pISSN 2320-6071 | eISSN 2320-6012

DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20233415

Review Article

COVID-19 and fear processing

Pravin R. Rathod[1]*, Santhi. P. Rathod[2], Rishabh R. Kandwal[3], Geo J. Panicker[3]

[1]Department of Anatomy, Spartan Health Sciences University, West Indies
[2]Department of Histology, Spartan Health Sciences University, West Indies
[3]School of Medicine, Spartan Health Sciences University, West Indies

Received: 09 September 2023
Revised: 06 October 2023
Accepted: 09 October 2023

***Correspondence:**
Dr. Pravin R. Rathod,
E-mail: drpravinrathod123@gmail.com

ABSTRACT

The world faces a global crisis that encompasses health, financial, and psychological aspects as a result of the coronavirus disease. While the health crisis is significant, it is important to recognize that the human and social crises that have emerged are equally impactful. These crises have resulted in various negative outcomes, such as social rejection, economic disparity, unemployment, and mental distress. Fear is a significant psychological barrier that can impede recovery from any disease process, and thus, it plays a critical role in determining the mortality and morbidity of any given disease. The COVID-19 pandemic has generated a pervasive fear of infection that has further exacerbated the situation. This study explored the mechanisms by which humans may have elicited conditional fear, using the COVID-19 pandemic as a specific case study. Our goal was to examine the process of fear in humans by exploring our knowledge of neuroanatomy and the systemic response regulated by the autonomic nervous system.

Keywords: COVID-19, Amygdala, Conditional fear, Memory

INTRODUCTION

Fear is an unpleasant emotional sentiment induced by external peril or internal perceived danger. It induces changes in the person's psycho-physio-somato-spiritual functioning, thus making them ready to flee, fight, or freeze.

Fear induction is a multifaceted phenomenon, depending on one's genetic makeup, family and social environment, past experience, cognitive growth, education, and cultural habits.[1]

Fear is judged as rational, which has some reasonable cause, or irrational, which occurs without any excitable stimulus. Irrational fear is called a phobia.[2] To most of us, fear is uncontrolled emotional anxiety.[3]

Objectives

The objective was to understand the mechanism for fear formation in humans during COVID-19- by studying the neuronal circuit responsible for fear processing in the amygdala and associated structures.

We are still in the pool of COVID-19 infection caused by the coronavirus, which started in Wuhan City, Hubei province of China, in December 2019. The WHO declared COVID-19 a pandemic infection on March 11, 2020. This new virus infection disseminated with trajectory growth. Many cities, towns, and suburbs were in lockdown. Currently, numerous countries are grappling with the impact of the pandemic, which has resulted in 770,085,713 confirmed cases and 6,956,173 deaths worldwide, alongside a remarkable 13,499,983,736 vaccinations administered globally (data retrieved on 30th August 2023, at the WHO website).[4]

At the outset, the disease was initially perceived as an influenza-like illness. However, as it disseminated rapidly on a global scale, coupled with distressing mortality rates, it evoked heightened apprehension and anxiety. This heightened fear of infection gave rise to an atmosphere of unease, particularly within populations such as travelers, the elderly, and individuals with compromised immune systems, where the rapid spread of the disease was observed. Finally, the sudden and widespread shutdown in the later phase triggered more fear formation.[5]

The process of fear formation can be broadly divided into three stages: perception of a threat, processing of the threat in the brain, and the generation of a fear response. Our research tries to understand the three stages of fear formation.

Perception of threat

The pervasive imposition of lockdown measures by governmental authorities on local, national, and global scales profoundly influenced human emotional states, acting as the initial catalyst for the establishment of enduring adverse memories.

The process of fear memory consolidation was initiated through repetitive exposure to a range of stimuli, with particular emphasis on auditory and visual cues. Notably, the emergence of a digital fear stage was developed by the recurrent dissemination of COVID-19-related events and information across various social media platforms, including news channels, WhatsApp, Facebook, etc. The proliferation of misinformation, incomplete analyses, and conflicting commentary further augmented the fear phenomenon, ultimately creating an atmosphere of confusion and uncertainty.

