The World Journal of Biological Psychiatry, 2007; 8(3): 141–174

REVIEW

Consensus paper of the WFSBP Task Force on Biological Markers: Biological Markers in Depression

RAINALD MÖSSNER[1], OLYA MIKOVA[2], ELENI KOUTSILIERI[1], MOHAMED SAOUD[3,4], ANN-CHRISTINE EHLIS[1], NORBERT MÜLLER[5], ANDREAS J. FALLGATTER[1] & PETER RIEDERER[1]

[1]*Department of Psychiatry and Psychotherapy, University of Würzburg, Würzburg, Germany,* [2]*Department of Psychiatry, Medical University of Sofia, Sofia, Bulgaria,* [3]*Université Lyon, Lyon, France,* [4]*SHU de Psychiatrie, Centre Hospitalier Le Vinatier, Bron, France,* [5]*Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University Munich, Munich, Germany*

Abstract

Biological markers for depression are of great interest to aid in elucidating the causes of major depression. We assess currently available biological markers to query their validity for aiding in the diagnosis of major depression. We specifically focus on neurotrophic factors, serotonergic markers, biochemical markers, immunological markers, neuroimaging, neurophysiological findings, and neuropsychological markers. We delineate the most robust biological markers of major depression. These include decreased platelet imipramine binding, decreased 5-HT1A receptor expression, increase of soluble interleukin-2 receptor and interleukin-6 in serum, decreased brain-derived neurotrophic factor in serum, hypocholesterolemia, low blood folate levels, and impaired suppression of the dexamethasone suppression test. To date, however, none of these markers are sufficiently specific to contribute to the diagnosis of major depression. Thus, with regard to new diagnostic manuals such as DSM-V and ICD-11 which are currently assessing whether biological markers may be included in diagnostic criteria, no biological markers for major depression are currently available for inclusion in the diagnostic criteria.

Introduction

The aim of this article is to review recent evidence on biological markers of depression that could be detected in different ways – by testing body fluids or cells, by brain imaging or other methods. Depressive disorders are heterogeneous and diagnosed on the basis of a patient's symptoms, not on the basis of a laboratory test. So the search for biological markers for depression is partially due to the need of finding diagnostic adjuncts.

The treatment of depressive disorders varies both in type and effectiveness. Antidepressant drugs have been used for over 40 years, but they still present the problem of delayed onset of action. Normally it takes about 14 days for the patients responding to a given antidepressant to improve during which time they are still depressed and suicidal. So a biological marker would be useful to distinguish early improvement under drug treatment (first days, even hours). Biological markers may give an insight into the underlying biological basis of depression, which can be used to develop more effective drug treatments.

The idea behind identifying biological markers is that by using them, psychiatrists could reveal the specific depression profile of each patient and select the optimal treatment. The term 'biological marker' is used here to describe a biological change associated with depression that could be used to indicate the presence and severity of the condition and predict drug or other treatments' response as well as the clinical prognosis.

Neurodevelopment/neurotrophic factors

Neurodevelopment factors

The human brain, the most complex of all organs, contains *100 billion neurons* and 10 times as many

Correspondence: Prof. Dr. Peter Riederer, Department of Psychiatry and Psychotherapy, University of Würzburg, Füchsleinstr. 15, D-97080 Würzburg, Germany. Tel: +49 931 201 77210. Fax: +49 931 201 77220. Email: peter.riederer@mail.uni-wuerzburg.de

ISSN 1562-2975 print/ISSN 1814-1412 online
DOI: 10.1080/15622970701263303

glial cells. These cells of the human brain connect and organize into functional units with specific roles to sense, perceive, process and act on information from outside and inside the individual to promote survival and other actions of the human being.

