THE AMYGDALA – A CLOSELY INTEGRATED NETWORK

Corresponding Author: Rowena Kong (Email: rowena.kong@alumni.ubc.ca)

**ABSTRACT:**

The amygdala is a crucial brain region responsible for emotional processing and fear conditioning and learning. The major classes of neuroreceptors and pathways present in this region are significantly engaged in such functions that extend to memory associations, cognition, appraisal and responsiveness to emotional and fearful stimuli. There is evidence of a rich integration of neurofunctions and connection with the rest of the human physiological systems. Gender differences in amygdala reactivity to stimuli are also discussed to aid understanding of external factors that may play a role in causation of such differences.

 INTRODUCTION

 Decades long period of neuroscientific research and exploration to this day have highlighted the significant and notable functions of the amygdala in human and mammalian brains in the areas of emotional processing, fear-motivated control and various neuropsychopathological conditions. Delving into the diverse internal distribution and rich innervation of dopaminergic, serotonergic, noradrenergic and cholinergic receptors in this interesting neurological component, the amygdala is a definite necessity and crucial role player in the normal and healthy functioning of an individual. Its importance is as essential as our need to “feel” emotions and act humanely and appropriately as a result of the fear of danger in life. In the absence of fear, an individual heeds no internal and external warning alarms in a world of uncertainty. Without emotion, morals, compassion and humanitarian causes may neither persist nor exist. As a result, the amygdala came into our neuroscientific realm of discovery and attention. This particularly notable region of our brain has come to guide our emotional attention, processing and response, with a substantial focus on fear as a distinct component of our conditioned experiences and learning.

**Emotion and Fear Processing – A Close Attachment**

 Studies of the important functions of amygdala stressed the intimate connection between emotional processing and fear conditioning through evocation of relevant memories of past stimuli and events, the negative emotional conditioning made possible through close neurointeractivity with memory storage and modulatory role by the cholinergic inputs in the basolateral amygdala region that bears connection with the basal forebrain [1-3]. Therefore, the deeply interactive integration of various classes of neuroreceptors in their processing and functional roles unite in instances to affect a human nature outcome of response and reaction to external stimuli and situational events. Fear learning and conditioning closely relate to emotional processing in the brain due to the emotional essence, nature and valence of fear, that swiftly leads to imagined and/or recalled negative valence of consequences, again aided by memory representation, consolidation, retrieval and modulation function by cholinergic(muscarinic) processing in the amygdala, which thereby, fine-tunes the relevance of certain cues and attaches their significance and correlation(s) with prior experience(s) that are remarkable for such instance. Further towards the highly integrative nature of the mammalian body, such fear conditioning may extend onto the physiological component of sympathetic nervous system activation from amygdala’s stimulation of norepinephrine/noradrenergic and stress hormone cortisol release, that in turn activate and run on a negative feedback loop with the HPA(hypothalamic-pituitary-adrenal) axis, re-affecting the reactivity of relevant brain regions, including the amygdala once again[4-6]. It is therefore essential to appreciate the close relations of the components and valence nature of emotion and its important subset of fear and their far-reaching impact on human neurophysiology. Norepinephrine release in the medial amygdala, leading to cortisol release, likely the outcome of fear induced and conditioning, further strengthens the negative emotional valence of fear.

**Efficient Integration of Neuro-Networks**

 It can be said that the emotional awareness or consciousness induced by a certain stimulus, situation or event activates emotional, motivational and valence-dependent dopaminergic and serotonergic processing that in turn direct the course of memory activation and retrieval, leading to cognitive evaluation, decision and final response or outcome of action by an individual [7-8]. One can see the highly interdependent workings of each subset of functions assigned to various neuroreceptor classes and transmission pathways that enable an individual to optimally react to and interact with the external environment and circumstances.

