The neurobiology of depression

Eleni Palazidou[*]

East London Foundation Trust, Tower Hamlets Centre for Mental Health, Mile End Hospital, London E1 4DG, UK

Introduction or background: Depressive disorder is a long term, relapsing condition associated with high levels of disability and mortality. It has a neurobiological basis and is associated with functional and structural brain abnormalities.

Sources of data: The data discussed have been obtained mainly from meta-analyses, randomized controlled clinical trials and key review papers as well as animal studies.

Areas of agreement: Genetic vulnerability and stress are key factors in its aetiopathogenesis. Dysregulation of the hypothalamo-pituitary-adrenal (HPA) axis reduces hippocampal volumes and prefrontal cortex (PFC) activity in depressed patients and disrupts homeostasis within the neurocircuit of depression. Antidepressant drugs increase brain-derived neurotrophin, restoring neuronal growth and activity and modulate interactions between the neurocircuit anatomical structures.

Areas of controversy: It remains to be confirmed whether structural changes in the brain are purely abnormalities in neuroplasticity and are fully reversible, whether they predate depression and whether they increase in the long term.

Growing points: Investigation of the molecular mechanisms mediating gene and environment interaction is a growing and potentially fruitful area of research in the neurobiology of depression. Further elucidation of the neuroanatomical and physiological connections between the limbic structures and PFC may help identify key areas to target in treatment. The role of the dysregulation of the HPA axis and identifiable stressors in the recent or remote past which are not always present in depression need further study.

Areas timely for developing research: Prospective studies examining the interaction between changes in brain function and structure in relation to stress and identified relevant genes and how these may be influenced by antidepressant drug treatment and the long-term course of depression would help clarify their role in the pathophysiology of this disorder.

*Correspondence address. East London Foundation Trust, Tower Hamlets Centre for Mental Health, Mile End Hospital, 1st Floor Burdett House, Bancroft Rd, London E1 4DG, UK. E-mail: eleni. palazidou@doctors.org.uk

Introduction

The last 50 years have been witness to a diversity of theories, each one claiming to have the key to the aetiology of depression, based on the narrow perspective of its own discipline (genetic, social, psychological or biochemical). However, in the last decade or so, thanks to technological advances, major leaps have been made in our understanding of the workings of the brain, particularly, its significant capacity for plasticity in interacting with the environment (physical and psychological). It has become increasingly clear that both psychosocial and biological factors are highly relevant and far from contradicting each other, they are inextricably linked in the genesis of this multifaceted condition.

This paper aims to give a brief overview of the key research findings in the pathophysiology of depression and show how these can be integrated into a 'psychobiological model' of understanding the nature of this condition. The pathophysiology will be discussed in relation to the clinical presentation and course of the depressive illness and how it can inform the clinical management of this disorder and help optimize its long-term outcome.

Depressive disorder: course of illness

The importance of treating this condition cannot be overestimated. The World Health Organization global burden of disease study places unipolar affective disorder amongst the 10 leading medical causes of disability in the world and second only to ischaemic heart disease.[1]

Depression is a highly prevalent psychiatric disorder with a lifetime risk close to 20% and is associated with high levels of morbidity and mortality.[2] Depressed patients are at higher risk of serious physical health problems such as coronary artery disease and diabetes[3] and worsening of the prognosis of other medical conditions.[4]

Follow-up studies show depression to be a long term, relapsing condition associated with significant morbidity and mortality and a tendency towards chronicity. Three quarters of the patients experience more than one episode of depression and the risk of recurrence is higher if the first episode occurs at a younger age and if there is a family history of depression.[5] The risk of recurrence increases with each new episode and as the number of depressive episodes increases, the influence of life stress on recurrence wanes.[6]

Given these findings, the need for effective treatment in the first episode of depression is obvious. Maintenance treatment for several months during remission is essential after an acute episode of

depression to prevent relapse[7] as well as long-term treatment to prevent recurrence in patients with more than one episode.

