Brain imaging: a key to understanding depression

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According to the World Development Report 1993 one third of people with a mental illness suffer from a depressive disorder. There is a need for early diagnosis and effective treatment in order to limit the impact on patients' lives. Knowledge gained from brain imaging research may help to improve our understanding and treatment of depression.

Recent developments in brain imaging methods provide unprecedented insights into the neural substrates of emotions, leading to a new understanding of affective disorders. Neuroimaging studies of patients with major depression suggest functional disruption of brain areas known to mediate emotions as well as generalized and localized changes of brain structure. These findings are likely to lead to a revision of our concepts of causes of major depression and will hopefully help to advance treatment methods.

EPIDEMIOLOGY

A study on mental illness in general health care across 14 countries (Sartorius and Üstün, 1993) revealed that major depression is the most frequently treated disorder in primary health care, with a lifetime prevalence of a current *International Classification of Disease-10* (ICD-10; World Health Organisation, 1992) diagnosis of 10.4%. About 22–33% of inpatients in general hospitals suffer from depressive disorders during the course of their physical illness (Üstün and Sartorius, 1993). Unrecognized depressive disorders can lead to non-compliance in the treatment of physical illness, impairment in everyday routine, and, in the most tragic instances, to suicide. Given these facts, GPs and hospital doctors need appropriate tools to detect depression and choose effective treatments.

DIAGNOSTIC CRITERIA

Major depressive episodes feature symptoms far more severe than common grief or reactions to loss or stress. *Table 1* gives the diagnostic criteria for depression according to the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association, 1994).

TABLE 1.
Diagnostic criteria for a major depressive episode according to the *Diagnostic and Statistical Manual-IV*

Five or more of these criteria need to be present during the same 2-week period:
At least one is either depressed mood or loss of interest or pleasure
Feelings of sadness or emptiness
Markedly diminished interest or pleasure in all or almost all activities, nearly every day, or most of the day
Weight loss
Insomnia/hypersomnia
Psychomotor agitation or retardation
Fatigue or loss of energy
Feelings of worthlessness or excessive or inappropriate guilt nearly every day
Recurrent thoughts of death, recurring suicidal ideation

From American Psychiatric Association (1994)

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AETIOLOGY

Research over the past 40 years has stressed the importance of genetic and environmental factors in the pathogenesis of depression.

Genetic factors

Some molecular genetic studies have aimed to identify specific genes responsible for personality traits related to depression (quantitative trait loci), assuming that psychopathology is the result of a quantitative expression of different traits. These personality traits are likely to be influenced by a number of different genes (rather than a single gene), accounting for different mental disorders with similar basic symptoms (Eley and Plomin, 1997). For example, individuals with reduced function of the serotonin transporter gene (5-HTT, reducing serotonin transporter expression) have higher levels of neuroticism, depression and anxiety (Eley and Plomin, 1997).

Twin and adoption studies enable estimates of the proportion of variance in levels of depression that is accounted for by genetic factors. Monozygotic twins share 100% of their genes, dizygotic twins share an average of 50%. Assuming that affective disorders are inherited, monozygotic twins should have a higher risk of developing the disorder compared to dizygotic pairs. The strongest support for heredity in the group of affective disorders can be found for bipolar disorder suggesting 30–80% heritability (Johansson et al, 2001). Studies on major depression produced varying results, stating population prevalence of 2–25% for first-degree relatives, with slightly higher rates for early-onset and reoccurring depression (National Institute of Mental Health, 1999). A meta-analysis on seven twin studies on major depression showed an overall heritability of 37% (Sullivan et al, 2000). Taken together, these studies indicate that genes do indeed play a substantial role; however, additional factors are needed to fully explain the development of affective disorders.

