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Where in the Brain Is Depression?

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Abstract

Major Depressive Disorder is a serious medical illness which is responsible for considerable morbidity and disability. Despite decades of research, the neural basis for depression is still incompletely understood. In this review, evidence from neuroimaging, neuropsychiatric and brain stimulations studies are explored to answer the question regarding the localization of depression in the brain. Neuroimaging studies indicate that although many regions of the brain have been repeatedly implicated in the pathophysiology of depression, not many consistent findings have been found until present. In recent times, the focus of neuroimaging has shifted from regional brain abnormalities to circuit level connectivity abnormalities. However, connectivity models are inherently more complicated, and the validity of these models remains to be tested. Neuropsychiatric studies of illnesses such as Parkinson's Disease and stroke provide promising clues regarding areas involved in depression, but again consistent findings are rare. Similarly, stimulation of a variety of brain regions and circuits has been reported as being effective in depression. Therefore, the current knowledge indicates that the pathophysiology of depression may be distributed across many brain regions and circuits. In future studies, this distributed nature of depression needs to be further investigated, primary and secondary areas affected need to be identified, and new paradigms to explain complex mental functions need to be explored.

Keywords

Depression; Major depressive disorder; MDD; Unipolar depression; Limbic system; Resting state connectivity; Neuroimaging; fMRI; MRI; PET; Parkinson's disease; Stroke; Deep brain stimulation; DBS; Transcranial magnetic stimulation; TMS; Vagus nerve stimulation; VNS; Mood disorders; Psychiatry

INTRODUCTION

Where in the brain is depression? The question sounds quite simple, yet the answer has puzzled investigators for centuries due to the heterogeneity in the presentation of depression, and the complexities in examining the human brain. Its elusiveness is both unfortunate and worrisome as major depressive disorder (MDD) ranks as the leading cause of disability globally and ranks third in the ten leading causes of the global burden of disease (WHO 2004). To improve the diagnosis and treatment of MDD, a better understanding of the neuropathophysiological basis of this disabling illness is essential. The literature on the

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neurological basis of depression is extensive. Therefore, the scope of this review will be focused on major depressive disorder (MDD) or unipolar depression (1). Furthermore, this review will be restricted to human neuroimaging, neuropsychiatric, and brain stimulation studies while exploring the question regarding the location of depression in the brain.

EVIDENCE FROM NEUROIMAGING STUDIES

The published literature of brain imaging findings in depression has had substantial growth over the past 15 years. Imaging studies can be divided by the imaging modality used i.e. magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT). The findings from these studies can broadly be divided into whether regional brain abnormalities were being studied and found or whether brain circuits or connectivity between brain regions was studied.

Regional Brain Abnormalities in Depression

Mclean introduced the concept of the brain being composed of three different assemblies, radically different in their chemistry and structure and in evolutionary terms eons apart, the so called triune brain (2). According to this description the brain can be divided into the prefrontal neocortex (involved in higher cognitive processes as well as regulation of emotions by their connections to the limbic region), the limbic or mammalian brain (involved in emotions which guide self preservation and procreation of species) and the reptilian complex composed of the basal ganglia and brain stem structures (involved in routine motor function/reflexes as well as social communication such as territorial and courtship displays) (2). Regional brain imaging studies have investigated abnormalities in each of these brain subdivisions to investigate the location of depression in the brain.

Cortical abnormalities—Cortical brain areas implicated in depression are the dorsal and medial prefrontal cortex, the dorsal and ventral anterior cingulate cortex, the orbital frontal cortex and the insula.

