Newer Developments

Newer Trends in Neuroimaging of Depressive Disorders

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Introduction

Major depressive disorder (MDD) is the most common psychiatric disorder. Unipolar depressive disorder constitutes the fourth most common cause of disability in both sexes, all ages as per the Global Burden of Disease, 2000.[1]

It is also the most important precursor of suicide, will be the second cause of global disease burden by the year 2020, according to the World Health Organization.The lifetime prevalence of Major depressive disorder is 10-25% for women, 5-12% for men.[2]

In National Comorbidity Survey , 30-40% of the General population found a lifetime criterion-based depressive disorder of which most had major depressive disorder, most were women.[3] The prevalence rates of depression from India range from 1.5/1000 to 37.74/1000.[4] Higher rates of depression have been reported in rural compared to urban population.[4,5] Preponderance of females in depressive disorder is consistent finding from India.[4,5]

Despite the high prevalence figures of MDD ,the etiology and the pathophysiology of MDD are not fully understood .There is increasing evidence that MDD is a "functional" disorder.[6] These conditions were not associated with gross brain pathology or with clear animal models for spontaneous, recurrent mood episodes, the availability of noninvasive tools allowing assessment of the human brain proved critical in understanding their neurobiology. The recent development of neuroimaging techniques that permit in vivo characterization of the anatomical, physiological and neurochemical correlates of mood disorders thus has enabled significant advances toward understanding the pathophysiology of these conditions. Notably, the results of neuroimaging studies and the post mortem studies guided by neuroimaging results have given rise to neurocircuitry-based models in which both functional and structural brain pathology play roles in the development of mood disorders.

Neuro Imaging Techniques

Computed axial tomography and Magnetic Resonance Imaging (MRI) scans have permitted sensitive ,noninvasive methods to assess the living brain, including cortical and subcortical tracts,as well as white matter lesions. In vivo, structural and functional imaging studies have confirmed that abnormalities of some specific regions of the brain (e.g., the frontal cortex,[7,8] cingulate cortex,[7,9] basal ganglia,[10-12] hippocampus,[13,9]and parietal lobe[8,14,15]) are involved in the etiology of MDD. Postmortem studies of patients with MDD have also revealed abnormalities in the frontal cortex[16] and basal ganglia.[17] In the last 2 decades, it has been suggested that cortical–subcortical neuronal circuits play an important role in the pathogenesis of MDD, especially the frontal– striatal– thalamic neuronal circuits.[11,18,19] The limbic–thalamic–cortical networks have also been reported to be crucial in the etiology of MDD.[11,13,14]

White matter, which connects regions of the brain anatomically and functionally, has been considered to play an important part in the pathophysiology of MDD. Structural imaging studies have reported a significant increase of white

matter hyperintensities, which suggests that a change in water content in the frontal[20,21] and parietal[21] lobes occurs in patients with major depression, mostly in late-life depression. Ventricular enlargement,cortical atrophy, and sulcal widening also have been reported in some studies. Some studies have reported significant bilateral reduction of white matter volume in the anterior cingulate cortex, the gyrus rectus[7] and the hippocampus[13] in patients with MDD. Such kind of studies have reported more focal defects in relevant neurobehavioral systems. The other studies found that cognitive impairment was correlated with lesions in white matter of patients with major depression.[12,22]

Diffusion Tensor Imaging (DTI) is a variation of magnetic resonance imaging that measures the diffusion of water in tissues. DTI is particularly useful for examining cerebral white matter and neural fiber tracts.[23] It yields an index of principle directionality of diffusion termed fractional anisotropy (FA).[24] In white matter, the principle direction of water diffusion is along the myelinated tracts, so DTI is a quantitative method to evaluate the integrity of white matter connectivity in vivo. The 2 major methods employed to analyze DTI data are manual measurements of regions of interest (ROIs) and voxel-based analysis. A conspicuous limitation of the manual ROI method is its lack of standard guidelines for the delineation of specific regions of the brain that can not avoid artificial errors completely. However, voxel-based analysis has no such shortage and can detect the abnormal regions throughout the brain. Both approaches have been widely used in neuroimaging studies of psychiatric diseases such as schizophrenia,[25] bipolar disorder[26] and depression.[27-30]