Environmental factors

Stressful life-events in early childhood, e.g. abuse or neglect, can lead to permanent changes in the hypothalamus–pituitary–adrenal axis, corticotrophin-releasing factor and the hippocampus (Heim and Nemeroff, 2001), hence providing the endocrinological basis for the development of depression. Corticotrophin-releasing factor is secreted from neurons in the hypothalamus and transported to the anterior pituitary. There it stimulates pituitary corticotrophins that secrete the adrenocorticotropic hormone, a stress hormone stimulating the adrenal cortex to release glucocorticoids (cortisol). A feedback loop to the anterior pituitary, hypothalamus and hippocampus maintains cortisol at a normal level. Persistence of stressful circumstances can lead to hypercortisolaemia and resistance to hippocampal feedback inhibition (Heim and Nemeroff, 2001).

These studies demonstrate how environmental factors may directly contribute to aberrant neurochemistry underlying affective disorders.

Neurotransmitters

An influential hypothesis regarding the aetiology of depression was formulated by Schildkraut (1965). He argued that a deficiency of the catecholamine noradrenaline to be responsible for the symptoms of major depression. In agreement with this assumption, treatment with reserpine, which depletes catecholamines, elicits depressive episodes in susceptible individuals. However, further research could not confirm noradrenaline as the sole factor in the development of depression (Goodwin and Bunney, 1971). Coppen (1967) found that only serotonin depletion facilitated a decrease in noradrenaline levels. Similarly, antidepressant medication increasing serotonin levels has symptom-reducing effects.

Recent research has focused on impaired neuroplasticity and cellular resilience (Manji et al, 2001). Stress, genetic and neurodevelopmental factors were found to contribute to a decrease in brain-derived neurotropic factor (BDNF) expression, which is responsible for sustaining cell survival. Postmortem and brain imaging studies have demonstrated reduced brain volume and neuron loss in subgroups of depressed patients, suggesting that some forms of depression may result from stress-induced BDNF reduction (Manji et al, 2001).

TREATMENT OF MAJOR DEPRESSION

The most important treatment options are pharmacotherapy, psychotherapy, a combination of pharmacotherapy and psychotherapy, and electroconvulsive therapy.

Pharmacotherapy

Antidepressant medication is typically indicated for moderate to severe forms of depression and is successful in 67–70% of cases (Depression Guideline Panel, 1993).

According to their site of activity antidepressants can be categorized into selective serotonin and noradrenaline reuptake inhibitors, monoamine oxidase inhibitors, and monoamine receptor agonists or antagonists.

Psychotherapy

The most effective treatment methods are cognitive-behavioural therapy and interpersonal psychotherapy in combination with antidepressant medication (Doris et al, 1999). Cognitive-behavioural therapy is based on social learning theories and the functional analysis of behaviour (*Figure 1*). Interpersonal psychotherapy aims at clarification of interpersonal role disputes and transitions, abnormal grief reactions or social isolation (*Figure 2*).

Electroconvulsive therapy

Electroconvulsive therapy may be used in very severe cases, after unsuccessful pharmacotherapy, or in specific medical conditions, which make treatment with antidepressants impossible. Electrodes conveying electrical currents are placed on frontotemporal sites bilaterally or unilaterally on the non-dominant side, in order to limit temporary cognitive side effects such as confusional states and anterograde or retrograde amnesia (National Institute of Health, 1985).

BRAIN ABNORMALITIES IN DEPRESSION

Advances in neuroimaging techniques such as magnetic resonance imaging (MRI), computed tomography, positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and single-photon emission computed tomography allow the investigation of brain function in vivo (Sheringham et al's article in this issue gives information on these techniques). Application of these techniques to psychopathology has proven a powerful tool in the detection of neurochemical, neuroanatomical, and functional abnormalities of mental disorder.