In addition to the number of episodes, the prognosis is influenced by the duration of illness remaining untreated. The more protracted this is, the poorer the response to treatment and the lower the likelihood of achieving remission.[8] Unfortunately, many patients do not achieve full remission for various reasons which include poor compliance, premature ending of treatment, the use of inadequate treatment and other factors. Subsyndromal states encourage relapse[9] and progression to chronicity. Long-term (over 2 years) depression is common; it is clinically more serious than episodic depression and is associated with more functional impairment and high comorbidity (cardiac and respiratory syndromes). Such patients suffer significantly more from social phobia and benzodiazepine abuse and both their somatic and psychological well-being are impaired.[10] Comorbid anxiety and depression have a detrimental effect on the course of each other. Pre-existing anxiety is a risk factor for later depression; individuals with anxiety states tend to develop either depression alone or comorbid anxiety and depression as they progress through adulthood. Depression alone and depression comorbid with anxiety is more persistent than anxiety alone over time and this applies to both threshold and subthreshold disorders.[11]

All these clinical observations on the course of depression can be understood better in the context of the currently available knowledge of its neurobiology.

Neuroanatomy of depression

The limbic system was identified as playing a role in the experience of emotion in the early 1930s and in 1937 James Papez described the 'system of emotion', a major pathway of the limbic system, connecting a group of brain structures surrounding the brainstem (the cingulate gyrus, hippocampus, the hypothalamus and the anterior thalamic nuclei). He understood this circuit to form a functional route of communication between the above structures enabling cortical control of emotion as well as playing a role in the storing of memory.

In the absence of appropriate technology, further study to elucidate the connection between brain structures and human experience and behaviour was limited to clinical observations of the effects of localized neurological disorders, such as strokes or tumours and accidental trauma. The emergence of neuroimaging techniques, magnetic resonance imaging (MRI), positron emission tomography (PET) and functional fMRI, established the importance of the 'neurocircuit of emotion' which has been expanded to include other important brain

areas and in particular the prefrontal cortex (PFC). These brain sites and their connections, which have been widely studied, are responsible for maintaining emotional stability and their malfunction is considered central to the pathophysiology of depression.

Prefrontal cortex

The PFC lies anteriorly to the premotor (involved in the planning of complex motor actions) and the primary motor area (mediates conscious movement) of the frontal cortex and has 'heteromodal' function, integrating complex sensorimotor information with motivation and affect. It is divided into three major sections: (i) the dorsolateral, (ii) the paralimbic (orbital and medial aspects of PFC and (iii) the anterior cingulate cortex (ACC). The ventromedial (VMPFC) and the dorsolateral (DLPFC) connect with each other via the cingulate gyrus and the hippocampus. The VMPFC is necessary for the normal generation of emotions, in particular social emotions[12] and it regulates autonomic and neuroendocrine responses, pain modulation, aggression and sexual and eating behaviours.[13] The orbital PFC plays a role in correcting behavioural or emotional responses (generated in part by the amygdala). The DLPFC has been implicated in cognitive control, solving complex tasks, maintenance and manipulation of information in working memory.

The PFC, the amygdala and particularly the hippocampus are the brain structures most widely studied in relation to depression. Magnetic resonance studies show a reduction in the brain volume of depressed patients compared with healthy controls, with large volume reductions in the anterior cingulate and orbitofrontal cortex and moderate reductions in the hippocampus, the putamen and the caudate.[14]

PET studies have shown abnormalities in regional cerebral blood flow and glucose metabolism in multiple prefrontal cortical and limbic structures implicated in emotional processing. The VMPFC and the LOPFC show increased activity while the DLPFC shows a decrease in activity, in depression.[15] Decreased activity of the DLPFC in depression has been associated with psychomotor retardation and anhedonia. Response to treatment is associated with a decrease in metabolic activity, and chronic antidepressant drug treatment reduces metabolism in the amygdala and ACC in subjects with persistent, positive treatment response. In contrast, the persistence of the abnormal metabolic deficits in the dorsomedial/dorsal anterolateral PFC in depression during treatment may relate to histopathological changes reported in these regions in post-mortem studies.[16]

Computer-assisted three-dimensional cell count showed a reduction in both neuronal and glial density in the orbitofrontal and dorsolateral PFC of depressed patients and these changes were also present in depressed subjects who had not been exposed to antidepressant drugs.[17]

The amygdala

The amygdala are involved in recruiting and coordinating cortical arousal and neuroendocrine response to underdetermined (surprising and ambiguous) stimuli as well as in emotional learning and memory. Abnormal activation of the amygdala correlates with the severity of the depression. They have been implicated in the tendency to ruminate and may also play a role in bipolar depression and anxiety.[15,18]

The evidence in terms of the amygdala volume in depression has been inconsistent. A recent meta-analysis of MRI studies, which took into account the possible role of medication on the size of the amygdala, demonstrated that this is actually reduced in unmedicated depressed patients.[19]

