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Brain structures associated with obsessive-compulsive disorder

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Obsessive-Compulsive Disorder (OCD) is characterized by absurd, recurrent and uncontrollable thoughts (obsessions), which are followed by persistent urges to perform certain stereotyped actions (compulsions). The repetitive actions performed by OCD patients serve to neutralize the anxiety precipitated by obsessions. Most of the patients suffering from OCD realize the irrational nature of their thoughts and rituals but feel hopeless and helpless in controlling them. The probable causes of OCD include heredity, brain damage due to accidents/infection, abnormal brain glucose metabolism and serotonergic dysfunction. The brain regions impaired in OCD include basal ganglia, orbito-frontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex, amygdala, thalamus and brainstem. The repetitive rituals (compulsions) and aggressive behavior, which is predominant in OCD patients is probably due to serotonin depletion. Entire brain functioning is disturbed in patients suffering from OCD, thereby producing devastating effects at the work-place as well as at homes of the patients.

Background:

Obsessive-Compulsive Disorder (OCD) is characterized by absurd, recurrent and persistent thoughts (obsessions) followed by certain stereotyped actions (compulsions). The Patients affected by OCD feel compelled to carry out certain stereotyped actions, although they recognize that their behavior is at times irrational. The repetitive actions performed by OCD patients serve to neutralize the anxiety precipitated by obsessions. OCD may be defined as the trigerring in the mind of uncontrollable, egodystonic and recurrent thoughts, impulses or images.

Obsessive-Compulsive disorder can impair all areas of brain and produce devastating effects on patients and their families. The brain regions impaired in OCD include basal ganglia, orbito-frontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex, amygdala, thalamus, brainstem and striatum. Selective serotonin reuptake inhibitors (SSRIs) and to some extent tricyclic antidepressants form the main stay in the symptomatic treatment of OCD. However, none of the above medicines provide complete relief and permanent cure from OCD. Therefore, there is a great challenge before neurobiologists to discover new strategies for the management of OCD.

Brain structures associated with OCD :

Dorsolateral prefrontal cortex (DLPC):

It is the most important cortex part for cognitive functions in human beings. The involvement of the DLPC in working memory was initially demonstrated in primate studies. The DLPC also plays a role in adaptation to changes in the environment. DLPC plays a crucial role in focusing attention on specific stimuli and in decision-making (Miller, 1999). Lesions of DLPC disturb the subject's ability to process temporal information and impair the successful performance of goal-directed behaviors. Functional neuroimaging data have shown diminished activity in the DLPC of patients suffering with psychiatric disorders such as major depression and OCD, which may account for the difficulty in overcoming compulsive behaviors (Saxena *et al.*, 1998).

Anterior cingulate cortex (ACC):

Neuroimaging studies indicated that the ACC is involved in a variety of cognitive processes such as attention, motivation, reward, error detection, working memory, problem solving and action-plan (Bush *et al.*, 2000). There are two major regions within ACC *viz.* a dorsal region, known as the cognitive region, and a ventral or affective region. The cognitive region is a part of attentional netwok and is closely connected with the DLPC, premotor, and parietal cortices whereas, the affective region is linked to the amygdala, nucleus accumbens, hypothalamus, anterior insula, hippocampus and OFC and sends projections to the neuro-vegetative,

viscero-motor and endocrine systems. Excessive activation of ACC has been reported in patients presenting psychiatric disturbances such as phobias, OCD and mood disorders. Moreover, electrophysiological studies in man have demonstrated its particular role in error detection processes.

Basal ganglia-thalamo-cortical circuits:

Basically, the role of the basal ganglia is to integrate the various inputs arriving from the cortex and to use this information for selecting certain motor and/or cognitive programs. The point of entry of information to the basal ganglia is through striatum, which receives converging information from the limbic and associative cortices. It then sends projections to the output structures, *i.e.* the globus pallidus pars internal is (Gpi) and the substantia nigra pars reticulata (SNr), through two pathways: one direct and the other indirect. The indirect pathway successively involves the globus pallidus pars externalis (Gpe) and the subthalamic nucleus (STN). In addition, the cortex sends direct inputs to the STN and the connections between the Gpe and Gpi. These two pathways seem to play opposite roles in controlling cortical activity. Activation of the direct loop facilitates the triggering of programs at the cortical level through a double inhibition. On the other hand, the indirect loop blocks the activation of thalamic relay by increasing the activity of the Gpi, a GABA-ergic inhibitory structure. Dopamine of nigral origin seems to facilitate the direct pathway through Dl receptors and plays an inhibitory role on the indirect pathway through D2 receptors. The pathological activation of segregated closed loop circuits involving cortex-basal ganglia-thalamus-cortex pathways would produce reverberating activity and result in a persistent discharge of the innate programs characteristic of OCD. The clinical manifestations of neuronal disorders of the basal ganglia can be viewed as a disruption of information processing at the cortical level due to the loss of the focusing action of subcortical inputs.