**Implication of the Autonomy of the Amygdala**

 With numerous studies pointing to significant highlighted reactivity of the amygdala towards and under the influence of external emotional stimuli tested in research subjects, it may be worth considering an essential aspect of the autonomous function of the amygdaloid complex in neuroactivity processing and inducing optimal individualised response(s). In a way synonymous with heightened dopaminergic response towards goal-directed motivation and reward learning in the mesolimbic region of the brain, the amygdala appears to be capable of a well-rounded central processing functionality in addition to working as an efficiently integrated unit bestowed with enriched innervations originating from and proceeding to surrounding basal forebrain, hippocampal and limbic regions. In and of itself, the amygdala may be effectively and unitarily processing the emotional, valence, attentional, conditioning, memory consolidation, cognitive, motivational and responsive components of our individualised reaction(s) towards emotional stimuli and situational events. The less significant and under-threshold activation of other region(s) of the brain registered concurrently as compared with the amygdala during studies when subjects are exposed to stimuli lends support to its autonomous capability in the core area of emotional processing and conditioning [9-11]. Nevertheless, this is not to undermine nor neglect the importance and participation of other brain regions in concert under such conditions, but rather to delineate the distinct role(s) and capability of the amygdala in this respect. Additionally, with the major classes of neuroreceptors and pathways available in place to function for this region, an integrated processing network provides for a cumulative emotional, and at times, physical, response in outcome.

**The Basis of Gender Differences in Amygdala Reactivity**

 With the overwhelming evidence of the amygdala as the central player in emotional processing and fear-motivated control and conditioning in the mammalian brain, it is worth noting gender differences in amygdala activation to emotional stimuli. Studies performed on this front have identified greater response from male subjects to positive valence stimuli while female subjects retained more persistent response to negative valence stimuli, with significant activity of the left amygdala in both genders [9-10]. It was reported that females showed greater response to fearful face stimuli than males, an implication of the greater involvement of fear-processing amygdala [11]. These gender differences likely have an evolutionary basis due to the history of opportunity suppression and a weaker physical build disadvantage of women by male-dominated societies. On the other hand, the contribution of the female hormone, oestrogen, to amygdala activity in the brain is further emphasised in a study of ovariectomised rats, which had their dopamine and serotonin levels compromised upon organ removal, a suggestion of dampened emotional response by males under certain condition(s) [12]. This oestrogen deficiency could have resulted in impaired motivation, of which dopamine levels are likely responsible, and decreased general affective appraisal and response by reduced serotonin. Once more, this reminds of the highly integrated and deeply interactive neurohormonal network spanning all systems of our human physiology.

DISCUSSION AND CONCLUSION

 Overall, it is clear and well supported that the functions of the major classes of neurotransmitter pathways, i.e. cholinergic, dopaminergic, serotonergic and noradrenergic both within and beyond the amygdala, are distinct in focus, yet highly collaborative in nature. As an example, cholinergic receptors and neurotransmission are distinctively and majorly involved in carrying out memory aspects of cognitive function while inputting their outcome or serve as connecting point/channel(s) with other classes of neurotransmitters. Each subset of memory retrieval and association, affective mood, reward or fear conditioning and learning and brain-to-peripheral sympathetic nervous system responses and processing are essential in calling an individual person’s attention to decision and action. It is the sound and profound integration of these neural networks that lead to a purposeful brain component working seamlessly for an individual pertaining to his/her emotional state and response(s) to external stimuli and circumstances. On the other hand, emotional processing and fear conditioning could be more integrated and closely attached to produce heightened responses by the functional role of the amygdala in women more than men, who are oppositely more attuned to positive stimuli compared to women. We shall not leave out the contributing factors of our ages of human history of evolutionary, societal and cultural impacts on opposite genders' upbringing and neuropsychological health as a result. Retrospective longitudinal analysis could be performed to shed light on this front. Future research should also investigate in detail the reason behind and critical factors that define the significant roles the left amygdala play (more than the right amygdala) in greater emotional reactivity and the extent that its volumetric variation in patient groups could affect a wide spectrum of neuropsychopathological conditions [13]. A probable hypothesis could be this limbic structure’s slight modest proximity to the key verbal and language processing region in the left hemisphere cortex of the brain, further strengthening memory associations and characteristic semantic aspects of perceived external stimuli, and in turn a bidirectional modulation of this language centre by the amygdala [14-16].

