer feeding time (Klarer et al. 7069).

It is essential to mention that these experiments predominantly rely on the assumption that all rodents have an innate fear of open spaces and unknown foods. If this were not the case, then research under these assumptions would be considered invalid.

Testing Learned/Conditioned Fear

The primary method for testing learned fears is the Pavlovian fear conditioning technique, commonly known as classical conditioning. An animal is trained to associate an initially neutral stimulus with a negative/fear response. This can be done by utilizing pain and shocking the mouse's foot when neutral stimuli are present. In mice, this leads to a conditioned fear response, usually in the form of freezing behavior. During experimentation, the period of freezing behavior is monitored and documented for future reference (Klarer et al. 7069).

Discussion:

Controversy About the Fear of Pain

It is not clear whether mammals are genetically afraid of pain. Do they fear pain because it is innately ingrained into the brain? Or alternatively, is it because experiencing pain is an unpleasant event, becoming a stimulus associated with fear: ergo, a learned fear. Because the two options are integrated at their core levels, it is difficult to distinguish whether pain is an innate or learned fear.

Although pain is widely used to study fear acquisition, it is debated whether it should be classified as an innate fear. Animals can avoid harm from natural threats without experiencing them through innate fear responses. While pain can elicit defensive behaviors without conditioning, it may be more accurate to view pain as a universal signal of harm that may have developed to help animals avoid stimuli not registered by their innate fear systems. If this is true, then the pain should not induce innate fear but instead, function as an informative unconditioned stimulus to drive conditioned responses associated with the context or cue of the pain (which serves as the conditioned stimulus). Evidence for this interpretation can be found in the immediate shock deficit. Several experiments have shown that rodents do not show defensive behaviors like freezing, passive avoidance, or potentiated startle when the shock is delivered in a novel context without delay. This suggests that defensive responses observed when rodents receive a shock after exposure to a context for a specific time frame are most likely conditioned responses to the context, not innate responses to the foot shock (Silva et al. 548).

Potential Pathway of Fear

The close anatomical conservation across mammalian species of the amygdala, medial hypothalamus, and PAG (periaqueductal grey) nuclei which are known to be involved in fear processing in rodents suggests that similar circuits for different classes of fear also exist in other mammals, including humans. Furthermore, stimulation studies suggest functional conservation of these circuits across species. Scientists speculate that the predator fear circuit in humans may become activated under grave physical threat or fear of death and that panic attacks may reflect an extreme predator-related behavioral response. Thus, evidence is abundant for the anatomical

conservation of fear circuitry across species. Due to this, scientists have been able to investigate the neuropathways of innate and learned fear by studying rodents. However, much remains to be done to understand how these circuits have adapted to provide appropriate species-specific defensive responses (Gross et al. 656).

The Innate Fear Circuit

It is predicted that the innate fear of pain, predators, and aggressive conspecifics- where a member of the same species displays aggressive behavior towards others (in order to secure resources)- are processed in three mostly independent pathways operating primarily in the amygdala, hypothalamus, and the PAG. Predators and aggressive conspecifics elicit innate fear responses through the activation of distinct nuclei of the amygdala, which are in turn connected to distinct regions of the ventromedial hypothalamus, dorsal premammillary nucleus, and PAG to produce stimulus-appropriate defensive behaviors. Hence, the fear of predators involves the lateral amygdala, the posterior part of the basomedial amygdala, the posteroventral part of the medial amygdala, the dorsomedial part of the ventromedial hypothalamus, the ventrolateral part of the premammillary nucleus and the dorsolateral PAG (Gross et al. 652).

Fear of aggressive conspecifics (slightly) differs from that of predators, including the posterodorsal medial amygdala, the ventrolateral part of the ventromedial hypothalamus, the dorsomedial premammillary nucleus, and the dorsomedial PAG. Additionally, several interconnected nuclei of the medial hypothalamic circuit engage in predator and conspecific fear, acting as a responsive circuit. They include the anterior hypothalamic nucleus, medial preoptic nucleus, and the ventral premammillary nucleus. Conversely, painful stimuli activate the central amygdala to induce defensive behavior via the ventrolateral PAG. Thus, different classes of threatening stimuli recruit parallel and independent circuits to produce fear (Gross et al. 652).

The previous paragraph discussed how different types of fear activate distinct brain regions in rodents. In this paragraph, we will focus on how predatorial fear is triggered by olfactory and contextual cues, and how the medial amygdala plays a key role in processing these signals. A rodent can be triggered into an innate fear response via two main motives: scent or contextual clues while in the presence of a live predator. Olfactory and vomeronasal cues signal approaching predators via a direct connection with the olfactory bulb to the medial amygdala. It has been shown that rats exposed to a predator's scent have more significant activity in the posteroventral medial amygdala. Confirming this, lesions on the posteroventral medial amygdala result in a reduced innate fear response when exposed to predator pheromones. When exposed to an aggressive conspecific, the posterodorsal medial amygdala primarily activates. This may indicate that olfactory-based fear and conspecific aggression depend on separate medial amygdala subnuclei regions (Gross et al. 653).

Exposure to a live predator activates two additional amygdala regions, the lateral amygdala and posterior basomedial amygdala. These regions receive sensory information from visual and auditory cues. While efferent signals from the medial amygdala relay the olfactory data about predators and conspecifics, the posterior basomedial amygdala is proposed to relay non-olfactory information to the medial hypothalamus (Gross et al. 653).