The hippocampus

The hippocampus is the most widely studied brain structure in relation to depression, both in animals and man for several reasons: (i) it plays a fundamental role in learning and memory[20]; dysfunction in the hippocampus may be responsible for inappropriate context-dependent emotional responses;[21] (ii) it is rich in corticosteroid receptors[22] and is closely linked anatomically and physiologically to the hypothalamus via a bundle of axons, the fornix, providing regulatory (inhibitory) feedback to the HPA axis;[20,21] (iii) it is one of the two brain areas where neo-neurogenesis is known to continue in the mature brain in animals and man, hence its high capacity for neuroplasticity.[23,24]

Although the adult brain as a whole is hard wired, new neuron growth continues to occur in the subgranular layer of the dentate gyrus of the hippocampus and also the olfactory bulb. Whether and how much neurogenesis occurs in other brain regions in adulthood is not known. The new neurons arising from neural progenitor cells, which are maintained throughout adult life, project to the CA3 hippocampal region, receive afferents and exhibit electrophysiological properties very similar to those of mature dentate granule neurons. Basal neo-neurogenesis is limited but this can be activated by adrenergic and serotonergic agonists such as the antidepressants and brain neurotrophins and be suppressed by ageing, stress, corticosteroids and glutamatergic agents.

According to some evidence, although hippocampal function may be affected, as shown by impairment in hippocampus-dependent verbal

Table 1 Functional and structural changes in the limbic and PFC areas implicated in depression.

Substrate	Volume	Histological changes	Metabolic activity	Antidepressant effects
Orbital/VMPFC	↓	↓	↑	
Anterior cingulate cortex	↓			↓ Metabolic activity
Hippocampus	↓	↓		↑ Volume
Amygdala	↓?			↓ Metabolic activity
DLPFC	↓	↓	↓	

Table 2 Neurochemical/hormonal abnormalities in depression.

Substrate	Concentration/activity
Cortisol, CRH	↑
Proinflammatory cytokines	↑
BDNF	↓
5-HT neurotransmission	↓
NA neurotransmission	↓

memory tests, both in patients with first-episode depression and those with multiple episodes, it is only in the latter group that the hippocampal volume is reduced; this would suggest that dysfunction of the hippocampus predates detectable structural changes.[25,26] Clinical improvement is believed to be associated with the reversal of structural changes as remitted patients have larger hippocampal volumes compared with non-remitted patients.[27] However, medication-free, remitted subjects with a history of recurrent depression, have smaller hippocampal volumes and it has been suggested that such structural abnormalities may be a trait characteristic for depression.[28] This view is supported by the finding that adolescents at high risk of depression, particularly those who also experienced early life adversity and who are not currently depressed, have smaller hippocampal volumes.[29,30] Further studies are needed to clarify the relationship between the hippocampal size and the course of depression.

