

Depression May Be a Complication of Various Brain Disorders: Neuroimaging Evidence

Introduction

Depression is a complex multifactorial psychiatric disorder affecting a large number of people. The heightened risk of suicide and economic burden make depression a major health concern [1]. Compelling data suggest that higher mental functions, executive function, awareness, planning, strategic thinking, initiative and processing sensory input are the domain of prefrontal cortex function and in particular Brodmann areas 8,9,10,42 and 46 [2].

It is noteworthy that the core depression symptoms of diminished joy, energy, self-confidence, problem-solving ability and ability to make strategic plans are also manifestations of diminished prefrontal cortex function.

Recent studies have also suggested that the mediating influence of prefrontal cortex function is crucial in depression and in antidepressant strategies [3]. The etiology and pathophysiology of depression have been subjects of intense speculation. A number of molecular mechanisms have been advanced yet inconsistent results over time have weakened their basic foundations. Is it possible that most depressions are secondary to complications and progression of various brain disorders?

This possibility may be supported by several observations. For instance it has been observed that a great many psychiatric disorders often precede or accompany depression and have been diagnosed by the Diagnostic Statistical Manual Of Psychiatric Disorders as comorbid conditions [4]. DSM architecture precludes any possible complication of psychiatric disorders and classifies them as comorbid conditions. This raises the possibility that some DSM disorders may represent complications of various brain dysfunctions. This study will try to investigate whether depression is a complication of various brain disorders.

Methods

Literature searches conducted from October 2013-December 2014 used the National Institutes of Health PubMed database to identify peer-reviewed studies of adolescents and adults with major depressive disorder and co-morbid conditions for any year, covered by the database. The following terms were used to define comorbid conditions: stroke, cerebrovascular accident, diabetes, Parkinson's disease, Alzheimer's disease, multiple sclerosis, Huntington's disease, Fahr disease, tumor, generalized anxiety disorder, substance abuse, alcoholism, panic disorder, bipolar disorder, bipolar depression postconcussional syndrome, traumatic brain injury, posttraumatic stress disorder. The following terms were used to define brain areas: frontal, cortex, cortical, amygdala, limbic. These were searched for association with antidepressants, depression, anxiety, treatment efficacy, remission or response .or for specific drugs and drug classes used to treat depression such as imipramine or a selective nor epinephrine uptake inhibitor. Most of the searches required

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association in human subjects and results were included if they were published in English, included depressed individuals and for whom group statistics reveal significance of experimental effect of smaller than $p < 0.05$. References were reviewed to discover other relevant studies. With few exceptions the studies used functional magnetic imaging (fMRI) and position emission tomography (PET).

Inclusion exclusion criteria

In this review we included all studies that examined the relationship between depression comorbidity condition.

Summary of Literature Results

Goal of the search was to identify brain and psychiatric disorders most commonly associated with depression and in which a statistically significant relationship was reported. When multiple publications from the same study population were available we included the 3 most recent publications.

Results

Pathophysiology

In general depression represents a decline of prefrontal cortex function consistent with prefrontal cortex influence in regulating mood, motivation, initiative and executive function [2,3]. Both clinical and neuroimaging studies reveal that in most depressions there seems to be hypo functioning of prefrontal cortex and hyper functioning of other brain regions -in particular sub cortical limbic regions [3,5]. This observation seems to be of significance for it suggests that in brain function bilateral relationships involving prefrontal cortex favors prefrontal cortex influence and decline of prefrontal cortex influence elicits exponentially magnified adverse consequences [3,6].

Evidence suggest, the phylogenetic governing influence of prefrontal cortex over central and peripheral nervous system makes prefrontal cortex function a target for stress associated with any dysfunction in those systems [6].