Orbito-frontal cortex (OFC):

The OFC is a large brain region, which encompasses both rostral and ventromedial areas. Because, it receives multimodal inputs from the temporal association cortex, amygdala and hypothalamus as well as limbic components of the basal ganglia, it has been viewed as the highest integration center for emotional processing (Krawezyk, 2002). By analogy with the Dorsolateral prefrontal cortex (DLPC), which is the prefrontal area for parietal lobe, the OFC can be regarded as the prefrontal area for the temporal lobe. The OFC seems to play a role III situations involving incentives/bonus/rewards and in conditions, where the subject has to make rapid alterations in behavior to accommodate the environmental changes. Several lines of evidence suggested that OFC played a crucial role in the decision-making process based on rewards. Patients with orbitofrontal damage experience great difficulties in decision making. They also tend to take risks, whether profitable or not (Miller, 1985). Experimental lesions of OFC in monkeys have shown impairment in reward-related learning tasks and irrespective of the nature of the sensory context. These monkeys also exhibited an absence of emotional reaction to environmental stimuli. OFC neurons become particularly active, when the animal is placed in a situation where, it expects and receives a reward. Interestingly, face selective neurons have been reported in OFC, which may be relevant in the detection of facial expression which is a critical point in social decision. These neurons may be involved in the association between a positive reward value and a particular facial expression. The OFC seems to playa predominant role in motivational aspects of decision-making. Among the more posterior cortical areas, the left inferior parietal cortex and parieto-occipital junction are involved in cognitive tasks related to visual imagery. The underactivity of these regions could probably explain the spatial memory deficits and visual memory deficits observed in OCD patients. The repetitive rituals (compulsions) and aggressive behavior, which is predominant in OCD patients is probably due to serotonin depletion.

Striatum:

The striatum is known to be formed by two types of information-processing modules: the striasomes and the matrisomes. The striasomes receive information from the limbic structures such as amygdala, OFC and ACC (Eblen and Graybiel, 1995). In turn, they send projections to the dopaminergic neurons of the substantia nigra. These anatomical findings suggest that the striasomes could also playa role in the emotional modulation of cortical information. The matrisomes receive information from the lateral parts of the premotor and prefrontal cbrtices, which are involved in the anticipation behavior and planning (Flaherty and Graybiel, 1994). The cholinergic inter-neurons of the striatum, *viz.* tonically active neurons (TANS), may be playing a particular role in integrating the information flowing through the striasomes and matrisomes. These neurons could constitute a neural system that is involved in the processing of several aspects of information, such as the detection of unpredicted events or the context of stimulus discrimination (Ravel *et al.*, 2001).

The limbic part of the striatum (ventral striatum) under the control of the dopaminergic afferents might be involved in reward-driven learning processes. On the other hand, the dorsal striatum seems to be involved in the procedural learning of behavioral routines that are performed almost without conscious effort. In particular, in the context of procedural learning, the disruption of the "readiness" and "release" functions ascribed to the striatum might support some aspects of OCD pathophysiology. However, the striatum could also playa part in other processes potentially disrupted in OCD, such as emotional modulation of information and representation of the expected consequences of action. On the other hand, the performance of repetitive behaviors in OCD patients might have a positive effect on the reduction of anxiety, a process that can be assimilated to some form of reward.

Amygdala:

In the past decade, much research has been focused on the neural substrates that are involved in the expressions of fear and anxiety. The amygdala and its various outputs might playa major role in mediating the clinical signs and symptoms of fear and anxiety (Le Doux, 2000). Schematically, the amygdala is comprised of several nuclei, such as the lateral nucleus, basolateral nucleus and central nucleus. However, recent evidence supports the fundamental idea that the amygdala is not only involved in negative emotions such as fear and anxiety but also in reward and motivational processes through reciprocal connections to the nucleus accumbens and the OFC. Thus, the amygdale appears to play an important role in the expressions of emotion and motivation, probably through its connections with the OFC, ACC and ventral striatum. A dysfunction of this structure, as suggested by some neuroimaging studies in OCD patients, might mediate the non-specific anxiety experienced relative to obsessive thoughts.