Tables 1 and 2 summarise the most consistent findings from neuroimaging, histopathological, neurochemical and pharmacological studies. Additional neuroanatomic sites relevant to mood state are the medial thalamus and the ventral striatum and pallidum as well as the hypothalamus and these are extensively connected with the MPFC (Fig. 1). This system also links with relevant structures in the midbrain/brainstem (for example, the serotonergic raphe nuclei and the adrenergic nucleus coeruleus). This cortical-striato-pallido-thalamic-limbic circuit is responsible for maintaining emotional stability and appropriate responses to emotional stimuli as well as regulating neurotransmission, autonomic and neuroendocrine function. Communications within this neurocircuit and its regulatory effects on other parts of the brain is far
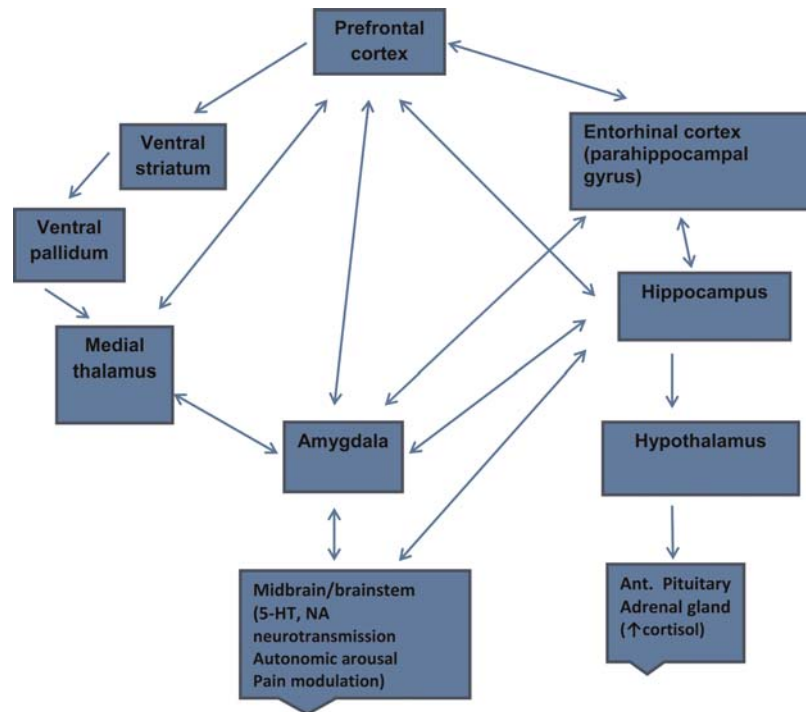
Fig. 1 Schematic connections between the pre-frontal cortex and limbic structures within the limbic-cortico-striato-pallido-thalamic circuits related to the medial and orbital pre-frontal cortex networks implicated in depression. A decrease in the inhibitory control of the limbic structures by the PFC is associated with cognitive, behavioural and other signs of depression as well as abnormalities in neuroendocrine function, pain modulation and neurotransmitter activity (affecting the raphe, serotonergic nuclei and NA-ergic nucleus coeruleus), through its connections with the hypothalamus and the midbrain, in particular the periaqueductal area.

too complex and a lot more work is required before fully comprehensive mapping becomes available. Nevertheless, based on the hitherto available evidence it has been hypothesized that in the depressed state the balance amongst the structures within the neurocircuit is disrupted probably as a result of decreased activity in the PFC which impairs its regulatory (inhibitory) action on the limbic structures which in turn are overactive. This dysregulation may be responsible for the clinical depressive syndrome and the associated autonomic, neuroendocrine disturbances and other visceral functions[31] (see Figs 1 and 2).

Subcortical white matter abnormalities
So far the attention has been focussed mainly on the grey matter of the neurocircuit of depression, neglecting to a great extent the connections between these structures. White brain matter abnormalities had attracted interest initially in the elderly depressed (late onset
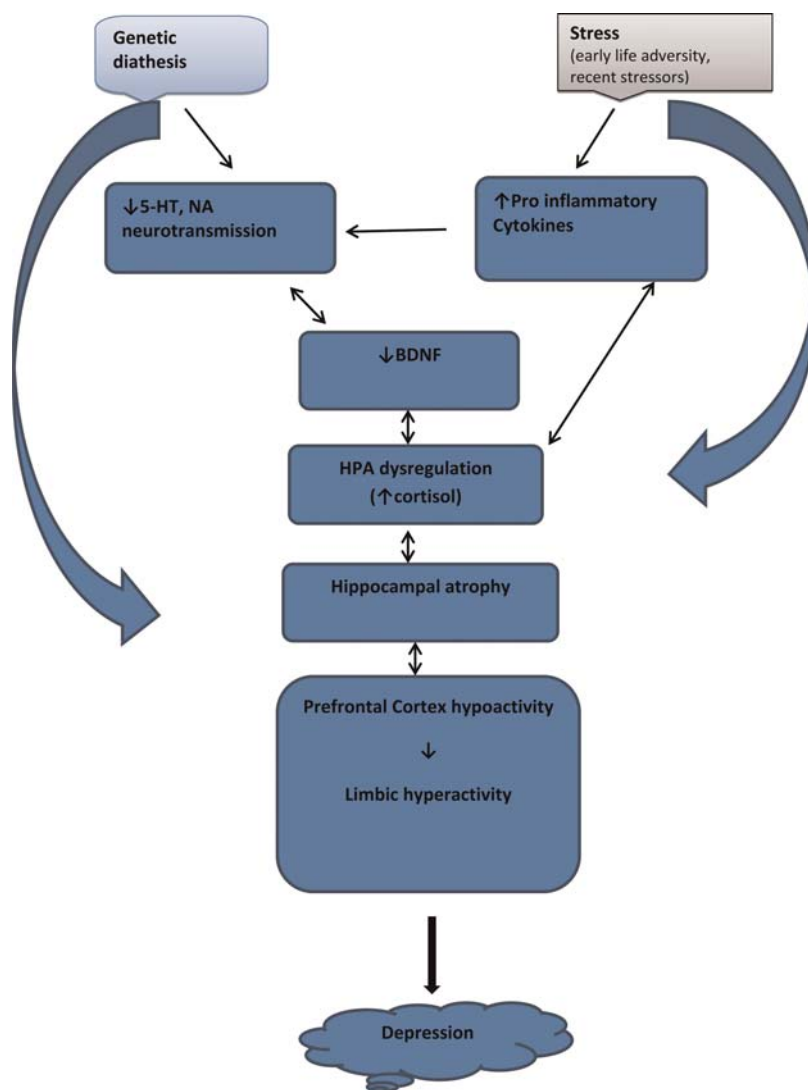
Fig. 2 Schematic representation of the neurobiology of depression.