Prefrontal cortex catecholamine's are crucial for depression

Prefrontal cortex dopamine and nor epinephrine neurotransmission influences creativity, executive function, initiative, willpower, motivation, attention, judgment and concentration. A selective deficit and delayed alternation performance is produced by 90% depletion of dopamine in the prefrontal cortex of rhesus monkeys [7]. The deficit is so profound that it is hard to distinguish it from that produced by gross surgical ablation. Unlike ablation however this can be reversed by moderate doses of l-dopa or apomorphine but not high doses which compromise improvement. The inverted U-shaped response to catecholamine stimulation reinforces the need for optimal predominant roles of prefrontal cortex dopamine and nor epinephrine for optimal executive function and mood control [7]. Indeed the predominant auto receptor that regulates catecholamine release the alpha-2 receptor produces only half of signaling in the prefrontal cortex of medicated or non medicated depressed suicide cases compared to controls [8]. A likely result of this deficit excessive catecholamine release is associated with the stress-induced disruption of cognitive functions. Low doses of alpha 2 adrenergic agonists can improve of this cognitive decrement by lessening excessive baseline noradrenergic firing which enhances prefrontal cortex responses to salient information and attenuates catecholamine overload during stress [9,10].

The role of prefrontal catecholamine's in optimizing executive function and metabolism is supported by PET imaging with C glucose. This tracer reveals that decreases in prefrontal cortex metabolism during catecholamine depletion by tyrosine hydroxylase in depression which concomitantly invokes depression, anxiety and anhedonia. These behavioral responses occur to a greater extent in depressed patients in remission [11].

Diminished executive function in depression

Executive function a domain of prefrontal cortex is compromised in unipolar depression [5], late life depression [12] and in with patients with treatment resistant depressions [13]. Importantly executive function improves when unipolar depression is in remission and does so to such a degree that complete recovery from depression can restore normal executive function [14]. Conversely depressed patients with the greatest decline in executive function are less likely to remit [15].

While executive function is compromised in depressed patients neither verbal learning visual spatial memory delay recall recognition memory nor other memory domains of the temporal cortex and hippocampus appear to be so at risk [16,17].

Bidirectional relationship between metabolic activities of prefrontal cortex and limbic brain

A reciprocal relationship between metabolic activities of prefrontal cortex and limbic brain is well-established in human depression and in response to stress. Major depressive disorder is most commonly associated with decreased metabolism in the dorsolateral prefrontal, anterior prefrontal, orbit frontal and ventral anterior subgenual cingulate cortex [3,5]. Decreases in frontal cortical metabolism during depressed mood have also been identified with C glucose PET imaging [11]. fMRI investigations reveal heightened amygdala activity at baseline

and elevated response to negative and positive emotional stimuli [18,19]. Even positive social feedback in depressed individuals elicits an increase in amygdala fMRI signal which is not seen in normal controls [20].

The reciprocal nature of prefrontal and sub cortical-limbic metabolism in depression is further documented at the two ends of the depression spectrum, notably, dysthymia and severe depressive illness [5,21]. Each illness is characterized by decreases in the flow of blood to the dorsolateral cortex including the frontal lobes any increases in ventral orbital areas including the subgenual and anterior cingulate cortex. Functional connectivity between the frontal cortex and sub cortical or limbic area is also diminished in depression [22]. Connectivity between the dorsolateral prefrontal and dorsal cingulate cortices is decreased in major depression [22].

Numerous conditions of diverse origin precede depression

Compelling clinical observations and or neuroimaging evidence suggest depression may develop following the emergence of amygdala dysfunction [17,18,21], chronic pain [23-25] multiple sclerosis [26-29] stroke [30-32], Huntington's disease [33-35], Fahr disease [36-38], concussion [39-41], traumatic brain injury [42-44] epilepsy [45-47] brain tumors [48-50] and Parkinson's disease [51-54].

There is also evidence that in many depressions, stress and generalized anxiety is a precursor to depression [55,56]. Diabetes may precede depression or depression may precede diabetes [57]. A meta-analysis by Nouwen and colleagues indicated that people with type II diabetes had 24% increase risk of developing depression compared with non diabetic controls [58]. Conversely major depression seems to signal increased risk for onset of type II diabetes [59].