A decreased metabolism in the prefrontal cortex, especially dorsolateral and dorsoventral brain regions, is a frequently replicated finding in MDD (3, 4). Furthermore, deficient prefrontal perfusion in these regions, coupled with a reduction in problem-solving abilities and higher propensity to act on negative emotions, has been implicated in suicidal behavior (5). Whether this finding is a primary abnormality or secondary one is not clear. However, this finding has been successfully used to formulate a therapeutic strategy to stimulate the dorsolateral prefrontal cortex (DLPFC) using transcranial magnetic stimulation (as described in the section of stimulation therapies)(6). The decrease in DLPFC metabolism/blood flow in depression has also been found to reverse with antidepressant treatment (7). Structural brain MR imaging research suggests that a decreased frontal lobe volume (8–10) may also be present in depression. A decreased volume of the orbitofrontal cortex has also been implicated in depression (11), although functional changes have been less frequently described.

The anterior cingulate cortex has been a subject of much study in the pathophysiology of depression particularly after the seminal PET studies of Drevets and colleagues who demonstrated decreased metabolism in the subgenual cingulate in familial depression (12) and studies by Mayberg and colleagues who described abnormalities of the subgenual and dorsal ACC in depression (13). The ACC has been shown to have a functional division between its dorsal and ventral parts. The dorsal ACC has been implicated in cognitive aspects of emotion including conflict resolution of emotional stimuli with negative valence (14–16), while the ventral (subgenual) ACC has extensive bilateral connection with limbic regions such as the amygdala and dorsomedial thalamus as well as cortical mood regulating

areas such as the lateral and medial orbitofrontal cortex and the medial prefrontal cortex (14, 15). The outputs of the vACC to the hypothalamus, which controls the endocrinological systems, and the autonomic systems, which are frequently involved in the stress response, make the vACC of particular interest in depression.

The insula particularly its anterior subdivision (17) has been implicated in experience of emotions such as disgust(18), self-reflection (19) and assessment of internal visceral states(20), and response to stimuli of taste and smell. In depression, insular activation has been reported to be increased in response to disgust inducing stimuli (21) and negative pictures (22) and insular volume has been noted to correlate with depression scores (23). One study on the other hand reported increased insular activation in response to negative stimuli after antidepressant treatment (24). On the whole these findings suggest increased sensitivity of the insula to internal visceral and cognitive processes during depression.

Subcortical Limbic brain regions—The main subcortical limbic brain regions implicated in depression are the amygdala, hippocampus, and the dorsomedial thalamus.Both structural and functional abnormalities in these areas have been found in depression. Decreased hippocampal volumes (10, 25) have been noted in subjects with depression. Subjects who remit with treatment have even been shown to have larger pre-treatment hippocampal volumes (26); while those with smaller hippocampal volumes were reported to be more prone to relapse (27). Decreased amygdala core volume (28) has been reported in depression. The exact significance of these volumetric abnormalities is not known. In the case of loss of hippocampal volume, a definite pathophysiology related to hypercortisolemia related neurotoxicity has been postulated (29). However, this finding has also been found in anxiety disorders such as post-traumatic stress disorder (PTSD) (30) and may be more related to the effects of trauma in early life (31). Recent research has revealed that a variety of antidepressants have neurotrophic effects (32). It is possible that antidepressants may act by their ability to reverse neurodegeneration in critical areas of the mood regulating circuit (32, 33). In the case of amygdala, increased volume reported in some studies may be related to medication effects.

Functional studies have usually shown an increased metabolism or activation of limbic regions in depression (7, 34–36). Increased activation of the amygdala in the resting state as well as in response to stimuli has been reported in a number of PET and fMRI studies (22, 37, 38). Conversely, in children, the amygdala response to the experimental task was reported to be blunted, which was interpreted to be due to possible higher baseline metabolic activity (39). However, in another study hypometabolism of the amygdala and paralimbic regions was reported in more severe treatment resistant depression (4). Increased duration of amygdala response to negative stimuli has been reported by Siegle and colleagues (40).

The dorsomedial thalamus has been conceptualized as an integral part of the subcortical mood circuit with reciprocal connections to the dorsal and ventral prefrontal cortex as well as the striatum and the amygdala. A few studies have reported an increased activation of the thalamus in depression (41, 42) but surprisingly most studies have noted no difference.