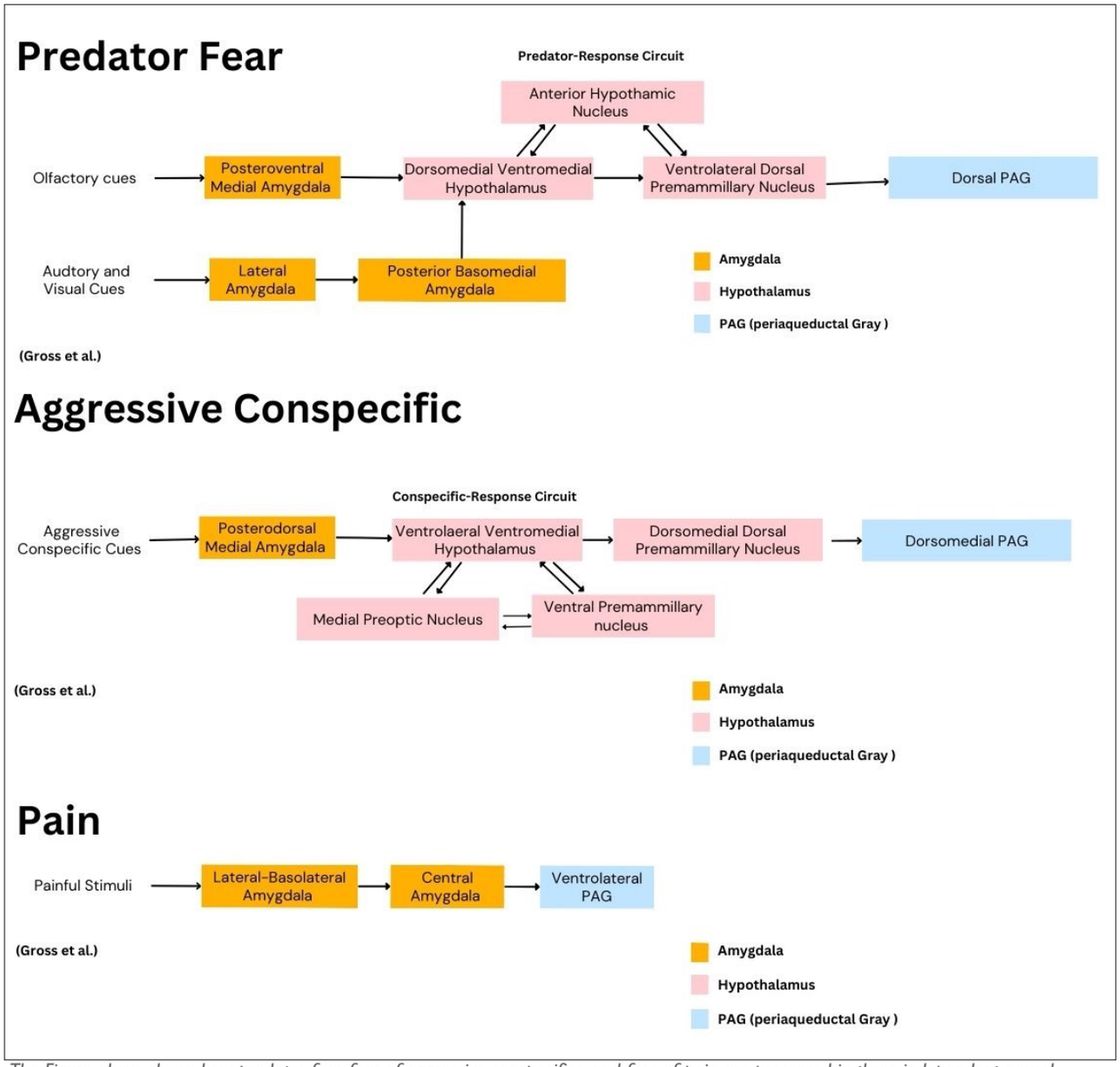
A key brain region involved in the fear response to predators is the medial hypothalamus. The medial hypothalamus receives different types of sensory information from the amygdala, which detects and processes potential threats. Depending on the nature of the threat, such as olfactory or non-olfactory cues, different parts of the medial hypothalamus are activated. The medial hypothalamus has been divided into two networks. The first network is activated by exposure to a predator. It is comprised of the anterior hypothalamic nucleus, the dorsomedial part of the ventromedial hypothalamus, and the ventrolateral dorsal premammillary nucleus. Any blockage of the dorsal premammillary nucleus will significantly reduce fear response. This network is also affected by contextual cues that travel from the ventral hippocampus via the lateral septum to the anterior hypothalamic nucleus.

The second network is activated by exposure to an aggressive conspecific. It entails the medial preoptic nucleus, the ventrolateral part of the ventromedial hypothalamus, the tuberal nucleus, and the ventral premammillary nucleus. Additionally, conspecific fear will activate the dorsomedial premammillary nucleus, a virtual interface between the hypothalamic circuit and the PAG, which is crucial for activating a social defense response such as freezing (passive) and fleeing (active). This differs from predator fear which will activate the ventrolateral dorsal premammillary nucleus (Gross et al. 653).

The lateral amygdala is crucial for associative learning between learned and innate fear. When blocked, either pharmacologically or with lesions, the acquisition and expression of fear are prevented. The lateral amygdala projects to the central amygdala via the basolateral amygdala. For example, any blockage of the central amygdala prevents the expression of learned fear of foot shock but will not restrict predator fear conditioning. By contrast, any lesions on the medial amygdala will result in the

opposite, allowing foot shock conditioning and blocking learned predator fear. This suggests further segregation between the fear of predators and the fear of pain circuits (Gross et al. 652).