Each of these cells contains the same genetic material (genotype). However, each cell type utilizes actively different portions of it so each individual neuron expresses different properties and functions. Differentiation is the process by which cells become specialized, expressing those components of the genome, which confer special properties associated with the functions of the neuron in the mature brain. This process takes place throughout development. While the majority of neurons exist already by birth (neurogenesis), most of them have not completed their individual growth and specialization. Over the 3 years following birth, the important processes of neuronal migration, axo-dendritic projection, myelinization, synaptogenesis, and neurochemical differentiation continue to take place. As the brain develops, neurons migrate and differentiate in response to chemical, 'microenvironmental' stimuli (morphogens), which confer information to and direct specific differentiation of the cell. So, the neuron's unique structure, biochemisty and function are the result of its unique environmental history, i.e. the specific pattern of exposure, timing and quantity of these microenvironmental stimuli. Some of the most important microenvironmental stimuli are receptor-mediated signals from neurotransmitters and hormones, which act as morphogens. That is why the 'stress response' is extremely important for brain organization (Perry and Pollard 1998). This well-characterized set of adaptive physiological responses to real or perceived danger involves a series of complex, interactive neurophysiological reactions in the brain, the autonomic nervous system, the hypothalamic–pituitary adrenocortical (HPA) axis and the immune system. The neurophysiological activation (e.g., increased release of norepinephrine) seen during acute stress is usually rapid and reversible. When the stressful event is of a sufficient duration, intensity, or frequency, however, the brain is altered. Stress-induced 'sensitization' may occur. The neurochemical systems mediating the stress response (e.g., locus coeruleus noradrenergic systems) change, becoming more 'sensitive' to future stressors related to the original experience. The molecular mechanisms underlying this phenomenon are not well understood but are related to the same cascade of molecular processes involved in learning and memory. The stressful experience, via a cascade of neurochemical events, alters the microenvironmental milieu of the CNS, resulting in altered gene expression. The new gene products may then result in 'permanent' or structural changes which are associated with sensitization, learning, memory and, in the developing brain, differentiation. In the adult, mature brain, increases in, or unusual patterns of, catecholamine activity may result in sensitization. In the developing brain, however, neurotransmitters, in addition to their roles in cellular communication, play an important role in the basic neurodevelopmental processes (Lauder 1988). Trauma-related alterations in catecholamine activity during childhood, therefore, may alter brain development, resulting in altered functional capabilities of the 'traumatized' brain. Changes in the pattern, timing and quantity of catecholamine (or any critical neurotransmitter system) activity during development might be expected to result in altered development of catecholamine receptor/effector systems and the functions mediated, in part, by these systems. A trauma-induced prolonged stress response will result in an abnormal pattern, timing and intensity of catecholamine activity in the developing brain. The time during development that this prolonged or abnormal catecholamine activity is present, determines to some degree the nature and severity of the disrupted development. In general, the earlier and the more pervasive the trauma, the more neurodevelopment will be disrupted.

There is some evidence to suggest that prenatal or maternal traumatic stress has significant impact on neurodevelopment. The development of the human brain continues beyond birth and its development remains vulnerable to the abnormal patterns of neurotransmitter and hormone activity associated with traumatic stress. Young children victimized by trauma are at risk for developing permanent changes in brain development with potential impact on all aspects of emotional, cognitive and behavioural functioning. There are times in development, called critical periods, during which a set of signals must be present for the neurons to differentiate normally. In addition, there are times when an undifferentiated neuron is especially 'receptive' or sensitive to a set of signals. At these times, termed sensitive periods**,** the neuron will use this set of signals to facilitate further specialization as part of a larger functional subsystem in the brain. For humans, some extreme illustrations of the principles of development during these sensitive periods have been described in the literature. Children raised with little or no exposure to verbal language never develop the neural apparatus needed for optimal speech or language development (Freedman 1981); children raised in sensory-deprived settings have major deficits in developing integrated neurosensory processing; children with various visual deficits (e.g., strabismus), for example, develop abnormal visual and perceptual