For numerous conditions of diverse etiology and of diverse pathophysiology to precede depression may support the possibility that depression may be a final pathway for many independent disorders. This is consistent with the observation that in those conditions depression may be secondary to a primary disorder of significance there seems to be high comorbidity of depression and substance use disorders in published literature. However the evidence does not seem to support a causal correlation of substance abuse leading to depression. For instance studying the relationship between substance abuse and depression Alexander and Fava concluded that among 950 depressed outpatients cocaine and alcohol overuse conformed to a pattern of self medication, a complication of the underlying depressive disorder [60].

Bipolar depression

Because of its complexities bipolar disorder requires special discussion. There seems to be often contradictory research findings of bipolar depression and its relation to manic episodes. It has been reported that an initial manic episode is followed by a depressive episode in over 50% of time [61]. In general presence of psychotic features or mixed with manic states make an initial depressive episode more likely to become bipolar spectrum [62]. Strober et al. [62] reported that psychotic features predicted (80% of confidence) of future manic episodes for patients with initial depressive episodes [62].

In general patients with bipolar disorder have different outcome based upon initial clinical manifestation. Unipolar depressed patients, patients with mixed episodes and depressed patients with psychotic features have different recovery rates [63]. Functional magnetic resonance imaging studies reveal distinct abnormalities for bipolar patients that distinguish them from patients with unipolar depressions [64,65]. These studies suggest in bipolar disorder there may be diminished prefrontal modulation of subcortical and medial temporal structures that results in dysregulation of mood [64].

Goldberg et al. [66] observed that young depressed in patients with psychotic features may be at especially high risk for eventually developing mania [66]. The probability for developing a bipolar spectrum disorder increases in linear fashion for patients at risk for polarity conversion during the first 10-15 years after an initial depressive episode [66].

Taken together medical literature provide support for the observation that bipolar and unipolar depressions are two distinct and different disorders substantiated by different course of illness and functional abnormalities in neuroimaging studies.

Amygdala dysfunction as a precursor to depression: molecular and neuroimaging evidence

A study by Sibille et al. [36] that demonstrated the crucial role of amygdala in male subjects with familial major depression is of major significance [36]. The study demonstrated that the biological liability of major depression is reflected in a persistent molecular pathology that affects the amygdala and support the hypotheses of maladaptive changes in amygdala as a putative primary pathology in major depression.

Abnormal size of the amygdala predicts emotional memory in major depressive disorder and furthermore people with depression have significantly enlarged amygdala and significantly reduced hippocampal size compared with controls [38].

The role of amygdala in childhood depression has been demonstrated by neuro imaging findings. Pediatric depression is associated with increases in amygdala size in patients with the largest amygdala with the greatest levels of anxiety and impairment in learning emotional facial expressions [67].

It has been demonstrated that augmented amygdala activity influences decision-making and other cognitive functions of the prefrontal cortex including a lessening of frontal cortex activation during tasks that require heightened attention.

Furthermore fMRI studies demonstrate heightened amygdala activity in depression [16,17,36]. Even positive social feedback in depressed individuals elicits an increase in amygdala fMRI signal which is not seen in normal controls [18].

Collectively all of the above findings are consistent with the observation that amygdala dysfunction may yield to depression.

Depression and remission vary with pre-frontal and sub cortical limbic metabolic activity

Remission from depressive illness normalizes hypo functioning in frontal, prefrontal and orbit frontal regions [36] while it reduces activity in part orbito, parietal temporal regions including the amygdala [16] and hippocampus and parahippocampal gyrus

[19,36]. The normalization of limbic cortical circuit abnormalities in the treatment of depression occurs even with the relief from depression due to placebo treatments which increase frontal cortex activity and diminished thalamic activity [68]. Conversely a return to higher amygdala metabolism during remission elevates the risk for relapse [16]. Various neurological disorders with depression -Parkinson's disease, Huntington's disease, stroke show neuro imaging evidence of diminished glucose metabolism in prefrontal cortex [7,53,54].