Efferent signals from the central amygdala moving to the ventrolateral PAG are vital for suppressing unnecessary behavior, such as hunger or digestion, and eliciting a freezing response. The medial subnucleus of the central amygdala receives inhibitory projections from the lateral central amygdala, which promotes the activation of cortical arousal and risk assessment. A fear response of either freezing or risk assessment occurs depending on the degree of ambiguity of the external stimuli. For instance, the response to an actual predator usually results in freezing. In contrast, responding to more vague cues, such as odor, will more often result in a risk assessment response. Fear responses dependent on the central amygdala can be switched between freezing via the lateral PAG and risk assessment through the substantia innominate, several layers that are composed partly of gray and partly white brain matter found under the front part of the thalamus and the lentiform nucleus. Additionally, any lesions in the



The Figure above shows how predator fear, fear of aggressive conspecifics, and fear of pain are processed in three independent neural pathways that include subnuclei of the amygdala, hypothalamus, and periaqueductal grey (PAG) (gross et al. 652).

dorsal PAG will completely inhibit a fear response to predators (Gross et al. 653).

Predator response has also been linked to activity in the cerebellum. Lesions occurring in the cerebellar vermis are found to have reduced the freezing response. The cerebellum's influence on fear is assumed to be caused by projections from the fastigial nucleus to the superior colliculus via the dorsolateral periaqueductal grey. However, the exact route remains unclear (Gross et al. 653).

Learned Fear Circuit

The circuit for learned fear is divided into two main categories: the encoding of fear memory and the retravel of fear memory. The encoding of learned fear to predator-associated or painful stimuli requires projections from the relevant areas of the PAG via the thalamus to cortical association areas that are involved in higher-order processing of contextual cues, including the anterior cingulate cortex, retrosplenial cortex, and postrhinal cortex. Additionally, the hippocampus and lateral amygdala are crucial in memory for all fear classes. The hippocampus and lateral amygdala are also essential for fear retrieval upon exposure to contextual cues previously associated with a threat. Importantly, retrieval of predator fear memory recruits identical medial hypothalamic and PAG nuclei as those involved in processing innate fear of predators, with the only difference being the trigger for activation of the medial hypothalamus. During innate fear processing, signal input mainly comes from the accessory olfactory system. In contrast, during the retrieval of predator fear memory, the medial hypothalamus is activated by the hippocampus and lateral amygdala via the lateral septum and the posterior basomedial amygdala (Gross et al. 654). This would indicate a more integrated network between innate and learned fear, contradicting the theory of two completely segregated networks.

During conditioning to a painful stimulus, the ventrolateral PAG will relay information to instruct associative plasticity in the amygdala. Supporting this theory, the inhibition of the ventrolateral PAG has been shown to prevent fear conditioning of foot shock. The neuropathway between the ventrolateral PAG and lateral amygdala remains unclear but is speculated to involve projections from the midline and intralaminar thalamic nuclei to the cortical memory system. The dorsolateral PAG is necessary to encode contextual memories of predator cues. Any blockage of glutamatergic neurotransmission in the dorsolateral PAG has been shown to prevent conditioning to predator exposure (Gross et al. 654).