capabilities (Lipton 1970). In humans there is very little information regarding these 'windows' of vulnerability; the majority of the irreversible sensory processing deficits have resulted from deprivations during the first three years of life. There are, of course, critical and sensitive periods for the development of important brain systems and functions other than neurosensory processing. There is overwhelming evidence suggesting sensitive, if not critical, periods for brain functions associated with 'mental health' including attachment, affect modulation, anxiety regulation, and behavioural impulsivity (Provence 1983), all of which utilize to varying degrees the same neurobiological subsystems which mediate the 'stress response'. The sensitive periods for the stress response 'apparatus' in the brain – developmental phases during which an individual is most vulnerable to traumatic stressors – occur when the stress-mediating catecholamine systems are undergoing neurogenesis, migration, synaptogenesis and neurochemical differentiation. The functional capabilities of the CNS systems mediating stress in the adult are determined by the nature of the 'stress' experiences during the development of these systems, i.e. *in utero*, during infancy and childhood. Increased psychiatric symptoms and disorders are observed in adults who have severe, unpredictable early life stressors (Rutter 1984). A provocative study (Breier et al. 1988) reported the effects of parental loss during childhood on the development of psychopathology in adulthood. They examined a number of adults who had suffered a parental loss during childhood and found that the subjects with psychiatric disorders and symptoms had significant biological and immunological changes related to early parental loss relative to control groups. The authors concluded that early parental loss (a traumatic event) accompanied by the lack of a supportive relationship subsequent to the loss (an external stress reducing factor) is related to the development of adult psychopathology. Other studies have documented relationships between developmental trauma and borderline personality disorders, depressive disorders (Kaufman 1991), dissociative disorders and a variety of other medical and psychiatric conditions**.** According to Gale and Martyn (2004) impaired neurodevelopment during foetal life may increase susceptibility to depression.

Clearly, these many studies provide correlative data indicating that developmental stress is a major expressor of any underlying constitutional or genetic vulnerability and may be the primary aetiological factor in the development of certain neuropsychiatric disorders. The abnormal pattern of stress-mediating neurotransmitter and hormone activations during development alters the brains of traumatized children. The specific nature of these func ional alterations is seen in all of the brain functions, which are directly or tangentially related to CNS catecholamine systems. Unfortunately, the CNS catecholamines (and likely other important neurotransmitter systems altered by these experiences) are involved in almost all core regulatory activities of the brain. The brainstem and midbrain catecholamines are involved in regulation of affect, anxiety, arousal/concentration, impulse control, sleep, startle, autonomic nervous system regulation, memory and cognition. Clearly the physical signs and symptoms seen in traumatized children include dysfunction and dysregulation in these domains. Indeed, the 'core' symptoms seen in severely traumatized children may be traced back to dysregulation of these root neurophysiological regulatory functions.

It has been proposed that stress-induced changes in the hippocampus may be central to the development of depression in genetically vulnerable individuals. New evidence implicates the prefrontal cortex (PFC) in addition to the hippocampus as a site of neuropathology in depression. The PFC may be involved in stress-mediated neurotoxicity because stress alters PFC functions and glucocorticoid receptors, the PFC is directly interconnected with the hippocampus, and metabolic alterations are present in the PFC in depressed patients. Postmortem studies in major depression and bipolar disorder provide the first evidence for specific neuronal and glial histopathology in mood disorders. Three patterns of morphometric cellular changes are noted: cell loss (subgenual PFC), cell atrophy (dorsolateral PFC and orbitofrontal cortex), and increased numbers of cells (hypothalamus, dorsal raphe nucleus). The relevance of cellular changes in mood disorders to stress and prolonged PFC development and a role of neurotrophic/ neuroprotective factors are suggested, and a link between cellular changes and the action of therapeutic drugs is discussed (Rajkowska 2000).

Neurotrophic factors

Neurogenesis. The development and maintenance of the vertebrate nervous system requires continuous supply of a number of polypeptide hormones known as neurotrophic factors. During the period of target innervation, limiting amounts of neurotrophic factors regulate neuronal numbers by allowing survival of only some of the innervating neurons, the remaining being eliminated by programmed cell death. Increasing evidence indicates that several neurotrophic factors also influence the proliferation, survival and differentiation of precursors of a number of neuronal lineages. In the adult, neurons

continue to be dependent on trophic factor support. Thus, neurotrophic factors are important signalling molecules for the development and maintenance of neurons, acting throughout development on many types of neuronal populations (Ibanez 1995; Mamounas et al. 1995). They increase cell survival by providing necessary trophic support for growth, but also by exerting inhibitory effects on cell death cascades (Thoenen 1995; Pettmann and Henderson 1998; Riccio et al. 1999).

