

Section 1

General

Chapter

1

Brain Imaging Methods in Mood Disorders

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1.1 Introduction

Mood disorders are the most common mental illnesses with a lifetime prevalence of up to 20% worldwide (1). Major depressive disorder (MDD) and bipolar disorder (BD) are significant health problems in the United States and worldwide (2). In the United States alone, the lifetime prevalence of MDD is up to 17%, and that of BD about 2.1% (2) that can go up to 4% of individuals with mood episodes not meeting episodic criteria included. Both are chronic illnesses characterized by recurrent episodes of depression and mania and depression in MDD and BD, respectively. Severe and disabling forms of BD and MDD are associated with increased risk of suicide, decline of physical health, and reduced productivity, and both conditions are associated with high rates of completed suicide of up to 8% (3). Furthermore, MDD and BD are associated with substantial economic burden of over \$200 billion (4) and \$45.2 billion each year (5), respectively, in USA alone that are primarily related to lost productivity (6).

1.2 Clinical Features

Typically the depression symptoms are similar in both conditions and characterized by symptoms such as depressed or irritable mood, tiredness, lack of interest in pleasurable activities, poor sleep and appetite, low self-esteem, cognitive difficulties, and suicidal thoughts. BD is characterized by recurrent periods of elevated and depressed mood and energy levels with marked deficits in cognitive function interspersed with periods of euthymia. Mania and depression episodes are also associated with impairment in reward processing with excessive pleasure-seeking behavior (7). The diagnoses of MDD and BD are primarily clinical and are currently made by the use of clinical interview, or by using

reliable diagnostic interviews such as the Diagnostic and Statistical Manual of Mental Disorders, or DSM, and the International Classification of Diseases (ICD). The precise boundary between major depression and BD is a matter of current active research, but patients who suffer from milder forms of mania (hypomania) are now classified as bipolar II disorder. Whether the presence of lesser degrees of mood elevation in patients with major depression should lead to a diagnosis of bipolar spectrum disorder is still uncertain, and more research is required (8, 9). DSM-5 also contains a new illness specifier for “mixed episode” when mania and depression symptoms overlap and thus illustrate the diagnostic complexities when based on clinical signs and symptoms alone.

Furthermore, cognitive deficits, long duration of illness, persistent depression symptoms, and level of education have been associated with employment among people with BD (10, 11) and contribute to poor clinical outcomes in patients. Cognitive deficits (verbal learning, memory, sustained attention, and executive functioning) (12, 13) are present as early in the first manic episode even after clinical remission (14); are unaffected by medication status (15); and are shown to be strongly predictive of subsequent occupational recovery (16).

Current treatments are usually selected on a trial-and-error basis, uninformed by illness- or treatment-specific biomarker (17, 18), with nearly 50% of depressed patients unfortunately not adequately responding to treatment (24, 26). In BD, conventional antidepressants are either not effective (19) or may increase the risk of a switch into mania (20) and thus associated with treatment resistance and substantial morbidity (17). Accordingly, personalizing treatment by developing noninvasive and clinically useful biomarkers of antidepressant response is a critical priority.

1.3 Etiology and Pathophysiology of Mood Disorders

The etiology of mood disorders is multifactorial and is conceived as an illness with a polygenic basis and environmental interactions contributing to the etiology and pathogenesis of the illness. MDD runs in families, and twin and adoption studies have shown that this can be accounted for in some measure by genetic factors (21, 22), although heritability estimates (37%) are substantially less than those for BP (85%) and schizophrenia (83%) (23). Progress in identifying specific genes predisposing to mood disorders through association and linkage studies is still ongoing. Genetic similarities with bipolar I disorder and schizophrenia are high, and so is the correlation of bipolar II disorder with MDD. Genome-wide linkage studies in BP found involvement of biological pathways that include glutamate signaling calcium channels, second messenger systems, and hormonal regulation (24).

The biochemical pathophysiology of depression and BP is not well known. Astute clinical observations and serendipitous discoveries of psychotropic medications led to the neurotransmitter-based theories that dominated the biological research over the last five decades. Monoamine hypothesis suggests that depression is caused by either a functional deficiency of noradrenaline (25–27) or serotonin function, or both, in the central nervous system (28–30). Similarly, dopaminergic models of the mania symptoms are well researched. Pathophysiology of BD is mostly unknown, but disrupted energy metabolism (31) and mitochondrial dysfunction have been proposed as pathophysiology of BD (32–35). Lithium's neurotrophic and neuroprotective effect is thought to be related to the treatment response in BD and changes in glutamate excitatory and inhibitory GABA mechanisms that underlie antiepileptic drugs are also relevant in the treatment of the BD.