These findings can be summarized the following way:

(a) Normalcy and remission associated with brain homeostasis established by the predominant influence of the prefrontal cortex over sub cortical and limbic functions.

(b) Depression and relapse are associated with diminished prefrontal metabolic activity, decline of executive function any increased suck cortical and limbic activity.

High co- morbidity between depression and anxiety disorders

Bivariate twin analysis applied to lifetime diagnoses of major depression and generalized anxiety disorder in a population-based sample of 1033 pairs of female twins showed that the liability to major depression and generalized anxiety disorder is influenced by the same genetic factors [69].

A study by Moffitt and colleagues indicated that generalized anxiety precedes depression and eventually develops into depression. The reverse pattern seems to occur almost as often. This study concluded that generalized anxiety disorder and major depression relation is a strong and could be classified in one category under distress disorders [70].

A study by Pine and colleagues indicated a positive correlation between anxiety and depressive disorders in adolescence and the risk for adult anxiety and depressive disorders [55]. Studies of comorbid generalized anxiety disorder and major depression in 12 months in two national surveys indicated that the substantial amount of generalized anxiety disorders occur independently of major depression and that the role of impairment of generalized anxiety disorder is comparable to that of major depression [71].

Antidepressant strategies support depression as secondary to other disorders

Many pharmacological treatments of depression rely on medications that have an inhibitory effect on limbic brain function by lessening dopaminergic activation and activating prefrontal cortex function [3]. The examples include selective serotonin reuptake inhibitors and antipsychotics such as aripiprazole and olanzapine [3]. Thus their effects on mood rely on their primary antidopaminergic and calming properties. This is also consistent with their relatively lengthy delayed action. Treatments that directly affect prefrontal cortex dopamine function work much faster i.e. electroconvulsive treatment light treatment and TMS. Selective serotonin inhibitors and anti-dopaminergic agents may exert their influence by treating the primary psychiatric dysfunction i.e. hyperactive limbic system [3,33].

Discussion

Converging molecular, phylogenetic, clinical and neuroimaging

evidence suggest a great majority of people who suffer from depression first suffer from another disorder which may or may not be observable that leads to prefrontal cortex dysfunction and depression.

Pathophysiology may explain why depression is a common complication of many psychiatric disorders. The answers may be hidden in the phylogenetic governing influence of prefrontal cortex mediating normalcy and psychiatric disorders. Because of its governing influence almost any abnormality in brain function or structure will affect prefrontal cortex and therefore over time may disrupt robust functioning of prefrontal cortex. In essence any external or internal stress is mediated by prefrontal cortex at the risk of its chronic exposure to “stress due to over load” and “chronic wear and tear”.

Pathophysiologically it may also be informative to observe the similarities between diabetes and diabetic retinopathy or hypertension and stroke and various underlying pathological conditions that may elicit depression.

It seems plausible that the recognition of depression as a complication of various primary psychiatric and neurological conditions has been delayed partly because of DSM’s insensitivity to pathophysiology and regional brain function. DSM’s current architecture guarantees that possible complication or progression of psychiatric and neurological disorders be classified as comorbid conditions of significance, what may be true for depression may also be true for other psychiatric disorders. Some psychiatric disorders which are classified as primary disorders may also represent complications or progression of various primary brain conditions.

Limitations of this study include its retrospective nature and lack of author initiated experimental data. Further studies to validate our findings are necessary.

Conclusion

The hypotheses proposed in this study suggest that clinical observations and neuroimaging studies reveal evidence consistent to state the following: depression may be a progression or complication of various brain disorders. Some common examples of primary dysfunction include amygdala dysfunction, stroke, chronic pain.

“Depression is a complication of other brain orders” may open up new avenues for treatment. Furthermore it may have potential implications for many other psychiatric disorders that are currently classified as primary psychiatric conditions.

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