Proliferation and maturation of neurons have been demonstrated to occur at a significant rate in discrete regions of adult brain, including the hippocampus and subventricular zone, although many of the newborn cells degenerate 1–2 weeks after birth. Very little is known about the intracellular signal transduction pathways that control adult neurogenesis. There are indications that the cAMP–CREB pathway regulates the survival, differentiation and function of newborn neurons (Nakagawa et al. 2002). Adult neurogenesis is an extremely dynamic process that is regulated in both a positive and negative manner by neuronal activity and environmental factors. It has been suggested to play a role in several important neuronal functions, including learning, memory, and response to novelty. In addition, exposure to psychotropic drugs or stress regulates the rate of neurogenesis in adult brain by regulating the expression and function of growth factor cascades, suggesting a possible role for neurogenesis in the pathophysiology and treatment of depression and others illnesses (Smith et al. 1995; Nibuya et al. 1999; Duman et al. 2001). Several neurotrophic factors (such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF)), as well as cytokines and insulin-like growth factor-1 (IGF-1), increase cell survival (Mamounas et al. 1995; Pettmann and Henderson 1998). This occurs through binding of these factors to membrane receptors and regulation of intracellular signal transduction pathways that can control apoptosis, including regulation of Bcl-2 family members. Signal transduction cascades that are currently believed to mediate many of the effects of neurotrophic factors include the mitogen-activated protein kinase (MAPK) cascade, the phosphatidylinositol-3 kinase (PI3K)–Akt pathway, and the phospholipase C cascade (Segal and Greenberg 1996). Recent studies have demonstrated that the activation of the MAPK pathway can inhibit apoptosis by inducing the phosphorylation of Bad (a major proapoptotic protein) and increasing the expression of Bcl-2 (a major antiapoptotic protein), the latter effect likely involves the cAMP response element–binding protein (CREB) (Bonni et al. 1999; Riccio et al. 1999). Accumulating data suggest that not only is Bcl-2 neuroprotective, but it also exerts neurotrophic effects and promotes neurite sprouting, neurite outgrowth, and axonal regeneration (Chen et al. 1997; Chen and Tonegawa 1998; Holm et al. 2001). It is important to note that both lithium and valproate increase Bcl-2 (Moore et al. 2000). Estrogen is also a neurotrophic factor. Estradiol can induce BDNF expression, and recent data suggest that structural and electrophysiological effects of estradiol in the hippocampus might be mediated by BDNF (Scharfman and Maclusky 2005). Disruption of the relationship between estrogen and BDNF could contribute to neurological and psychiatric disorders that have been associated with the hippocampus, such as depression and Alzheimer's disease. The cAMP response element-binding protein (CREB) is a critical integrator of neural plasticity that is responsive in a brain region-specific manner to a variety of environmental and pharmacological stimuli, including widely prescribed antidepressant medications. CREB is an ubiquitous key-element of intracellular signal transduction cascades that may contribute to symptoms of depression (Newton et al. 2002). Its transcriptional activity depends on phosphorylation at Ser-133. By measuring CREB-phosphorylation in T-lymphocytes it was found that the responders to psychopharmacological treatment with different treatment regimens showed a significant increase in CREB-phosphorylation compared to the non-responders. These results indicate for the first time that the increase in CREB-phosphorylation might be a molecular state marker for the response to antidepressant treatment (Koch et al. 2002). However, other studies do not support such a hypothesis (Lai et al. 2003). Furthermore, activation of both protein kinases, PKA and PKC was associated with reduced CREB-P in melancholics relative to normal controls. Finally, PKA activity was found to correlate positively with Hamilton depression scores after 16 weeks of treatment with serotonin reuptake inhibitor antidepressants. These data further implicate signal transduction abnormalities in melancholic major depression, particularly PKA and PKC. This suggests an abnormality of factors controlling the expression or degradation of these enzymes (Akin et al. 2005).

