Viewpoint Paper

Neuropsychology of Generalized Anxiety Disorder

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INTRODUCTION

Anxiety is a response that is future oriented and has a global perspective involving cognitive and emotional components. The person is inordinately apprehensive, tense and uneasy about the prospect of something terrible happening. Anxiety disorders are characterised by excessive fear and anxiety and related disturbance in behaviour. Generalised Anxiety Disorder (GAD) is characterised by anxiety and worry that is not associated with a particular object, situation or event but seems to be a constant feature of a person's day to day existence [1]. Symptoms of GAD include restlessness, sleep disturbances, fatigue, irritability, muscle tension and trouble concentrating. The diagnostic criteria for GAD is as follows [2] –

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):

(Only one item is required in children.)

1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).

F. Enquire about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Anxiety is a natural emotion occurring in responses to real or perceived threat in the environment and plays an important role to prepare an organism to cope with it. Being an emotion, it is not only cognitive, it also has somatic responses. These responses and perception of threat are largely guided by the ventral striatum and the prefrontal cortex. Philip Bard was among the first to study the role of the thalamus and

the hypothalamus in the expression and autonomic responses in emotions. The thalamus also plays a role in activating the cortex to help direct the emotion to the appropriate stimuli [3]. In a study by Dimond, it was found that the left and the right hemispheres could have different emotional views of the world- a lesion in the left hemisphere could result in a more negative view of the stimuli [3]. Emotional responses require perception of the stimuli. The cortical and sub-cortical regions of the temporal and parietal lobe are involved in object recognition and spatial location, thus playing a role in the perception. The key role in emotions however, is played by the limbic lobe (or the limbic system). It consists of the hippocampus- associated with memory, focus and motor control through trial and error; amygdala- associated with fear and anxiety; hypothalamus- responsible for regulating hormones.
The hippocampus, since responsible for memory functions is activated during anxious arousals. The activation of the hippocampus implies that previous experiences related to the stimuli can further aggravate the anxiety. The amygdala, as stated is responsible for regulating emotions and detecting possible threats. It is also responsible in aiding the hypothalamus for releasing hormones suitable for the response to the perceived threat. The hypothalamus plays a critical role in anxiety by controlling the autonomic nervous system and release of hormones and neurotransmitters. One of the hormones released by the endocrine system is the corticotrophin-releasing hormone (CRH). High levels of this stress hormone are related to anxiety behaviours. The CRH also helps in regulating the hypothalamic-pituitary-adrenocortical (HPA) axis. In various studies conducted, it was found that by stimulating points in the hypothalamus, it was possible to elicit escape behaviour or defensive aggression [4], thus brain damage or pressure on the regions of the limbic system can produce excessive anxious behaviours.

While it is easy to assume the independent role of the limbic system in GAD, one would be wrong to assume so. The limbic system and the other regions of the brain work in unison through neural networks. Thus, disturbances in neural networks in relation to the limbic system would play a key role in the neurology of determining Generalised Anxiety Disorder. Various studies have been conducted to study the role of other brain areas in worrying, a common symptom in GAD. In a study conducted [5], it was found that a deregulation in the areas of the medial prefrontal cortex and the anterior cingulate regions plays a role in excessive worrying in GAD patients. They exposed eight patients with GAD and twelve normal participants (control group) to mood inducing paradigms presented either as spoken statements or faces. They found that the anterior cingulate and dorsal medial prefrontal cortex were involved in triggering worry in both groups. However, for the patients with GAD, there was a constant activation in these areas even during the resting period post the worry-inducing phase. These regions are responsible in mentalization and introspective thinking. While the frontal lobe is not involved in eliciting emotional responses, it is responsible for cognitive skills related to resolving issues. Damage to the frontal lobe can lead to difficulties in concrete thinking and lead to the person being fixated on trivial concerns leading to elevated levels of anxiety [6].

A hallmark study was conducted at Stanford University in 2009 to understand the differences in neural networks between people with GAD and psychologically healthy people. The study involved sixteen people with GAD and 17 psychologically healthy people. Using fMRI scans, their blood flow fluctuations were measured while they spent eight minutes in the scanner while letting their minds wander. Findings showed that in healthy participants, the basolateral amygdala was linked to the temporal, occipital and prefrontal lobes. The centromedial amygdala was linked to the thalamus (controlling information flow and alertness), the brain stem (regulating release of serotonin and dopamine) and the cerebellum (controls motor coordination). In people with GAD, the neural pathways were different. The basolateral amygdala was connected more with the centromedial targets. This implied less processing of the information sent from the prefrontal, temporal and occipital lobes and the inability to determine the importance of a stimuli [7].
GAD is also associated with disrupted white-matter coherence in the posterior right hemisphere, thereby explaining the impaired cognition involved when dealing with anxiety [8]. Decrease in the gray matter in the amygdale has also been found in children with anxiety disorders as compared to normal participants. Thus, as supported by various studies, the concentration of grey matter in the amygdale plays an important

role in anxiety disorder. With decreased grey matter in the region in childhood, the condition could set a precursor for adult anxiety disorders too [9]. There has also been some relation between neuroticism and GAD. Genetic factors that affect neuroticism have seen to be overlapping factors that increase the liability for GAD, in males and females [10-11].

CONCLUSION

In conclusion, GAD is a function of disturbance in the areas controlling and regulating emotions and emotional responses. These areas of the brain are predominantly the limbic system- amygdala, hippocampus and hypothalamus. These areas however are not responsible independently, rather, they are closely related to the neural pathways that connect these areas of the brain to the prefrontal cortex and its deeper parts and the temporal lobe.

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