Basal Ganglia and Brain Stem—The striatum has been a focus of brain imaging studies in depression from the earliest time mainly because of its role in motor response, response to reward, and in motivation. One of the earliest report was of a decreased caudate volume in depression (43), although this finding has not been consistently replicated. The exact role of the striatum in depression still remains to be fully elucidated. Recent studies with reward related stimuli or positive stimuli have reported either no change (44), increased (45, 46) or decreased (47) activation in the striatum.

The nuclei of major neurotransmitters which are thought to be abnormal in depression or the changes in which are produced by antidepressants are found in the brain stem. The raphe nucleus contains the brain serotonergic neurons, the locus coeruleus the norepinephrine neurons and the substantia nigra and ventral tegmentum the dopaminergic neurons. Decreased serotonin transporter, which can also be used as an indirect measure of serotonergic neuron density, was reported in one study of depression (48). Another study by the same group reported decrease in serotonin transporter and increase in dopamine transporter after chronic antidepressant treatment (49).

In summary, various cortical, subcortical and brain stem regions have been shown to have abnormal activation or metabolism in brain imaging studies. However, few findings have been reliably and consistently reported. Several methodological reasons have been noted for the discrepant findings including demographic heterogeneity of population samples, heterogeneity in the severity and the quality of depression, medication effects, effects of substance abuse, and differences in image acquisition and analysis between centers, and results possibly being driven by outliers in small sample sizes (50). A more fundamental question regarding the discrepant findings may lie in whether higher brain functions and their abnormalities can be conceptualized solely in terms of activity in discrete brain regions.

Brain connectivity abnormalities

The disparate findings of local activity change in brain regions across studies and subject groups has led some investigators to propose that the abnormality in depression and other psychiatric disorders may lie in imbalances of connectivity between brain regions rather than increased or decreased activity of one particular area (51–57). Consequently, investigators have started to discuss and explore imaging findings in depression in terms of connectivity between brain regions. Mayberg and colleagues (13) first noted a reciprocal relationship between the decreased metabolism of the prefrontal cortex and an increased metabolism in limbic regions such as striatum and thalamus in depression leading to the hypothesis that corticolimbic connectivity abnormality may be present in depression. Drevets and colleagues' (12) discovery of decreased metabolism of the subgenual cingulate cortex in depression, a region which on one hand has connectivity to the cortical mood regulating regions such as the dorsal ACC and the medial and lateral OFC and other is has connections to the amygdala and dorsomedial thalamus as well as has outputs to the brain stem areas involved in vegetative functions, led to the hypothesis of abnormality of the amygdala-strital-pallidial-thalamic-cingulate cortex circuit in depression (58) fMRI task based studies have also implicated abnormalities of coupling between brain region activation in response to emotional stimuli in depression (59).

More recently, with the development of techniques to measure resting state connectivity a number of studies have reported corticolimbic abnormalities in depression. Using this technique Anand and colleagues (22) first reported decreased anterior cingulate connectivity with the amygdala, thalamus and striatum in depression. Grecius and colleagues identified subgenual cingulate and thalamic abnormalities using independent component analysis of brain resting state data (60). Subsequently a number of studies have reported either decreased or increased connectivity of the corticolimbic or intracortical connectivity in depression(60–63).

In summary, connectivity abnormalities in corticolimbic networks, as well as novel networks identified with newer techniques, are more comprehensive in terms of providing a more integrated model of the dysfunction in multiple brain regions in the pathophysiology of depression. However, at present, the biological validity of circuit level changes observed with increasingly complex mathematical techniques remains to be fully clarified.

EVIDENCE FROM NEUROPSYCHIATRIC STUDIES

Neuropsychiatric conditions offer an ideal glimpse into the possible association of mood, behavior, and anatomy.