Structural abnormalities

A number of studies suggest generalized abnormalities including enlarged third and lateral ventricles in post-stroke major depression. Increased white matter hyperintensities and volume reductions in frontal lobe areas and basal ganglia have been found in elderly unipolar depressed patients (Soares and Mann, 1997). Bilateral and unilateral hippocampal atrophy (Sheline et al, 1996; Bremner et al, 2000) and amygdala volume loss in patients suffering from recurrent major depression (Sheline et al, 1999) as well as amygdala enlargement in patients with bipolar depression (Altshuler et al, 1998) have been reported. These findings indicate that depression is caused by or results in structural brain abnormalities in regions important for emotion regulation, such as the frontal cortex, hippocampus and amygdala.

Functional abnormalities

The ability to reliably elicit emotions in a laboratory setting has led to a considerable amount of research in this area. Owing to similarities in the experience of negative emotional states in both healthy individuals and depressed patients, functional neuroimaging research into human emotions is of invaluable importance for further advances in the understanding and treatment of affective disorders. Mood induction studies in healthy individuals have demonstrated the involvement of the prefrontal cortex, anterior cingulate, and amygdala in mood regulation (Lane et al, 1997). The same areas are known to show abnormal metabolism in patients with major depression (Soares and Mann, 1997; Drevets, 1998).

The prefrontal cortex maintains representations of goals and the means to achieve them (Miller and Cohen, 2001). One of its functions is therefore the inhibition of reward-oriented, immediate affective responses in favour of goal-oriented appropriate behaviour. The main function of the anterior cingulate in this context is to assess the significance of emotional and motivational information and to mediate between emotion and attention (Bush et al, 2000). The anterior cingulate can be divided into a dorsal cognitive division connected to the

Figure 1. Cognitive-behavioural therapy. From Beck et al (1979).

Cognitive-behavioural therapy is based on Beck's theory (Beck et al, 1979) that depression is elicited and sustained by dysfunctional thinking patterns. Depression is therefore seen as a disturbance of cognitions. The central maladaptive elements of depression are a cognitive triad of recurrent negative views which shape how the person sees himself, the world and the future, implicit irrational schemata based on the past, and logical errors or silent assumptions.

The focus of cognitive-behavioural therapy lies in the logical analysis of automatic principles by which the depressed patient perceives, organizes and responds to situations. The therapy is aimed at monitoring automatic thoughts, identifying links between cognition, affect and behaviour, examining the evidence pro and contra maladaptive automatic thoughts, and learning to recognize and alter dysfunctional beliefs which predispose the person to distorted cognitions.

Figure 2. Interpersonal therapy. From Klerman and Weissman (1993).

Interpersonal therapy focuses on the patient's social network. The theory states that unsatisfactory relationships with significant others and perturbed social roles can be antecedents of depression. Abnormal grief reactions, interpersonal role disputes, difficult role transitions, and interpersonal deficits are prominent in depressed patients. These problems are addressed by the therapist in a cognitive behavioural and psychodynamic approach, aiming to minimize dependency in order to maintain mature and satisfactory interpersonal relationships.

posterior cingulate and parietal cortex, and a rostral ventral affective division, including the subgenual cingulate. The affective division has connections to the amygdala, periaqueductal grey, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and orbitofrontal cortex. The cognitive division of the anterior cingulate is responsible for visual attention and monitoring of cognitive conflicts, whereas the affective subdivision is involved in assessing motivational and emotional consequences (Bush et al, 2000). The amygdala assigns emotional significance to novel and ambiguous stimuli (Drevets, 1998).

Integrating dysfunction in the above mentioned brain regions in depression, the model of limbic-cortical dysregulation (Mayberg, 1997) suggests hypometabolism in the dorsal compartment (dorsolateral prefrontal cortex, dorsal anterior cingulate, inferior parietal cortex, and striatum) to be responsible for the symptoms of apathy, attention deficits, and psychomotor slowing apparent in major depression, and hypermetabolism in the ventral region (hypothalamus, insula, subgenual cingulate, and brainstem), to be responsible for symptoms of disturbed sleep, appetite and libido.