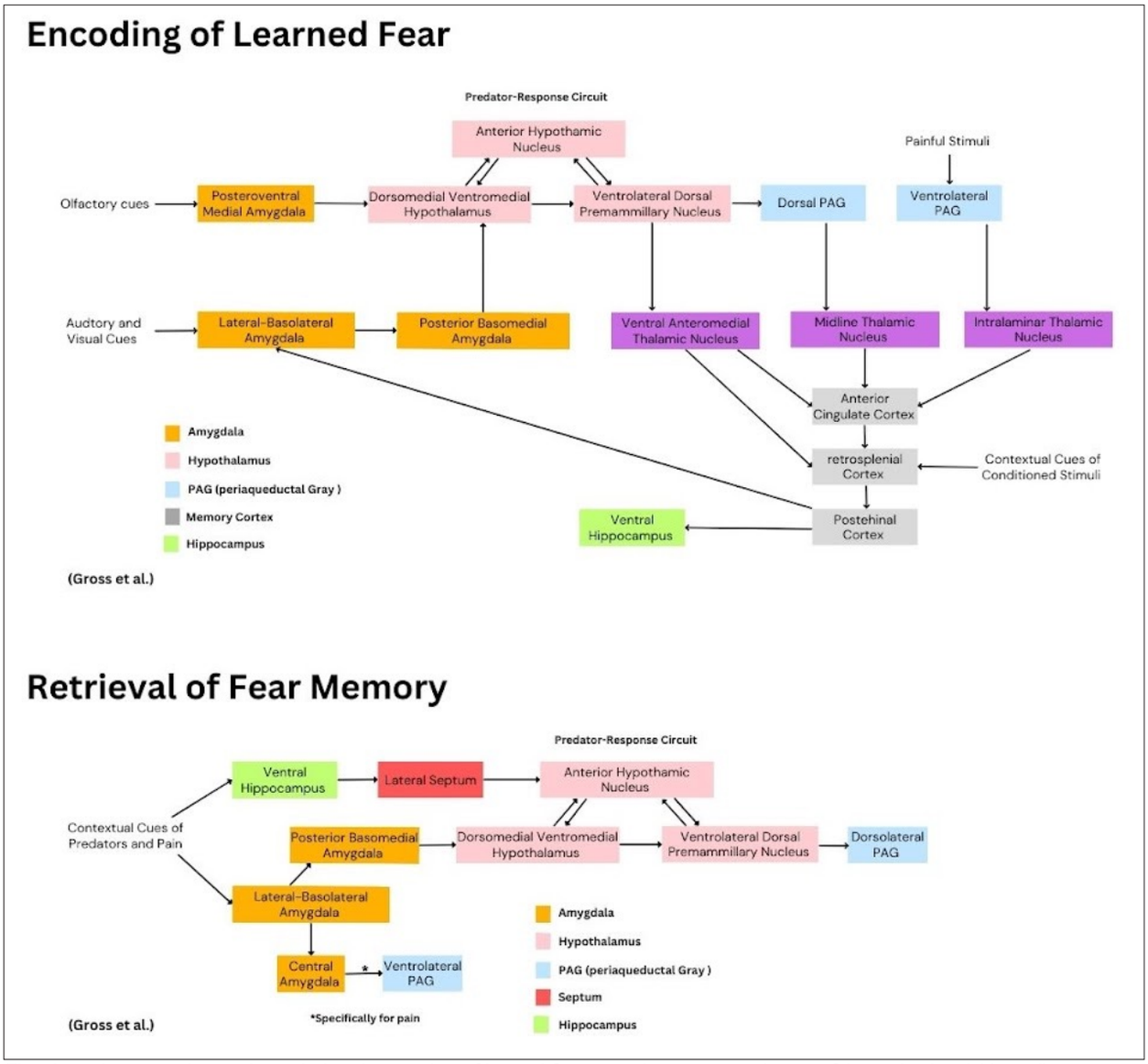
Within the cortical memory system, many structures are crucial for fear learning. Studies have shown that stimulating the anterior cingulate cortex aids in fear learning. On the other hand, the antagonism of glutamate receptors in the anterior cingulate cortex can prevent contextual and auditory conditioning to foot shock. These effects are likely mediated by the direct and indirect projections to the lateral-basolateral amygdala and hippocampus. The indirect path involves the retrosplenial cortex; only contextual fear conditioning is affected when damaged. The retrosplenial cortex is thought to influence contextual fear processing by sending projections to the postrhinal cortex, which is involved in the association of contextual information, possibly by its projections to the lateral-basolateral amygdala and hippocampus. Based on this perceived interconnectedness, the anterior cingulate cortex, retrosplenial cortex, and post-rhinal cortex are presumed to form a cortical network that is required for encoding the negative cues and associated context into the hippocampus and lateral-basolateral amygdala (Gross et al. 654).

The hippocampus is an essential structure in contextual fear learning, acquisition, and extinction of context conditioning. Lesion studies have shown that the ventral hippocampus has direct projections to the infralimbic cortex, the prefrontal cortex, and the basolateral amygdala, suggesting that this region plays a crucial role in modulating contextual fear responses. Additionally, the hippocampus is thought necessary for monitoring context-specific extinction recall through connections with the amygdala and projections to the ventromedial prefrontal cortex. Different hippocampal subregions engage in different human behaviors. The dorsal area is responsible for spatial-related behaviors, and the ventral region for anxiety-related behaviors. Increasing evidence suggests that the hippocampus and its subregions are involved in several aspects of fear conditioning. (Battaglia, Simone 219).

Therefore, the ventral hippocampus and its connections with other brain regions are critical for regulating the emotional and cognitive aspects of contextual fear conditioning. This is supported by experimental evidence that shows how the ventral hippocampus and lateral-basolateral amygdala are essential for acquiring and expressing contextual conditioning to painful stimuli. Lesions on the lateral-basolateral amygdala have been proven to prevent/ diminish the effect of fear conditioning to pain. Additionally, blocking the lateral amygdala prevents fear learning using predator threats. This would indicate that the lateral amygdala, attributed to encoding synaptic plasticity in foot shock conditioning, may also provide the same service in predator fear learning. This seemingly contradicts the concept of separated neural routes for pain and predator fear (Gross et al. 656).

The prelimbic region has been shown to influence the expression of fear conditioning to painful provocation. The prelimbic area receives input from the ventral hippocampus and is assumed to influence the basolateral amygdala (Gross et al. 656). Inactivation of the prelimbic cortex has been shown to reduce freezing behavior in previously conditioned rats. Furthermore, the neurons of the prelimbic cortex exhibit plasticity after fear conditioning. Although the exact mechanism remains unclear, it suggests that the prelimbic cortex is needed to express previously learned fear, possibly through BDNF (Brain-Derived Neurotrophic Factor). Test results indicate that BDNF expression in the prelimbic cortex is likely necessary to strengthen fear expression (Choi et al. 1,10).

The retrieval of fear memory of pain and predator is presumed to follow separate circuits that may be responsible for the different fear responses performed to the perceived threat. As mentioned, with innate fear, painful stimuli are more likely to elicit a freezing response through projections from the lateral-basolateral amygdala to the central amygdala and onto the ventrolateral PAG. In comparison, predator fear results in risk assessment behavior via projections from the lateral amygdala to the posterior basomedial amygdala, onto the medial



The above diagram indicates the path that the encoding of learned fear to predator-associated or painful stimuli takes. Additionally, it demonstrates the track taken for fear retrieval (Gross et al. 655).

hypothalamic circuits, and finally to the dorsolateral PAG. Associations for both types of fear stimuli stored in the ventral hippocampus may depend on projections from the lateral-basolateral amygdala (Gross et al. 654).