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disorder resulting in progressive degeneration of dopamine-producing cells within the substantia nigra pars compacta. Depression is the most common psychiatric illness in Parkinson's disease with a mean rate of 40%, and half of these cases meet criteria for major depression (64). Neurobiological studies have shown this may be mediated by dysfunction in mesocortical and prefrontal reward, motivational and stress response systems (64). Depression in PD has also been associated with morphological and functional changes in prefrontal cortex, cingulate and thalamus, as with 5-HT transmission reduction in posterior cingulate and amygdala-hippocampus complex (65), possibly correlated with severe white matter loss in the right frontal lobe (66).

Huntington's Disease

Huntington's disease (HD) is another neurodegenerative disorder associated with an abnormal repeat of the trinucleotide sequence in the gene IT-15 on chromosome 4. This abnormal sequence triggers the production of a mutant Huntington protein resulting in a cascade of cell death and cerebral degeneration. Patients with HD commonly present for management of depression before the onset of motor symptoms. In a study of 2,835 participants with definite HD, over 40% reported having active symptoms of depression (67). In fact, dysphoria, at 69%, was the highest reported neuropsychiatric symptom in another HD sample independent of illness duration and chorea severity (68). Structural volumetric measurements have demonstrated smaller cingulate volumes in premanifest and early HD (69); while functional imaging studies in HD have confirmed significantly impaired functional connectivity between anterior cingulate and lateral prefrontal regions in both hemispheres (70), along with paralimbic frontal lobe hypometabolism in depression in HD (71). It is interesting to note that these psychiatric signs and symptoms are paralleled by atrophic changes to the insular cortex (72).

Stroke

Although much has been written about poststroke depression (PSD) over the past 30 years, there is minimal agreement about relationships between lesion localization and depression (73). More than 20 years ago, Starkstein and colleagues (74) reported neural substrates associated with post-stroke depression. Investigating participants with circumscribed anterior and posterior lesions to the right and left hemisphere, they found the left anterior region (which included the insular cortex) most often associated with poststroke MDD.

Unfortunately, these associations may be less clear because the entire extent of stroke-affected areas may not be fully appreciated by neuroimaging methods alone (75). Proposals for factors contributing to depression in PSD include interruption of biogenic amine-containing axons, depressogenic properties of proinflammatory cytokines, and microvascular lesions affecting subcortical circuits responsible for mood regulation (75). In regards to laterality, early reports suggested a link between left hemispheric lesions, however contradictory reports have since been published, making any determination of laterality ambiguous (76) (77). The common manifestation of depression and executive dysfunction in the setting of vascular disease is common (78) and may thus suggest the contribution of DLPFC involvement in the etiology of depression.

Epilepsy

Depression in epilepsy is a well accepted association, with prevalence rates ranging from 13%–50% depending on the diagnostic criteria and surveyed population. There is limited consensus regarding specific brain regions that are associated with the manifestation of depression in epilepsy. The relationship between depression and temporal lobe structures (such as amygdala and hippocampus), combined with the high prevalence of depression in temporal lobe epilepsy (TLE) (79) provides an interesting area of further exploration. Furthermore, like other conditions, frontal lobe dysfunction is a common finding in those with depression and TLE (80).

Brain Tumors

Brain tumors have the advantage of assisting in the localization of depression due to their common association. Like stroke, methodological flaws related to study design, such as heterogeneous populations, have complicated the interpretation of the results. Nevertheless, there appears to be higher association of depression with head and neck cancers, in particular pituitary tumors, presumably via hypothalamus-pituitary-adrenal axis hormonal dysregulation (81) (82). Multi-focal tumor sites and tumors greater than 4 cm also appear to be related to higher incidence of depression, possibly via disruption of limbic interconnections by infiltration or mass effect (82), but this also is not wellaccepted. One report reviewing 42 studies of more than 4000 patients with gliomas concluded mild to moderate depressive symptoms may only rarely be due to tumor-associated structural or functional disruption of neuronal emotional networks (83).