depression) and were thought to be related to ischaemic vascular pathology. MRI white matter signal hyperintensities are significantly higher in the prefrontal areas but irrespective of their distribution they are associated with reduced frontal lobe metabolism and cortical atrophy.[32]

A recent study in first-episode major depressive disorder, treatment-naive, young adults, showed micro-structural abnormalities in the cortical–subcortical neural circuit, occurring early in the course of depression, which correlated with the severity of depressive symptoms.[33] Such abnormalities have been also shown in middle-aged depressed

patients[34] and these may possibly have an important role to play in the pathophysiology of depression.

Stress

Psychosocial research in the late 1970s highlighted the importance of stressful life events as triggers of depression in the presence of existing vulnerability, related to adverse early life experience.[35] Around the same time Carroll[36] noted abnormalities in the hypothalamo-pituitary-adrenal axis (HPA) with raised cortisol concentrations and dexamethasone non-suppression in depressed patients. These two seminal findings have informed research into the role of stress in depression, over the years and guided the focus on the effects of both the recent and the remote stressors on the HPA axis, brain function and structure and the clinical manifestation of depression.

Dysfunction of the HPA axis is a well established but not universal finding in affective disorders, being apparent in $\sim$50% of patients.[36,37] The pattern of HPA axis system dysregulation in depression showing atypical responses to dexamethasone, higher baseline cortisol values and an overactive response to psychological stressors suggests abnormalities within the axis's negative feedback system and corticotrophin-releasing hormone (CRH) production but intact pituitary and adrenal sensitivity.[38] Reduced mRNA expression of the glucocorticoid receptor, GR-alpha (the GR isoform which binds glucocorticoids) is found in peripheral blood cells of patients with major depressive disorder, while depressed as well as in remission. First-degree relatives of patients with bipolar disorder also showed GR-alpha mRNA reduction and taken together these findings suggest that HPA axis abnormalities, at least at the GR level, may be a trait marker in mood disorders.[39]

The neurobiological consequences of early adversity have been studied in man but these are not as yet fully understood. Depressed subjects with a history of childhood abuse have enhanced HPA axis responses to psychosocial stress[40] and attenuated adrenocorticotrophin and cortisol response to low-dose dexamethasone. However, such findings are not found in the non-depressed subjects with a history of childhood abuse.[41] Healthy subjects with high genetic load for affective disorders have elevated cortisol responses to dexamethasone/CRH challenge, the magnitude of which lies between the responses of healthy subjects without a family history of depression and those of depressed patients[42]; these persisted over a 4-year follow-up period.[43] These findings suggest that genetic vulnerability may be more important in depression than early life experience.[44]

Immunological mechanisms

Immunological mechanisms have also been implicated in the complex pathophysiology of depression with several pieces of evidence providing leads for further investigation. Proinflammmatory cytokines (signalling molecules of the immune system) elicit sickness behaviour (fatigue and lethargy) and symptoms of anxiety/depression and depressive illness is a recognised adverse event in patients receiving treatment with interferon. Severe depression is associated with immune activation and in particular with raised cytokine concentrations.

The activation of the inflammatory system response (IRS) may affect the function of other systems involved in the pathogenesis of depression. Raised proinflammatory cytokines are associated with peripheral tryptophan (serotonin precursor) depletion, may influence noradrenergic activity and they stimulate the HPA axis. Such neurotransmitter and neuroendocrine changes may be interpreted by the brain as stressors and potentiate the activation of the HPA axis. It has been suggested that impaired glucocorticoid receptor function may be related to chronic exposure to inflammatory cytokines associated with chronic physical illness or chronic stress[45] and this may explain to some extent the comorbidity of depression and chronic physical illness. Glucocorticoid resistance in turn may cause further increase in inflammation. More research with robust and consistent methodology is needed to establish the importance of the observed immune system changes in the pathogenesis of depression.