In this article, we will continue to explore the neural mechanisms of fear, both innate and learned. We will discuss the roles of specific areas in the brain in the pathways of innate and learned fear, such as the prefrontal cortex, hippocampus, paraventricular thalamus, and the dorsal PAG and basolateral amygdala circuit. We will also examine the major neurotransmitters of fear, such as GABA, epinephrine, and serotonin, and how they modulate fear responses. Finally, we will review some of the observed differences between innate and learned fear, including gut vagal modulations, the effects of zinc transporter 3, and prelimbic cortex BDNF. By understanding the neurobiology of fear, we hope to shed light on the causes and treatments of fear-related disorders.

Roles of Specific Areas in the Brain:
Prefrontal Cortex

The prefrontal cortex may also be a critical component in the neural circuit underlying fear conditioning. The prefrontal cortex can bidirectionally modulate the expression of previously learned fear. Activation in the dorsomedial prefrontal cortex occurs for long-term storage and retrieval of old memories. In contrast, the ventromedial prefrontal cortex forms reciprocal solid connections with the amygdala, lateral cortex, and other subcortical structures. This subregion is necessary for controlling fear relative to a stimulus that no longer predicts danger and acts as a relay station for "bottom-up" information from limbic and subcortical structures, signaling emotion detection and information from the lateral prefrontal cortex, conveying response selection and control (Battaglia, Simone 218).

Different contributions of anterior and posterior subregions of the ventromedial prefrontal cortex to fear-learning processes have been suggested, with greater anterior ventromedial prefrontal cortex activity in response to a safety stimulus. Data suggests that the ventromedial prefrontal cortex may also have a crucial role in fear acquisition, which is processed in its posterior subregion. Naturally occurring bilateral lesions in human ventromedial prefrontal cortex were found to compromise fear conditioning, providing potential evidence in support of the critical role of the mid-posterior ventromedial prefrontal cortex in acquiring fear (Battaglia, Simone 219).

The prefrontal cortex is also involved in the extinction of fear learning. Neuroimaging studies have reported that, in addition to amygdala activation, the ventromedial prefrontal cortex is crucial for the consolidation of extinction memory and is mainly involved in the recall of extinction in subsequent testing. This subregion may not simply inhibit the expression of amygdala-dependent conditioned threat responses but signal a change in previously acquired contingencies to select the most appropriate response to the current situation. The extinction of conditioned fear also involves the dorsolateral prefrontal cortex, possibly due to its capacity to shift attention from the stimulus to the context or its role as a site of explicit short-term memory processes in humans (Battaglia, Simone 219).

The Hippocampus in Fear Conditioning

The hippocampus plays a vital role in Pavlovian fear conditioning. Studies indicate that the hippocampus mediates the acquisition and consolidation of memory for the conditioned context. Lesions of the hippocampus made after fear training impair the performance of context fear but leave the performance of tone fear intact. This suggests that the hippocampus then stores information vital to expressing context fear. The context-conditioned stimuli combine the many stimuli that comprise the learning environment. The hippocampus may assemble a contextual representation, which can become associated with the foot shock unconditioned stimuli. The hippocampus stores the information necessary for a coherent context representation for a limited time after conditioning (Sanders et al. 219).

Neurotoxic lesion techniques have confirmed previous hypotheses of hippocampal function in fear conditioning. Post-training lesions of the dorsal hippocampus caused deficits in fear conditioning, indicating that the hippocampus has an essential but time-limited mnemonic role. However, pre-training lesions failed to affect context fear. Pre- and post-training lesions of the dorsal hippocampus produced a modest tone-conditioning deficit. These findings complicate matters as the hippocampus does not always play a role in context conditioning and sometimes appears to be involved in tone fear (Sanders et al. 219).

Scopolamine infusion into the hippocampus has been shown to reduce short- and long-term memory for context fear but has little effect on tone fear. This suggests that cholinergic mechanisms in the hippocampus acquire and consolidate contextual fear. Serotonergic processes have also been implicated in the acquisition of context fear. Infusion of a GABA receptor antagonist into the ventral hippocampus causes a selective impairment in the acquisition of context fear, indicating that cells of the ventral hippocampus are involved in the mnemonic processes underlying context fear conditioning. Tetrodotoxin administration into the ventral hippocampus impairs both

context and tone fear, likely due to the inhibition of signals in fibers of passage (Sanders et al. 221).

Paraventricular Thalamus

A study examined the role of the paraventricular nucleus of the thalamus in fear memory formation by examining the expression of c-Fos. C-Fos is a marker of recent neuronal excitation in the paraventricular nucleus of the thalamus following fear conditioning and after the fear memory retrieval test. Results showed that fear conditioning and memory retrieval increased the number of neurons expressing c-Fos in the paraventricular nucleus of the thalamus. The study also found that the paraventricular nucleus of the thalamus strongly projects to the central amygdala, with weaker projections to other amygdala nuclei, such as the basolateral amygdala. This finding is important because it reveals a new pathway for fear and anxiety processing in the brain. The involvement of the paraventricular nucleus of the thalamus–central amygdala pathway in fear conditioning was studied using a chemogenomic method to selectively inhibit central amygdala-projecting neurons in the paraventricular nucleus of the thalamus. Results showed that selective suppression of the central amygdala-projecting paraventricular nucleus of the thalamus neurons significantly impaired fear responses, indicating that the paraventricular nucleus of the thalamus is crucial for both the establishment and expression of fear memory (Penzo et al. 2).