Thalamus:

The diencephalic position of the thalamus in the brain explains why it receives large cortical inputs. It participates in emotional expression through the AN (anterior nucleus of the thalamus), which is connected to the MB (mammillary bodies) and, in turn, sends projections to the ACC. The putative role of the VA (ventral anterior nucleus of the thalamus) in cognitive functions involving attention and working memory is based on the link with DLPC. Discrete parts of the MD (medial dorsal nucleus of the thalamus) seem to be important in both emotional and cognitive processing through their preferential anatomical connections with the OFC and DLPC. Thalamic dysfunction has been associated with deficits in executive functions like planning, goal directed behavior, attention, and working memory (Lacerda *et al.*, 2003).

Brainstem inputs:

The mesocorticolimbic dopaminergic system emanates from the ventral mesencephalon, which encompasses the Ventral tegmental area (VTA), arid projects to the nucleus accumbens with other limbic ventral striatal regions and cortical areas, especially the OFC, DLPC, ACC. The effects of the lesions, receptor blocking agents, electrical stimulation and self-administration of drugs of abuse suggest the effective contribution of the mesocorticolimbic system in the attentional, emotional and motivational processes. Dopamine contributes to the organization and regulation of goal-directed behavior. The serotonin-producing neurons are mainly located in the brainstem raphe nuclei. The description of the anatomy and development of the brainstem raphe nuclei has shown that they form the largest and most complex neurochemical efferent system in the human brain. General theories have attributed a broad range of behavioral functions to serotonin, which is considered as a general inhibitor of motor behavior. In contrast, reduced serotonin function has been shown to increase exploration, locomotor activity, aggression and sexual behaviors in animals and human beings (Lucki, 1998). The repetitive rituals (compulsions) and aggressive behavior, which is predominant in OCD patients is probably due to serotonin depletion.

Pathophysiology :

The probable causes of OCD include heredity, brain damage due to accidents/infection, abnormal brain glucose metabolism and serotonergic dysfunction. The Group A Beta-Hemolytic Streptococcal (GABHS) infections produce anti-neuronal antibodies that adversely affect basal ganglia cells, which might lead to the development of OCD (Swedo *et al.*, 1998). The susceptibility marker that may predispose some individuals to develop OCD has been well identified. D8/17 (the antigen present on the surface of peripheral blood mononuclear cells) positive individuals develop OCD as a consequence of their autoimmune response to Group A beta-hemolytic streptococcal infection, a response that is believed to yield antibodies which cross react with basal ganglia antigens and produce tissue damage. The orbitofrontal cortex that had been demonstrated to be overactive in OCD is a region mediating the active expression of emotional response to

significant biological stimuli as well as the inhibition of behavioral response. Several theories have attributed a broad range of behavioral functions to serotonin, which is considered as a general inhibitor of motor behavior. In contrast, reduced serotonin function has been shown to increase exploration, locomotor activity, aggression and sexual behaviors in animals and human beings. The repetitive rituals (compulsions) and aggressive behavior, which is predominant in OCD patients is probably due to serotonin depletion. Beyond serotonin, other neurotransmitters like dopamine may be involved in OCD's pathophysiology, since a preferential combination of SSRIs and low-dose dopamine antagonists yield beneficial results. The wide use of selective serotonin reuptake inhibitors like clomipramine, fluoxetine, paroxetine is implicative of the fact that dysfunction of 5-HT could be probably the prime reason for developing obsessive-compulsive disorder.

Conclusion :

Obsessive-Compulsive Disorder (OCD) is an anxiety disorder featuring intrusive and troubling thoughts, which are perceived as the products of one's own mind unlike schizophrenia. OCD is characterized by absurd, recurrent and uncontrollable thoughts (obsessions), which are followed by persistent urges to perform certain stereotyped actions (compulsions). Most of the patients suffering from OCD realize the irrational nature of their thoughts and rituals but feel hopeless and helpless in controlling them. The probable causes of OCD include heredity, brain damage due to accidents/infection, abnonnal brain glucose metabolism and serotonergic dysfunction. The brain regions impaired in OCD include basal ganglia, orbito-frontal cortex, anterior cingulate cortex, dorsolateral prefrontal cortex, amygdala, thalamus and brainstem. Entire brain functioning is disturbed in patients suffering from OCD, thereby producing devastating effects at the work-place as well as at homes of the patients.

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