Additionally, the constant display of visuals depicting mass deaths, food shortages, overwhelmed medical facilities, stranded travelers, and civil retaliation played a significant role in solidifying fear in the docile mind.[6-8]

The COVID-19 pandemic triggered the development of a new conditional fear in individuals, generating a psychosomatic fear response.[9,10] While this fear did not elicit the same response in everyone, most people felt the danger of being infected every time.[11]

Psychological stress has had a significant impact on the mental well-being of individuals, particularly those who have pre-existing psychiatric imbalances, thus affecting their spiritual and mental well-being.[12,13]

As referenced in the Hindu religious text, the Bhagavad Gita states that, "For the one who has conquered the mind, the mind is the best of friends; but for one who has failed to do so, his very mind will be his greatest enemy."[14]

According to previous research, the detrimental effects of mental harm outweigh those of physical injury. Mental stress can lead to conditions such as depression, anxiety, irritability, social phobia, and panic attacks, as well as changes in behavior, including obsessive and paranoid tendencies.[15,16] As a result, investigating the mechanisms underlying stress and fear is critical.

Neurophysiological processing of the threat in the brain

Exteroceptive or interoceptive somatosensory stimuli are carried via ascending tracts to the thalamus, from where it's conveyed to the primary sensory cortex. The primary sensory cortex relays to the hypothalamus and amygdala, where the autonomic response in the form of a fight or flight spur is triggered.[17]

In the present COVID-19 pandemic condition, fear input was via digital form involving hearing and visual inputs from various social media. This implicates a unique visual and auditory pathway, ultimately relaying in the amygdala.

The amygdala is considered the main controlling area for fear processing and response. It is situated in the dorsomedial temporal pole, anterior to the hippocampus, in close proximity to the caudate nucleus's tail, and partially beneath the folds of the gyrus semilunaris, gyrus ambiens, and uncinate gyrus.[17] The amygdala nuclei have neuronal groups. They are arranged as basolateral complex, medial nucleus, cortical nucleus, central nucleus, and intercalated cell clusters. These nuclei receive various cortical connections, as shown in figures 1 and 2.[18] The lateral nucleus receives the audiovisual input.[19-21]

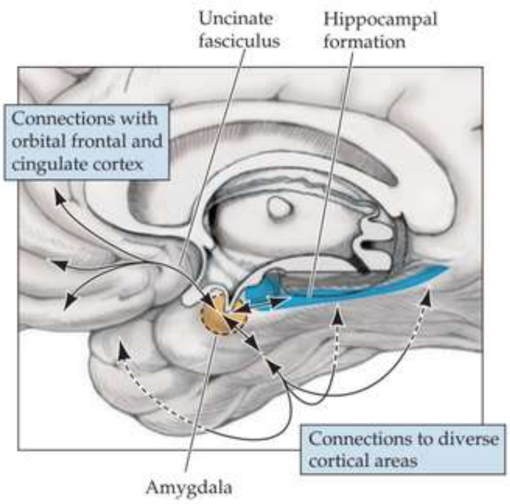

Figure 1: Anatomical location and cortical connection of the amygdala.

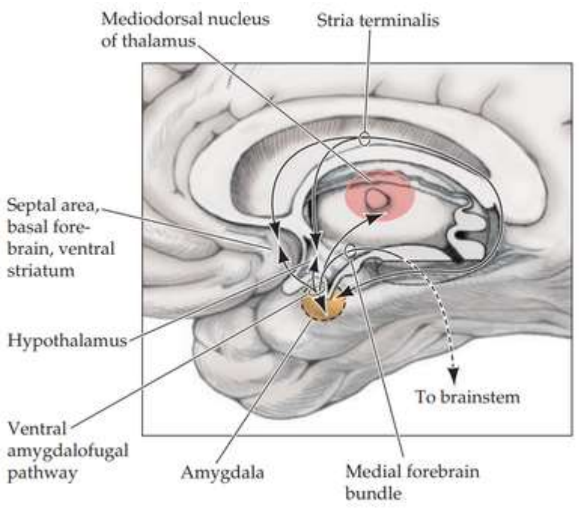

Figure 2: Sub-cortical connection of the amygdala.