The research continued into the mechanisms by which the paraventricular nucleus of the thalamus–central amygdala circuit contributes to fear regulation. Fear conditioning induces the potentiation of excitatory synapses onto SOM+ central amygdala neurons that store fear memory. Therefore, an experiment was done to determine whether the paraventricular nucleus of the thalamus is required for this plasticity by inhibiting the paraventricular nucleus of the thalamus neurons during fear conditioning. Results showed that fear conditioning significantly enhanced excitatory synaptic transmission onto SOM+ central amygdala neurons, and inhibition of the paraventricular nucleus of the thalamus neurons during fear conditioning did not affect this synaptic potentiation when examined 3 hours after conditioning. However, the same manipulation completely abolished synaptic potentiation measured 24 hours after conditioning, indicating that the paraventricular nucleus of the thalamus is required for the maintenance or consolidation but not the initial induction of central amygdala plasticity (Penzo et al. 3).

By examining whether the paraventricular nucleus of the thalamus inactivation impairs plasticity at the lateral amygdala–central amygdala synapses, researchers were able to ascertain the role of the paraventricular nucleus of the thalamus in fear memory formation. In an experiment, the paraventricular nucleus of the thalamus neurons was inhibited during fear conditioning using a chemogenomic method. Results showed that fear conditioning reversed the relationship between SOM+ and SOM– neurons, so AMPAR-mediated transmission was more robust in SOM+ neurons. Inhibition of the paraventricular nucleus of the thalamus during conditioning essentially blocked these synaptic changes, indicating that the paraventricular nucleus of the thalamus participates in fear memory formation by regulating the maintenance of fear conditioning-induced plasticity at the lateral amygdala – central amygdala synapses (Penzo et al. 3).

The study investigated the role of BDNF in the paraventricular nucleus of the thalamus-central amygdala SOM transmission. Research indicated that BDNF is a critical factor in the paraventricular nucleus of the thalamus-to-central amygdala communication. Deletion of tropomyosin receptor kinase B (TrkB), a receptor for BDNF, in the central amygdala or deletion of BDNF in the paraventricular nucleus of the thalamus was viewed to impair fear conditioning. This indicates that BDNF/TrkB mediates the paraventricular nucleus of the thalamus-central amygdala SOM interaction and plays an essential role in fear processing. This was further supported by the finding that BDNF deletion in the paraventricular nucleus of the thalamus or TrkB deletion in SOM+ CeL neurons reduced tone-associated memory and contextual memory or general fear responses (Penzo et al. 5).

Dorsal PAG and the Basolateral Amygdala Circuit

The PAG is commonly believed to be downstream of the amygdala and directs motor outputs toward appropriate defensive behavior. This is supported by findings that ventrolateral PAG lesions impair conditioned freezing behavior while dorsal PAG lesions do not block fear conditioning to a foot shock unconditioned stimulus. The PAG consists of dorsolateral and dorsal PAG separated from the ventrolateral PAG by the lateral column. The PAG participates in various functions, such as regulating cardiovascular function, nociception, and vocalization. The dorsal and ventral columns seem geared towards opposing forms of defensive behavior: escape and freezing, respectively (Kim et al. 2).

Stimulating the dorsal PAG in rats caused brief activity bursts, freezing, and ultrasonic vocalization. Unlike the amygdala, dorsal PAG stimulation led to fear conditioning, as shown by the rats' conditioned freezing to the conditioned stimulus. This effect was blocked when the basolateral amygdala was inactivated during dorsal PAG stimulation, suggesting that the dorsal PAG - basolateral amygdala

circuit engages in the unconditioned stimulus pathway. Previous studies support this idea and suggest a complex role for amygdalar nuclei in directing fear responses. While dorsal PAG stimulation can support fear conditioning, rats with dorsal PAG lesions can still experience fear conditioning, indicating that the dorsal PAG projection to the amygdala is just one part of the unconditioned pathways involved in fear conditioning (Kim et al. 9).

When rats were in a foraging apparatus to test innate fear, the basolateral amygdala and dorsal PAG were stimulated, displaying different responses than in the conditioning chamber. Basolateral amygdala stimulation caused rats to flee to the nesting area instead of freezing and emitting ultrasonic vocalizations. Similarly, dorsal PAG stimulation caused a fleeing response toward the nest. Amygdalar lesions/ basolateral amygdala inactivation blocked the effects of dorsal PAG stimulation. This suggests that the basolateral amygdala is downstream of the dorsal PAG in mediating fleeing responses during foraging. These findings are inconsistent with the contemporary fear model of the PAG directing motor output after activation by the amygdala. These differences may be due to how an environment can significantly influence the behavioral readout. The contextual modulation may also rely on cortical and hippocampal input (Kim et al. 9).

Basolateral amygdala stimulation and dorsal PAG stimulation produced similar fleeing behavior in the foraging apparatus, but the current intensity was lower for dorsal PAG animals. This may be due to the amygdala's non-fear-related functions interfering with each other when electrical stimulation activates amygdalar neurons indiscriminately. Optogenetics techniques can be selective, but it is still unknown if specific forms of learning are supported exclusively by neurons expressing particular genetic promoters. The fact that dorsal PAG stimulation required less intensity to elicit responses suggests that dorsal PAG neurons may be dedicated to defensive behavior and selectively stimulate downstream amygdalar neurons involved in fear-related behaviors (Kim et al. 10).

To summarize the above information, the paraventricular thalamus is a vital component of fear learning and memory, and it works with central amygdala, lateral amygdala, and BDNF. additionally, other brain parts like the prefrontal cortex, the hippocampus, and the PAG are involved in fear. The study explored how the top part of PAG, and the amygdala interact in fear learning in rats. The research found challenges the existing model of PAG-amygdala fear circuit. The research also alludes that the PAG stimulation was weaker, suggesting more specificity for fear. Additionally, the genetic basis of fear learning remains unclear.