1.4 Neuroimaging Techniques

Neuroimaging has played remarkably in the progress of clinical neurological practice and has been widely used in the diagnosis, prognosis, treatment, and monitoring of many neurological conditions. X-rays of the skull were the first neuroimaging tool but now are mostly replaced

by the use of newer technologies such as computed tomography (CT scans) and magnetic resonance imaging (MRI). Functional brain activity can be studied using magnetic resonance spectroscopy (MRS), positron emission tomography (PET), and functional magnetic resonance imaging and spectroscopy (fMRI and fMRS). MRI has become a powerful tool in medical practice and research due to its noninvasive approach and the unmatched anatomical detail that it captures. MRI combined with new methods of processing and analysis has transformed the field of structural and functional brain imaging. With the advent of higher-resolution scanners, MRI allows the study of changes in brain volume or size in greater detail than previous imaging techniques such as CT scans. MRI-based fiber tract studies use advanced techniques such as diffusion tensor imaging and magnetization transfer to study white matter integrity and fiber tracts involved in functional integration between anatomically separate cortical regions. Positron emission tomography is a three-dimensional imaging technique based on nuclear medicine principles to study biological, pharmacological, and physiological functions in vivo. Positron emission tomography, when combined with a suitable radiotracer, can be a potent tool to study a protein target such as receptors, transporters, enzymes, or similar biological targets. The uptake of (18 F) Fludeoxyglucose (18 F-FDG) by tissues has been widely used in clinical medicine as a marker for the tissue glucose uptake correlating with metabolism. Magnetoencephalography (MEG) and Electroencephalogram (EEG) are combined with other imaging modalities and used to study electrical brain signals and for mapping brain activity. Now, neurological diagnostic examination often involves neuroimaging to investigate brain tumors, degeneration, vascular and other lesions, and functional changes.

1.5 Clinical Applications of Neuroimaging

Multiple sclerosis (MS) is a good case example of the clinical application of neuroimaging. Multiple sclerosis is a chronic, progressive, relapsing, and remitting neurological disease characterized by damage to myelin and axons of the central nervous system causing several motor, sensory, and cognitive consequences, and also highly comorbid

with mood disorders. MRI has remarkably transformed the clinical diagnosis, treatment, and prognosis. It helped to establish the evidence of structural and functional lesions in MS and thus is widely used as a disease biomarker (36, 37). Until the 1980s, the diagnosis of MS was mainly made using clinical features but now it is primarily MRI based using McDonald's criteria (38).

Our understanding of putative neural substrates and pathophysiology of MDD and BD is increasingly advanced by imaging technology. Studies utilizing these techniques continue to provide growing insight into the pathophysiology of BD. MRI brain anatomical studies show widespread cortical and subcortical brain volume changes and increased rates of deep white matter hyperintensities in BD. Although several brain regions have been implicated as abnormal using MRI in BD, the prefrontal cortex (PFC) is of particular interest, and several studies have uncovered structural pathology in the PFC among patients with BD. These volume changes are consistent with postmortem studies that found reductions in neuronal size and neuropil volume in the hippocampus and reductions in glial cell numbers in PFC (39) and brain volume in BD patients (40). Functional MRI studies consistently found alterations in cortico-limbic-striatal responses to emotional stimuli in mood disorders in frontal, amygdalar, and striatal regions in response to negative stimuli when compared to positive stimuli (41). Deficits in cognitive control, memory, and attention are consistently observed in adults and children with BD and their family members, which indicates that dysfunctions in fronto-limbic and temporal circuitry and cognitive impairment are endophenotypic markers for BD (42). Mania and depression episodes are also associated with excessive pleasure-seeking behavior and reduced hedonic capacity, respectively, which suggests alterations in neural processing and regulation of reward function (7, 43). These findings support the hypothesis of a shared, interactive brain network for cognition and mood. Emerging neuropsychological and functional brain imaging studies suggest abnormalities in reward processing in patients with BD even during euthymic periods (7). Thus neuroimaging uncovers several areas of brain function abnormalities and may help develop a more comprehensive and evidence-based assessment of mood disorder symptoms.

1.6 Conclusion

Mood disorders, both MDD and BD, are devastating illnesses with deleterious functional and social consequences for both the affected individuals and their families. Multiple lines of evidence suggest anatomical alternations and impairment of neurocircuitry in the critical mood and cognitive circuits. Advances in neuroimaging have made phenomenal changes in the practice of neurology. Similar changes in the clinical practice of psychiatry are long overdue. The application of newly available methods from brain imaging to the study of mood disorders holds substantial promise to elucidate the brain mechanisms implicated in these illnesses. Neuroimaging combined with other developments in the field of clinical neuroscience can leapfrog the current deficits in our understanding of mood disorders and help develop biological markers and evidence-based treatments.

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