Neurochemistry

The introduction of the first effective antidepressant drugs in the late 1950s stimulated interest in the neurochemistry of the brain and in particular the neurotransmitter systems. Understanding the mechanism of action of the antidepressant drugs could pave the way to understanding the pathogenesis of depression. The earliest theory to emerge, which survives to the present, the 'monoamine hypothesis of depression', posited that depression is caused by a deficiency of the monoamines, noradrenaline, serotonin or both, in the brain and that antidepressant drugs restore these to normal. Pharmacological progress in the techniques available shifted attention from the neurotransmitters to their receptors in the 1970s–1980s. The 'beta receptor down regulation hypothesis' was proposed based on the robust and highly replicated finding, mostly in animal experiments, that chronic but not acute treatment with all effective antidepressant treatments, including electroconvulsive treatment were associated with a decrease in the density of

post-synaptic beta 1 adrenergic receptors; furthermore this coincided with the timing of clinical improvement.[46] However, further animal studies showed sensitivity and density changes in a number of other adrenergic and serotonergic receptors, located on the neuronal terminal and soma as well as post-synaptically, suggesting that receptor changes are probably adaptive mechanisms in response to increased neurotransmitter availability. Human studies showing the net effect of antidepressant drug treatment on the adrenergic system output in healthy and depressed patients was an increase rather than a decrease[47,48] did not support the beta receptor down-regulation hypothesis. Subsequent animal studies demonstrated that despite the reduction in density of the post-synaptic beta adrenoceptors, the post-receptor signal transduction cascade and related intracellular activity (protein synthesis, etc,) were actually increased. These findings revived and refined the monoamine hypothesis showing that antidepressants work by increasing monoamine neurotransmission in the brain. A large body of research showing low concentrations of serotonin and noradrenaline metabolites in plasma and cerebrospinal fluid impaired neuroendocrine responses on stimulation of noradrenergic and serotonergic receptors and a return of symptoms (after successful antidepressant drug treatment), with tryptophan or alpha-methyl-paratyrosine depletion (which reduce the concentration of serotonin or noradrenaline, respectively)[49] support the hypothesis that adrenergic and serotonergic activity is impaired in depression. All effective drugs available, at least to the present, for the treatment of depression increase the activity of one or both these systems.

Both the noradrenergic and serotonergic pathways project from their midbrain nuclei (the nucleus coeruleus and the raphe nuclei, respectively) into the limbic and prefrontal areas and the hippocampus, in close proximity to the structures implicated in the neurocircuit of depression. How significant the role of these monoamine systems is in the complex pathophysiology of depression remains to be seen as other neurotransmitter systems (e.g. GABAergic, glutamatergic) are also involved in the circuit network. So far these pathways remain key targets of the antidepressant treatment and it is believed that the therapeutic effects of antidepressants are achieved by a modulatory effect on the dysregulated neurocircuit. Further research and the development of drugs with novel mechanisms of action, targeting systems outside the monoaminergic pathways, may help clarify their importance.

Brain-derived neurotrophic factor

Brain-derived neurotrophic factor (BDNF), the focus of a substantial body of research appears to have been a crucial missing link in the

neurobiology of depression. It has been widely studied and unravelling its actions on the brain has helped bring together key research findings from neuroimaging studies, HPA abnormalities, the neurotransmitter system function and the effects of antidepressant drugs.

The hippocampus is rich in BDNF which plays a major role in neuronal growth, survival and maturation as well as arborization and synaptic plasticity in the adult brain. Stress suppresses BDNF synthesis in the hippocampus and antidepressant drugs increase its synthesis and signalling in the hippocampus and PFC.[50] In depressed patients serum BDNF concentrations are low, correlating with the severity of the depression and increase with antidepressant drugs or electroconvulsive treatment.[50,51] Such changes have also been found in the brain; in a post-mortem study of patients depressed at the time of death there were significant differences between the BDNF concentrations in the hippocampus of antidepressant-treated and untreated subjects.[50]

Genetics

Genetic factors influence susceptibility to depression but heritability estimates from twin studies at only 37% (in monozygotic twins) for unipolar depression are quite modest compared with twice as much in bipolar disorder.[52] Linkage and association studies have been searching for candidate genes with some success.