In summary, considering the evidence from various neuropsychiatric studies, the sites of neurodegeneration and dysfunction in PD and HD may best provide additional clues for our search for where depression lies in the brain. Consensus regarding biologic associations between depression and other neurological conditions, such as stroke, epilepsy, and brain tumors, are unfortunately much weaker.

BRAIN STIMULATION

Electroconvulsive therapy remains one of the most effective treatments of depression, but requires induction of a generalized seizure for its effectiveness. In recent times sophisticated electric stimulation therapies have been developed which require a more localized stimulation of the brain. Assuming that these electric stimulation therapies are stimulating an area of the brain closely associated with depression, the mechanism of action of these stimulation therapies could potentially provide clues regarding where in the brain depression is localized. The more frequently used localized stimulation therapies are reviewed below with this aim in mind.

Repetitive Transcranial Magnetic Stimulation (rTMS)

TMS involves inducing an electric current within the brain using pulsating magnetic fields that are generated outside the brain near the scalp (84). Using this technique the TMS device can only stimulate the surface of the brain immediately underneath where the magnet is placed. Drawing from neuroimaging findings of reduced metabolism of the prefrontal cortex in depression TMS therapy for depression has until present been restricted to the prefrontal cortex. Recently, stimulation of the left prefrontal cortex with TMS received Food and Drug Administration (FDA) approval for the treatment of depression resistant to antidepressant medications (85, 86). Other targets and techniques that have been explored is the application of slow TMS on the right DLPFC (87).

Even though TMS stimulates the dorsal prefrontal cortex, its effects are thought to be generated by downstream effects on the limbic system (88). Neuroimaging studies have shown changes in limbic regions such as the striatum and the amygdala though a correlation of these changes with changes in depression has not been demonstrated (89).

Vagus Nerve Stimulation (VNS)

VNS involves mild pulses at programmed time intervals applied to the left vagus nerve via an implanted subcutaneous pacemaker (90). This technique is thought to transmit electric impulses to the various brain regions which have vagal afferents. These areas are thought to be involved in emotion production and regulation e.g. the local coeruleus, dorsal raphe, hypothalamus, thalamus, amygdala, insula and the cingulate cortex (91–93). Brain imaging studies have also shown that these areas show local metabolic and activation changes with VN, although no one area has been found to be primarily influenced by the stimulation of this type (91–93). Therefore, it is difficult to draw more definitive conclusions regarding the localization of depression based on the mechanism of action of VNS.

Deep Brain Stimulation (DBS)

DBS involves stimulation of a small brain region using sterotactically implanted electrodes connected to a subcutaneous stimulator device. Using this technique, different investigators have stimulated different brain regions of their choice to achieve and antidepressant effect. These areas include the ventral capsule/ventral striatum (94), nucleus accumbens (95), white matter tracts adjacent to the subgenual cingulate cortex (96, 97), and the inferior thalamic peduncle, and lateral habenula (98), although large scale trials have been done only for the first three. DBS of these localized regions may lead to activation or deactivation, and through adjacent white matter projection other cortical and subcortical areas involved in mood may be affected. Brain imaging studies of areas near the subgenual ACC have shown decreased blood flow in the medial and frontal orbital areas as well as the hypothalamus (99). Stimulation of the anterior limb of the internal capsule led to activation changes in the ipsilateral striatum, medial thalamus, anterior cingulate and contralateral cerebellum (100). Stimulation of the nucleus accumbens has been shown to decreased orbitofrontal and dorasolateral prefrontal cortex and amygdala metabolism (101). Until present all of the DBS studies have been open label and results from double blind controlled trials are likely to available soon.

In summary, for the purpose of this review, DBS studies do not provide evidence regarding any particular area being definitively involved in depression. It is also not clear whether the efficacy of DBS is related to stimulation of a particular brain region or it is due to perturbation of a brain circuit composed of several brain regions involved in generation and regulation of mood.