Olfaction and fear association

During the pandemic, the indiscriminate use of hand sanitization by absolute alcohol induced a strong smell stimulus. The visits to hospitals, health clinics, pharmacies, and vaccination centers contributed to the major sensitization to fear centers. The use of antiseptic solutions at home and in medical procedures contributed to smell-induced fear memory in all of us.

The sense of smell reaches the cortico-medial group of the amygdala shown in Figure 3.[18] Besides, this amygdala additionally receives inputs from the rhinal cortex, gustatory, visceral somatosensory, hypothalamus, subiculum, and brainstem area.[22]

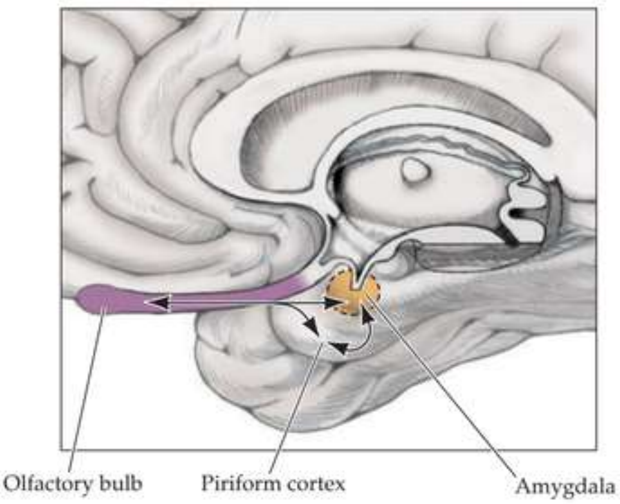

Figure 3: Olfactory connection of the amygdala.

During the COVID-19 pandemic, the lateral amygdala nucleus has received significant attention due to its role in processing sensory, auditory, and nociceptor afferents. In this context, audiovisual inputs have emerged as the predominant stimuli for fear registration. Research efforts have focused on understanding the underlying mechanisms of these pathways for fear processing. Extensive animal studies have been conducted to shed light on this subject.[23,24]

Auditory and fear association

Auditory stimuli reach the lateral amygdala (dorsal) nuclei. They are shared and sent to the basal nuclear complex of the amygdala, which is then sent to the central nuclear group for fear plasticity. Though it appears to be a simple process, it is a complicated circuit. The lateral amygdala nucleus or basal nucleus can work as a fear-learning area or memory modulator. The central amygdala nucleus complex acts as a learning area rather than the responder. Once the input has reached the amygdala nucleus, they send the efferent fibers to the periaqueductal gray matter or to the dorsal prefrontal cortex [anterior cingulate gyrus. prelimbic area, basal nuclei of amygdala] as response center.[19,20]

Role of visual-amygdala connection in fear processing

Parvalbumin-positive neurons in the superior colliculus of mice have been identified as a critical neuronal subtype for detecting vague, large, bright objects as visual stimuli. These neurons have been found to connect with the parabigeminal nucleus, which in turn connects to the amygdala, activating fear response and depression-related behaviors. This recent identification of neuronal connections has revealed a significant role in visual conditional fear plasticity. Additionally, the basolateral nucleus of the amygdala receives fibers from the parahippocampal gyrus and visual association area, creating fear in the form of visual phobia.[25]

Upon gaining access to the amygdala, the auditory and visual stimuli trigger the fear response. The amygdala plays a regulatory role in brain functioning, with the central nucleus influencing physiological, autonomic, and behavioral expressions of emotional state.[21]