Word Count: 1381

REFERENCES

[1] Unal CT, Pare D, Zaborszky L. Impact of basal forebrain cholinergic inputs on basolateral amygdala neurons. Journal of Neuroscience, 2015; 35:853-863.

[2] Power AE, McIntyre CK, Litmanovich A, McGaugh JL. Cholinergic modulation of memory in the basolateral amygdala involves activation of both m1 and m2 receptors. Behavioural pharmacology, 2003;14: 207-213.

[3] Muller JF, Mascagni F, McDonald AJ. Cholinergic innervation of pyramidal cells and parvalbumin‐immunoreactive interneurons in the rat basolateral amygdala. Journal of Comparative Neurology, 2011; 519:790-805.

[4] Kukolja J, Schläpfer TE, Keysers C, Klingmüller D, Maier W, Fink GR, *et al.* Modeling a negative response bias in the human amygdala by noradrenergic–glucocorticoid interactions. Journal of Neuroscience, 2008; 28:12868-12876.

[5] Weidenfeld J, Ovadia H. The role of the amygdala in regulating the hypothalamic-pituitary-adrenal axis. The Amygdala-Where Emotions Shape Perception, Learning and Memories, 2017; 10:67828.

[6] Ma S, Morilak DA. Norepinephrine release in medial amygdala facilitates activation of the hypothalamic‐pituitary‐adrenal axis in response to acute immobilisation stress. Journal of neuroendocrinology, 2005; 17:22-28.

[7] Yoshimoto K, Ueda S, Kato B, Takeuchi Y, Kawai Y, Noritake K, *et al*. Alcohol enhances characteristic releases of dopamine and serotonin in the central nucleus of the amygdala. Neurochemistry international, 2000; 37:369-376.

[8] Takahashi H, Yahata N, Koeda M, Takano A, Asai K, Suhara T, *et al*. Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study. Neuroimage, 2005; 27: 991-1001.

[9] Andreano JM, Dickerson BC, Barrett LF. Sex differences in the persistence of the amygdala response to negative material. Social cognitive and affective neuroscience, 2014; 9:1388-1394.

[10] Killgore WD, Yurgelun-Todd DA. Sex differences in amygdala activation during the perception of facial affect. Neuroreport, 2001; 12:2543-2547.

[11] Lee SA, Kim CY, Shim M, Lee SH. Gender differences in neural responses to perceptually invisible fearful face—an ERP study. Frontiers in Behavioral Neuroscience, 2017; 11:6.

[12] Izumo N, Ishibashi Y, Ohba M, Morikawa T, Manabe T. Decreased voluntary activity and amygdala levels of serotonin and dopamine in ovariectomized rats. Behavioural brain research, 2012; 227:1-6.

[13] Hajek T, Kopecek M, Kozeny J, Gunde E, Alda M, Höschl C. Amygdala volumes in mood disorders—meta-analysis of magnetic resonance volumetry studies. Journal of affective disorders, 2009; 115: 395-410.

[14] Citron FM, Michaelis N, Goldberg AE. Metaphorical language processing and amygdala activation in L1 and L2. Neuropsychologia, 2020; 140:107381.

[15] Isenberg N, Silbersweig D, Engelien A, Emmerich S, Malavade K, Beattie B, *et al*. Linguistic threat activates the human amygdala. Proceedings of the National Academy of Sciences, 1999; 96:10456-10459.

[16] Aryani A, Hsu CT, Jacobs AM. Affective iconic words benefit from additional sound–meaning integration in the left amygdala. Human brain mapping, 2019; 40:5289-5300.

Author Contribution:

RK drafted and contributed to editorial changes in the manuscript. RK read and approved the final manuscript.

The authors declare there are no conflicts of interest.