It has been shown that BDNF genetic variation influences brain structure in mood relevant areas. Met-allele carriers (val/met and met/met) have smaller hippocampal volumes in both depressed patients and healthy controls when compared with homozygous val-allele carriers.[53] It does not however appear to influence antidepressant drug response.[54] The NTRK3 gene which encodes tyrosine receptor kinase C, a receptor that binds BDNF, is attracting attention as a potentially successful candidate fitting in with the neuroplasticity theory.

The 5-hydroxytryptamine transporter- linked polymorphic promoter region (5-HTTLPR) has been extensively studied showing an association with bipolar disorder and suicidality. There is a disputed link with response to antidepressant drug treatment.[55]

As the influence of environmental factors seems particularly powerful in depression, some of the focus has shifted in recent years, to studies examining the interaction of genes and environment. For example the 3A serotonin genotype (HTR3A-42C>T) has been associated with grey matter loss in the hippocampus and frontal cortex of depressed patients who had been exposed to early life stress.[56]

A follow-up study of 1000 children through young adulthood, demonstrated that 5-HTTLPR short allele carriers were more prone to

serious depression if they had experienced stressful life events either in childhood or during the years preceding the depressive episode.[57] This finding, initially refuted by smaller meta-analyses, has now been supported by a more comprehensive meta-analysis.[58] Interestingly, the detrimental effect of the 5-HTT short/short allele appears to be moderated by monoamine oxidase A polymorphism.[59] Although not universally accepted, these results suggest that the capacity of early stress exposure to alter the brain's susceptibility to depression, may depend in part on the presence of some genetic vulnerability genotypes (possibly 5-HTTPLR), while other genotypes may play a protective role.

Epigenetic mechanisms, whereby environmental experiences can actually modify gene function without a change in DNA sequences, have also attracted a lot of interest as they may explain the relatively low concordance rates in monozygotic twins in depression.[60] Investigation of the molecular mechanisms mediating gene and environment interaction is an important field for further study.

The neurobiology of depression (integrating the evidence)

Animal and human research has identified a number of abnormalities, which like a jigsaw puzzle pieces, fit together to create a picture of a psychobiological model of the pathophysiology of depression. The main findings, which interact closely with each other, are decreased monoamine (serotonin and noradrenaline) neurotransmission, low BDNF concentrations, raised cytokines, dysregulation of the HPA axis, cortical and subcortical functional and structural brain changes and susceptibility/protective gene variations (see Fig. 2).

The structural changes in the brain in particular the hippocampus and PFC are believed to be due to abnormalities in neuroplasticity rather than neurodegeneration. Nevertheless, it remains to be confirmed whether these changes are indeed always reversible, particularly in the PFC and also whether or not they predate the onset of depression. The dysregulation of the HPA axis is responsible to a great extent for these abnormalities. Raised levels of circulating cortisol activate brain receptors stimulating gene transcription and protein synthesis. Although this may have a beneficial effect in the short term, enabling the brain to cope with smaller amounts of stress, persistent hypercortisolaemia in chronic stress can affect voltage-gated ion channels allowing increased calcium entry into the activated neurons and causing neuronal damage. Glucocorticoid-induced damage in the hippocampus may occur directly, via activation of the glutamate systems or via BDNF reduction. CRH also has direct toxic effects on hippocampal neurons. Stress is associated with reduced BDNF concentrations which

further impair neuronal survival. The decrease in BDNF concentrations may be due to the reduction in hippocampal neuronal tissue, as well as a direct effect of hypercortisolaemia; decreased activity in monoaminergic neurotransmission or other noxious factors (?glutamate effects) may also be responsible. The resulting impaired hippocampal function fails to adequately regulate (inhibit) the HPA axis, therefore sustaining 'toxic' hypercortisolaemia. The rise in cytokines levels may also contribute to the sustained HPA activation and abnormal IRSs may have a secondary or even a primary role in the dysregulation of the HPA axis.

This vicious cycle of events may be triggered off in susceptible individuals by stress (external: psychological or internal: physical) and sustained activation of the HPA axis. Pre-existing (functional or structural) abnormalities related to genetic diathesis (susceptibility minus protective genotypes), early life adversity or other causes may act as vulnerability factors. The intensity of recent life stress required to trigger a depressive state may depend on the degree of that vulnerability. It could be speculated the higher the genetic loading and other vulnerability factors, the lower the amount of life stress required to bring about a depressive episode and vice versa.