Major Neurotransmitters of Fear:
GABA

GABA (Gamma-Aminobutyric acid) is an amino acid produced naturally in the brain that functions as a neurotransmitter. It facilitates communication among brain cells by reducing the activity of neurons in the central nervous system. As an inhibitory neurotransmitter, GABA reduces nerve cells' ability to send and receive chemical messages throughout the central nervous system. This can produce a calming effect and majorly control nerve cell hyperactivity associated with anxiety, stress, and fear (Cleveland Clinic 2022 A).

Research has shown that gaboxadol, a GABA A receptor agonist, activates GABA A receptors in the hippocampus, creating a state-dependent contextual fear memory. Typically, when a specific context is paired with a foot shock during training, it creates a strong fear memory for that context, as shown by freezing behavior when the context is reencountered during testing. However, when gaboxadol is infused into the hippocampus before training or testing, freezing behavior during testing is reduced, indicating that the fear memory has been disrupted. This may be because the expression of the fear memory depends on the simultaneous activation of hippocampal GABA A receptors. Furthermore, the fear memory is expressed strongly when gaboxadol is infused into the hippocampus before training and testing. This suggests that GABA A receptors in the hippocampus create a neural state that controls contextual fear (Holmes et al. 1195).

Another function of GABA is the regulation of the amygdala and its neural system. Therefore, to activate the amygdala and express fear, there needs to be a reduction in GABAergic activity. This is supported by a study that showed that injecting muscimol, a GABA A receptor agonist, into the basolateral amygdala blocked fear behavior induced by predator odor (Garcia, René 464).

Norepinephrine and Epinephrine

Epinephrine and norepinephrine are hormones that play a role in the body's "fight-or-flight" response to stress. When experiencing stress, these hormones are released into the bloodstream and cause several physiological changes, such as increased heart rate, blood pressure, and blood sugar levels. These changes help prepare the body to respond to a perceived threat (Cleveland Clinic 2022 B).

Dopamine and norepinephrine also play essential roles in activating the amygdala in response to predator scent. Predator odor increases dopamine metabolism in the amygdala, which reduces GABAergic inhibitory control. Additionally, taking reboxetine, which increases norepinephrine levels, has increased basolateral amygdala

responses to fearful faces (Garcia, René 464).

A human study with propranolol, a drug that blocks the action of epinephrine and norepinephrine, showed that it reduces activity in the basolateral amygdala. In rodents, it also impairs unlearned fear of predatory threats. Increased activity in the amygdala, in turn, increases activity in the paraventricular nucleus of the hypothalamus through direct projections. This activates the pituitary gland, which releases an adrenocorticotropic hormone. This hormone stimulates the adrenal glands to secrete glucocorticoids, mainly cortisol in primates and corticosterone in rodents (Garcia, René 464).

A study in rodents showed that the smell of a predator increases levels of adrenocorticotropic hormone and corticosterone in the blood. In monkeys, a human intruder - triggering an innate fear response - also increases levels of these hormones and corticotrophin-releasing hormones. Lesions in the central amygdala, which reduce innate fear, also decrease levels of these hormones. The hypothalamic-pituitary-adrenal axis mediates these hormonal and autonomic responses and plays an adaptive role in responding to threats. Activation of this axis increases cardiovascular tone, respiratory rate, and metabolism while inhibiting functions such as feeding, digestion, growth, reproduction, and immunity. This axis is intricately linked to the hypothalamic-pituitary-gonadal axis and can inhibit each other. For example, a study in rodents showed that animals exposed to predator scent had lower testosterone and higher corticosterone levels than unexposed animals. However, findings in primates are mixed. In monkeys, animals exposed to a human staring directly at them exhibited less anxious behavior when given treatment that lowered testosterone levels (Garcia, René 464).

Serotonin

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a neurotransmitter that regulates mood, appetite, and sleep. It is also involved in the modulation of fear and anxiety. Research suggests that serotonin can inhibit the activity of neurons in the amygdala, which can reduce the fear response. The amygdala receives dense serotonergic projections from the dorsal raphe nucleus and has multiple subtypes of 5-HT receptors. Studies with 5-HT knockout mice have shown reduced binding density and function of 5-HT1A receptors in several brain areas, including the amygdala, and increased anxiety-like behaviors. Administration of vilazodone, an agonist of these 5-HT receptors, following predator stress interferes with developing anxiety-related changes. This supports the idea that reduced 5-HT activity in the amygdala is involved in mechanisms of innate fear. Furthermore, it is suggested that 5-HT inhibits fear circuits in the amygdala through local action on GABAergic interneurons. This means that serotonin may increase the activity of GABAergic interneurons, inhibiting the activity of other neurons in the amygdala and reducing fear responses (Garcia, René 464).

Observed Differences in Innate and Learned Fear Pathways

Despite many unknown factors involved in the neurological circuit and the difficulties differentiating between the innate and learned fear pathways, several variations have been observed. Furthermore, through experimentation, researchers have isolated specific factors that primarily affect only one of the two subdivisions of fear. These differences support the concept that innate and learned fears follow, at least partially, individual-specific pathways in the brain.