Concordant with this model is the finding that healthy controls, during experimentally induced sadness, and depressed patients before treatment, display increased cerebral blood flow in the subgenual cingulate and anterior insula, and decreased blood flow in dorsolateral prefrontal and inferior parietal areas. After successful treatment this pattern is reversed in patients (Mayberg et al, 1999).

Studies assessing neural activity in depressed patients during resting state have also observed lower levels of blood flow and glucose metabolism in the dorsolateral and dorsomedial prefrontal cortex (Drevets, 1998). Further support for decreased neural activity in the anterior cingulate, dorsolateral prefrontal cortex, and superior temporal gyrus in depression is provided by neuroimaging studies of depressed subjects using cognitive activation paradigms (Beauregard et al, 1998). Abnormal decrease in brain activation in these areas may also account for psychomotor slowing, attentional deficits and executive function impairments (Kennedy et al, 2001). A study of mood induction through cognitive materials has further revealed decreased activation in the medial frontal lobe and cingulate gyrus, and increased activation in parahippocampal and temporal lobe regions (Kumari et al, 2001).

A study by Sheline et al (2001) presenting fearful faces found increased activation in the left amygdala in unipolar depressed patients relative to controls. A PET study measuring regional cerebral glucose metabolism in a sample of treatment-resistant severely depressed patients demonstrated decreased metabolism in the right dorsolateral and bilateral medial prefrontal cortex, as well as anterior cingulate (Kimbrell et al, 2002).

IMPLICATIONS OF NEUROIMAGING STUDIES FOR TREATMENT

Changes in neural correlates after successful treatment of symptoms

Successful treatment with fluoxetine has been seen to increase metabolism in dorsal cortical regions, dorsolateral prefrontal areas, inferior parietal, dorsal anterior cingulate and posterior cingulate regions and to decrease metabolism in ventral limbic and paralimbic regions (Mayberg et al, 2000). These results represent the inversed pattern of the pre-treatment activation as well as of findings from healthy controls during induced transient sadness (Mayberg et al, 2000), supporting the model described above. Decreases in metabolism in the dorsal and rostral anterior cingulate and increases in amygdala activation return to normal levels after successful antidepressant treatment (Drevets, 1998; Mayberg et al, 1999).

Neural correlates as predictors of treatment outcome

Increased rostral anterior cingulate activity before treatment may be a predictor of better treatment outcome (Pizzagalli et al, 2001). Supporting this hypothesis are recent data (Kimbrell et al, 2002) showing decreased anterior cingulate activation in severely depressed patients compared to a euthymic subgroup and an inverse correlation between levels of activation and symptom severity. Increased cingulate metabolism at baseline also predicts a positive response to sleep deprivation treatment (Wu et al, 1992).

These studies suggest the intriguing possibility that functional imaging techniques may be used in the prediction of treatment response. Brain activation patterns may be studied to inform the development of new pharmacological agents, as well as the clinician's choice of antidepressant treatment.

CONCLUSION

Neuroimaging techniques have the potential to discover abnormalities in brain structure and function in people with depression. It still

remains unclear whether the structural and functional deficits revealed with neuroimaging techniques are a precursor to depression, caused by genuine pathophysiology, or to secondary effects of chronic illness and antidepressant treatment. These questions need to be addressed in future functional neuroimaging studies of depressed patients, populations at risk (such as offspring of depressed patients), and healthy individuals. **HM**

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KEY POINTS

- Depression is a disabling illness with a high prevalence.
- Depression is often co-morbid with physical illness, therefore awareness of depressive symptoms must be raised in general health care.
- Antidepressants act on serotonergic, noradrenergic, or dopaminergic neurotransmitter systems.
- Structural and functional neuroimaging studies provide evidence of dysfunction in brain areas responsible for mood modification.
- Neuroimaging studies of affect and cognition in healthy and depressed individuals aid our understanding of the functional neuroanatomy of depression.
- Further knowledge of the functional neuroanatomy of depression might allow the prediction of treatment outcome based on activation levels in specific brain areas.

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