DISCUSSION

A review of the neuroimaging, neuropsychiatric and brain stimulation therapy studies of depression indicates that like other abnormalities of higher mental functions, the location of depression is difficult to determine. Depression seems to lie in many brain regions as well as nowhere in particular. Several explanations can be construed and have been proposed regarding this state of affairs.

One possibility is that depression is localized in multiple brain regions simultaneously. This could arise from a common molecular abnormality in the neurons of multiple brain regions. Receptor abnormalities or abnormalities in signal transduction could be such possible abnormalities. To test this formulation it would be more pertinent to identify the underlying

molecular abnormality in depression. Neurochemical brain imaging and challenge studies as well as a tremendous amount of basic science research is being conducted and is still needed in this area.

A second possibility is that a separate system may influence the functioning of multiple brain regions involved in mood regulation and impairment of this system could lead to abnormalities in multiple brain regions. An example is the effect of the monoamine neuronal projections from the brain stem to multiple brain regions. Most antidepressants act on the monoamine systems and many substances which have euphoragenic effects also act on the monoamine system. Therefore, depression could be said to be located in an abnormality of the brain stem monoamine neurons or their projections to the rest of the brain. The catecholamine hypothesis, which postulated that depression may be due to the deficiency of catecholamines, was derived from the observation that medications that increase catecholamine neurotransmission had antidepressant effects. However, no consistent abnormality of the monoamine system has been found in depression to date (33).

Another strategy that has been suggested to preserve the hypothesis regarding a regional neuroanatomical basis of depression is to not treat depression as a unitary illness, but to divide it into its different symptoms while exploring their anatomical basis. In this formulation, for example, the cognitive abnormalities seen in depression could be attributed to abnormalities in the frontal cortex, anhedonia can be attributed to a ventral striatum abnormality and anxiety could be associated with amygdala hyperactivation. This formulation is attractive; however to validate it a correlation with the different symptoms of depression with the respective regional brain abnormality will have to be shown. To the best of our knowledge a consistent correlation between specific symptoms of depression and abnormality of activity in a particular brain region or circuit has not been found.

In light of the difficulty identifying a discrete and tangible structural or neurochemical abnormality in depression, it has been hypothesized that depression may involve abnormalities of functional connectivity involving many different brain regions. A more pure form of this conceptualization is that not only is there no particular brain region involved, but that that there is no localized abnormality present at all. Depression is therefore hypothesized as an abnormality of a functional interaction of neuronal oscillations among different regions or among brain networks. Recent studies of resting state connectivity have revealed the possibility of several different neuronal networks that may interact in the functioning of the human brain. However, the exact nature of the connectivity abnormality still remains to be elucidated.

Finally, in terms of connectivity, corticolimbic connectivity abnormalities are frequently cited as a cause of depression or for that matter a number of other psychiatric illnesses. An implicit assumption of this hypothesis is that depression may involve how one region may have effect the workings of another region e.g. regulating effects of the anterior cingulate cortex on the limbic regions such as the amygdala (22). The latter possibility also implies that some of the abnormalities in brain regions may be secondary to abnormalities in another primary region. At this time, it is very difficult to ascertain which regional abnormality may be primary and which one is secondary. The primary abnormality may lie in the subcortical or brain stem regions and the abnormalities in large cortical areas such as the dorsolateral prefrontal cortex may be secondary in nature. However, neuropsychiatric studies suggest that depression could arise from primary abnormalities in cortical areas such as the left frontal cortex as well.

CONCLUSION

In summary, depression, like other abnormalities of higher mental functions seems to be distributed across several brain regions although localized abnormalities can be found and depression can be reversed with localized interventions. In future studies, this distributed nature of depression needs to be further investigated, primary and secondary areas affected need to be identified, and new paradigms to explain complex mental functions need to be explored.

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