Gut Vagal modulation

One variation between the pathways is how the gut vagal afferents differentially modulate innate and learned fears. Vagal afferent signaling has been connected with mood regulation, anxiety, and fear. A study was done to observe the effects of complete disconnection of the abdominal vagal afferents on innate anxiety, conditioned fear, and neurochemical parameters in the limbic system. In this experiment, adult male mice underwent surgical procedures resulting in a left-side intracranial vagal rhizotomy and a transection of the vagus nerve's dorsal (left) subdiaphragmatic trunk. After verifying the complete separation of the vagal interface, the rats commenced the behavioral testing stage (Klarer et al. 7068).

Conducting the maze and open field test showed that the rats had a significant increase in the percentage of time and distance traveled in the open-spaced perimeters. Both tests provided data indicating reduced innate fear/anxiety behaviors. Additionally, the food neophobia test reiterated the results of decreased innate fear (Klarer et al. 7072).

However, the results were different when testing learned to fear. When administrating auditory cued conditioning, there was a significant increase in freezing time in the specimens with disconnected nerves. Furthermore, the extinction of the conditioned fear was impaired, causing the rats to express high freezing levels for a prolonged duration (Klarer et al. 7073).

A postmortem assessment of GABA, norepinephrine (NA), and serotonin neurotransmitter levels was done. The study displayed an increase of GABA and a decrease of NA in the ventral prefrontal cortex and nucleus accumbent, respectively (Klarer et al. 7075). These results align with GABA and NA's hypothesized roles in innate

fear's neurological pathways. Interestingly, there were no significant differences in the level of serotonin, which does not align with the supposed theory that less serotonin is required for an innate fear response (Garcia, René 467).

Zinc Transporter 3

A study utilizing knockout (KO) mice suggests that Zinc transporter 3 (ZnT3) is involved in associative fear memory and extinction but not innate fear. KO mice is a laboratory procedure where researchers inactivate or "knock out" an existing gene by replacing or disrupting it with an artificial piece of DNA. ZnT3 is highly enriched in the amygdala-associated neural circuitry and is colocalized with synaptic Zn2+, a potential modulator of neurotransmission and synaptic plasticity in fear conditioning pathways (Martel et al. 1). By knocking out ZnT3, the altered mice now lacked Zn2+, an ideal scenario to study zinc's effects on the neuropathway.

Using the open field and elevated plus maze tests showed no differences in the behavior of innate fear in the KO and control group (Martel et al. 8).

To study the effects of Zn2+ in learned fear, the KO mice and a control group underwent tone–shock paired conditioning, both weak (one-tone) and strong (five-tone) training. The study found that under the single-tone–shock-pairing protocol, the ZnT3 KO mice froze significantly less than the control group. However, ZnT3 KO mice were normal when five-tone pairings were used. The discrepancy between weak and strong conditioning could indicate different pathways depending on specific stimuli and intensity (Martel et al. 3).

Additionally, the ZnT3 KO mice were found to have a faster extinction rate for the cued fear conditioning. Based on the data, deficits in fear conditioning were related to affected memory and not to sensitivity to shock (Martel et al. 6).

Overall, the role of synaptic Zn in fear learning has been unclear but linked to synaptic plasticity in the amygdala and hippocampus. These two regions are critical for fear memory. Therefore, it would corroborate that only learned fear is affected by the lack of Zn2+ because of the role memory plays, or more specifically, does not play, for innate fear (Martel et al. 10).

Prelimbic cortex BDNF

Based on the BDNF-dependent plasticity in the prelimbic cortex, which is highly expressed in the prelimbic cortex and has strong connections to the basolateral amygdala, researchers undertook testing to show that BDNF is essential for the expression of learned fear memories. Researchers used neocritical KO mice to delete BDNF expression in specific areas of the neocortex selectively. The control and KO group's BDNF expression was evaluated using enhanced green fluorescent proteins to visualize and confirm the suppression. The results indicated that the control group had BDNF expression in the prelimbic and infralimbic regions. Consequently, the KO mice lost all expression in the prelimbic regions, retaining slight expression in the infralimbic area (Choi et al.2).

The mice were then tested for an innate fear response. The open field and elevated plus maze tests confirmed no differences between the control and BDNF-deficient groups. This indicates that the innate fear circuit is independent of prelimbic-BDNF expression (Choi et al. 3).

Additionally, the mice underwent cue-dependent fear conditioning. While the control group showed typical acquisition and expression, the same was not true of the KO group. During short-term memory testing (1 hour after fear conditioning), the BDNF-lacking mice showed a reduction in fear expression. Furthermore, 24 hours post fear conditioning, long-term memory testing yielded an even more significant reduction in fear response. (Choi et al. 4).

The two groups were also tested in fear of extinction. Consistent with the overall lower levels of fear, the KO group had faster extinction. However, these results would not necessarily indicate faster extinction rates due to suppression of prelimbic-BDNF. Instead, it would be more accurate to corollate this change to the fact that by the mice experiencing lower levels of fear, there was less to extinguish and therefore required less time (Choi et al. 5).

Conclusion

This paper has explored the presumed neurological pathways of innate and learned fear, explicitly highlighting the observed differences between the two. Based on the collected data, the research alludes to a conclusion that the neural pathways of fear are amalgamated and separate, a blend of the two main arguments regarding the neural pathway of fear. Learned fear is inherently more complex than innate fear, requiring additional brain regions for activation and modulation. However, it has also been shown that innate and learned fear have mutual characteristics, such as hypothalamic response circuits to predatorial fear and employing the same areas of the PAG for fear expression. Furthermore, it is discussed how neurotransmitter regulation, especially GABA, plays a key role in perpetuating fear. Despite the current mass of accumulated data, more research is needed to fully understand the topic and bring a satisfactory resolution to the debate involving the neurological pathways of innate and learned fear.

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