Despite the major role stress and the HPA axis appear to play in the pathogenesis of depression, given the multiple systems involved (neuroanatomical, neurochemical and immunological), insults other than the effects of stress hormones, cortisol and CRH, need to be also considered. Are hippocampal and prefrontal cortex volume changes in depression wholly attributable to stress and could they be present in the absence of stress and HPA abnormalities at any time? The decreased hippocampal volume of healthy subjects with a family history of depression suggests some of these changes may be genetically determined.[30] Cushing's syndrome is associated with a reduced hippocampal volume and cognitive dysfunction[61] and sometimes but not always with depression. Only 50% of depressed patients have measurable abnormalities in the HPA axis.[36] In many depressed subjects, there are no identifiable stressors either in the recent or remote past to explain the onset of a first depressive episode and in such cases perhaps there is either very strong genetic susceptibility possibly with multiple vulnerability genotypes present in the same individual or other unidentified mechanisms may be operating. It is possible that in such cases whatever the cause of hippocampal dysfunction, this may in turn cause secondary activation of the HPA axis (in the absence of any stressors) through reduced inhibition of the hypothalamus. Further research is needed to examine these questions.

Experimental lesioning studies, clinical observations of patients with degenerative disorders of the basal ganglia and neuroimaging structural and functional studies in depressed subjects implicate the

limbic-cortico-striato-pallido-thalamic circuits related to the medial and orbital PFC networks in depression. Abnormalities which interfere with the finely balanced interaction/communication within the neuro-circuit and in particular a decrease in the inhibitory control of the limbic structures by the PFC is associated with emotional processing, cognitive performance, behavioural and other signs of depression as well as abnormalities in neurotransmitter activity, neuroendocrine function and pain modulation. Price and Drevets[31] propose that impaired function within the circuits involving the medial prefrontal network and related limbic structures can account for these disturbances mood disorders. However, this does not explain what causes the impaired function in the first instance, in particular in the absence of any vascular, degenerative or other obvious abnormalities. The recently described subcortical white matter structural abnormalities merit further study to clarify their nature and possible significance in disrupting the connections between the neurocircuit brain structures and in particular decreasing PFC activity. Although in the old age onset depression these can be attributed to vascular changes, it is unlikely that vascular abnormalities can explain the white matter changes in the young.

Based on the evidence that after the first few episodes of depression, the influence of life stressors in further relapses diminishes, it has been suggested that a kindling process may be responsible for the seemingly spontaneous subsequent episodes.[6] It could also be speculated that perhaps at some point in the reduction of neuronal tissue a 'critical mass' is reached which cannot be sustained (in order to maintain a healthy homeostasis within the circuit brain structures) without on-going medication. This may explain the presence of low hippocampal volumes shown in medication-free remitted patients, although in some cases (those with a family history) the structural abnormality may be pre-existing (prior to the onset of depression). The persistence of such changes may result in a fragile system, with higher risk of relapse and therefore serious consideration needs to be given to long-term treatment in recurrent depression. Longitudinal studies examining the status of structural brain changes in relation to the longitudinal clinical course of depression over several years may help clarify these issues.

Conclusion

Based on the evidence available so far, it can be concluded that depressive disorder has a multifactorial aetiopathogenesis with genetic diathesis and stress (physical and psychological) playing a major role and

operating via a number of pathophysiological mechanisms. The latter include reduced activity in noradrenergic and serotonergic neurotransmission, a reduction in brain neurotrophins and hyperactivity of the HPA axis and the inflammatory response system. These are associated with functional abnormalities and structural deficits within the cortico-thalamic-striatal-limbic neurocircuit disrupting the system balance. The PFC which is functionally and structurally impaired is not able to regulate the overactivity within the cortical/limbic regions, resulting in the clinical manifestation of the depressive syndrome. Antidepressant drugs increase monoaminergic neurotransmission and BDNF concentrations and reverse some of the structural changes (at least in the hippocampus, enhancing neo-neurogenesis) and have a beneficial modulatory effect on the disrupted cortico-limbic neurocircuit function.

Depression is a long term, recurrent condition often taking a chronic course. It is associated with significant morbidity, comorbidity and mortality (suicide and physical illness). Early and effective antidepressant drug treatment with full remission is essential as well as long-term treatment in recurrent depression, in order to achieve and maintain optimum brain function and reduce the risk of recurrence or chronicity.

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