DTI studies of depressed patients using the ROI method mostly concentrated on late-life depression or geriatric depression. They found consistently decreased FA values in the white matter of the frontal cortex[27-30] and the anterior cingulate cortex (ACC),[29] suggesting the disruption of the structural integrity of white matter in geriatric patients with depression. Some studies of late-life depression mentioned that FA values of the inferior frontal lobe were negatively related to the severity of depression[27] and that lower FA values lateral to the ACC were associated with a low rate of remission. However, fewer studies have focused on white matter abnormalities (e.g., white matter hyperintensities;[31] the reduction of the white matter volume in the frontal lobe;[32] and decreased FA values in the right middle frontal gyrus, the left lateral occipitotemporal gyrus, the subgyral and angular gyri of the right parietal lobe[33]) in younger patients with MDD. These studies had small samples and relatively low field strength MRI systems.

Positron Emission Tomography (PET) and functional MRI scanning are currently quite powerful methods for visualizing brain activity during rest and various states of activation. Normal sadness is associated with an increase in blood flow and neuronal activity in the thalamus and medial PFC. This appears to be a nonspecific change associated with diverse emotional responses. More specific activation is seen in the left amygdala, hippocampal formation,and parahippocampal gyrus. Sadness generated by one"s own thoughts (as opposed to a video scenario)and anticipatory anxiety are associated with a relative increase in blood flow to the anterior insular cortex.

The most widely replicated PET finding in depression is decreased anterior brain metabolism, which is more pronounced on the left side.[34] Depression may be associated with a relative increase in nondominant hemisphere activity. These abnormalities have been observed in unipolar and bipolar depressions and appears to be state dependent. There is a reversal of hypofrontality after shifts from depression into hypomania, such that there are greater left hemisphere reductions in depression compared to greater right hemisphere reductions in mania. Other studies have observed more specific reductions of reduced cerebral blood flow or metabolism, or both, in the dopaminergically innervated tracts of the mesocortical and mesolimbic systems in depression. There is evidence that antidepressants atleast partially normalize these changes.[35]

Functional Neuroimaging Studies have been used to assess the relation between emotional processing biases and functional brain response in patients with mood disorders. A consistently reported finding in mood disorders is a mood-congruent processing bias, which is defined as a tendency to bias stimulus processing towards

negative information as compared to positive or neutral information [36]. In memory studies, currently depressed patients have enhanced recall for negatively toned material as compared to positively toned information[37]. In the context of attention paradigms, depression-related negative words produce more interference on emotional stroop tasks than do happy or neutral words.[38,39] The amygdala shows elevated levels of activity in MDD during exposure to sad faces[40], masked fearful faces [41]

Neural Circuits Affected by Mood Disorders

Evidence from neuroimaging, neuropathological and lesion analysis studies implicate brain networks like (the limbic-cortical-stiatal-pallidal-thalamic circuits, formed by connections between the orbital and medial prefrontal cortex, amygdala, hippocampal subiculum, ventro medial striatum, mediodorsal and midline thalamic nuclei and ventral pallidum) implicated in the pathophysiology of depression. The dysfunction that alters transmission through these circuits produce the pathological emotional symptoms of depression as included in the diagnostic criteria of current classifications. The animal models have further proposed the involvement of the sensory association areas and the dorsomedial/dorsal anterolateral prefrontal cortex, cingulate cortex, parahippocampal cortex in depression.

Antidepressant treatment effects

The effects of antidepressants treatment on circuitry-based models may elucidate common neurophysiological mechanisms that underlie their therapeutic benefits, despite the diversity of their primary actions in the brain. Cognitive-behavioural strategies for managing depressive symptoms may instead rely upon enhancing the function of these medial prefrontal cortex systems, thereby enhancing the normal role of cortico-limbic circuits in modulating emotions.

Conclusion

Major Depressive Disorder (MDD) will be the second cause of global burden of disease by the year 2020 according to World Health Organisation. There is an urgent need to understand the neurobiology of depression. The availability of non invasive in vivo neuroimaging techniques allow the assessment of the anatomical, physiological and neurochemical correlates of mood disorders. Neurocircuitry based models from neuroimaging form the basis for developing better therapeutic strategies.

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