The generation of a fear response

The amygdala provides stria terminals arising from the medial cortical nucleus, ending in the anterior hypothalamus, preoptic area, septum pellucidum, anterior perforated substance, habenular nucleus, anterior commissure, and other areas (Figure 2).[18] This amygdala-hypothalamus connection activates corticotropin-releasing hormones, activating the brainstem's autonomic nervous system.[19]

Fear elicits observable and quantifiable behavioral reactions through the autonomic nervous system. The amygdala modulates the hypothalamus, which triggers systemic effects such as heightened central nervous system blood flow, heightened vigilance, constricted pupils, increased respiratory rate, and enhanced cognitive processing. These responses are necessary for an organism to survive in threatening situations. Thus, preparing an individual for his survival response to fear.[26]

The hippocampus works in synergy with the amygdala to create meaningful plasticity for fear. The hippocampus stores surrounding scenes to create a virtual experience and retain permanent memory through the Papez circuit, which involves spatial and episodic memory for emotional response. Extensive work has been done on the Papez circuit to understand the formation of fear memory plasticity.[27] Thus, the amygdala and hippocampus create a new memory with the situation in which it was created, leading to fear memory consolidation.[28] Depending on the severity of stress, new permanent memory is created, resulting in conditions such as post-traumatic stress disorder and bipolar disorders.[29]

It is likely that the COVID-19 pandemic has significantly utilized these pathways for a fear foundation, with diverse functional brain areas associated with fear concretion.

Role of the associate brain area in fear processing

Cingulate gyrus

Cingulate gyrus, besides its role in the PAPEZ circuit, plays an important role similar to the limbic system in mediating or modulating fear responses.[30]

Cerebellum

A recent study shows that fibers are connected between the amygdala and cerebellum, influencing fear.[31]

Parietal lobe

Infra parietal lobe is connected to the visual area, thalamus, and temporal lobe in the visual pathway, which is well defined. The fusiform gyrus has been found activated in fear-conditioned faces.[32]

Frontal lobe

Personality or behavioral changes is the most important response seen in the COVID-19 pandemic. The frontal cortex maintains a person's personality and cognitive abilities from past experience. The frontal cortex has a wide neuronal connection that can influence any brain area. Thus, fear exposure in the frontal cortex modifies behavioral changes and improves cognitive ability.[33]

CONCLUSION

The COVID-19 pandemic has had a profound impact on human behavior and the way people perceive the world. As a species that has evolved to survive in diverse and challenging environments, humans possess unique abilities to learn, process, modulate, and memorize experiences. However, the outbreak of COVID-19, though not a life-threatening condition in all cases, triggered widespread panic and disrupted daily life. The negative effects of misinformation and fear amplified the spread of disease. In particular, conditional fear played a significant role in shaping individuals' responses to the pandemic. The amygdala, a key brain region involved in processing and expressing anxiety and fear, plays a critical role in how individuals respond to stressful situations. Psychological factors can significantly impact the morbidity and mortality of any disease, making mental health a crucial factor in mitigating the negative effects of stress. Thus, psychosocial health management plays a vital role in managing post-traumatic events. The WHO has recognized this and has launched a guideline for mental health and psychosocial considerations during the COVID-19 outbreak. The guideline provides comprehensive recommendations to the general population, healthcare workers, team leaders or managers in health facilities, caregivers of children, older adults, people with underlying health conditions, and people in isolation. These recommendations include the use of psychological first aid and the mhGAP Humanitarian Intervention Guide to provide necessary emotional and practical support to affected people. The guideline is available on the WHO website.

ACKNOWLEDGEMENTS

We thank Mrs. Rufina Charles, an educational expert, for editing the article and providing valuable input for the entire research format. We also acknowledge Community Health and Research Center of Spartan for inspiring research work.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Rathod PR, Rathod SP, Kandwal RR, Panicker GJ. COVID-19 and fear processing. Int J Res Med Sci 2023;11:4255-9.