Brain-derived neurotrophic factor (BDNF). BDNF is the neurotrophic factor in the focus of intense research for the last years. BDNF belongs to the neurotrophin family of growth factors and affects the survival and function of neurons in the central nervous system. Its normal physiological role is to encourage the outgrowth of dendrites from nerve

endings, and to help stabilize connections between neurons. BDNF is, however, an unusual neurotrophic factor because its widespread functions in the brain go beyond the traditional role of a growth factor to promote growth, survival, and maintenance of cells. Beyond promoting neuronal survival and resilience to injury, BDNF also has a powerful role in facilitating activity-dependent plasticity**,** which underlies the capacity for learning and memory. Brain regions where plasticity is particularly important include the hippocampus and cortex, critical centers for learning and memory. The hippocampus is a central component for encoding new information, and damage there severely impairs learning. From a plasticity point of view, insufficient BDNF would weaken synaptic encoding strength or capacity, while from the neurotrophic angle, reduced BDNF makes hippocampal neurons more vulnerable to insult and degeneration. BDNF is produced by neurons, particularly in the hippocampus and cortex. Neuronal activity, i.e., during encoding of information, stimulates BDNF gene transcription, transport of BDNF mRNA into dendritic spines, and BDNF protein release into the synaptic cleft (Hartmann et al. 2001). BDNF improves survival of cholinergic neurons of the basal forebrain, as well as neurons in the hippocampus and cortex.

BDNF acts on neurons at both presynaptic and postsynaptic sites by binding to its tyrosine kinase receptor TrkB, and internalization of the BDNF–TrkB complex-signalling endosome (Lu 2003). By enhancing synaptic transmission and neuronal excitability, BDNF modulates synaptic change, including hippocampal long-term potentiation (LTP), a neural mechanism associated with learning and adaptive behaviours in adult animals (Poo 2001; Tyler et al. 2002). BDNF-deficient mice show decreased synaptic innervation and reduced levels of synaptic vesicle proteins (Martinez et al. 1998; Pozzo-Miller et al. 1999), demonstrating that BDNF is important for normal synaptic signalling (Martinez et al. 1998). Two potent stimuli that rapidly increase BDNF levels in the hippocampus are exercise and learning. In rodents, voluntary daily wheel running consistently increases BDNF mRNA and protein levels in the hippocampus and other brain regions, including parts of the cortex (Cotman and Berchtold 2002). In addition, learning itself increases brain BDNF levels, particularly in the hippocampus. Interestingly, in humans, regular exercise is associated with benefits to brain health and cognitive function, which may in part be due to increased availability of BDNF. Indeed, physically active adults not only have a lower risk of cognitive impairment, but also a lower risk of depression and of developing AD or dementia of any type (Friedland et al. 2001; Laurin et al. 2001). Studies demonstrating that neurogenesis is increased by conditions that stimulate neuronal activity (such as enriched environment, learning, and exercise) suggest that this process is also positively regulated by, and may even depend on, neuronal plasticity (Kempermann 2002). BDNF and serotonin (5-hydroxytryptamine, 5-HT) are known to regulate synaptic plasticity, neurogenesis and neuronal survival in the adult brain. These two signals co-regulate one another such that 5-HT stimulates the expression of BDNF, and BDNF enhances the growth and survival of 5-HT neurons (Mattson et al. 2004).

Our contemporary knowledge on neurotrophic factors and depression is based on a number of postmortem studies and animal models of depression and antidepressants' action. Some observations from animal studies suggest that BDNF and NGF may play a role in depression and (because of the different brain regional concentrations of BDNF and NGF found in male and female animals) may be relevant to gender differences in vulnerability to depression (Angelucci et al. 2000). There is emerging evidence – primarily from postmortem studies – that supports a role for abnormalities in neurotrophic signalling pathways in depression. Decreased levels of CREB, BDNF, and the TrkB receptor have been reported in suicide victims (Dwivedi et al. 2003a,b; Yamada et al. 2003). It has been indicated from postmortem studies that a transcription factor likely mediates neural plasticity in the mammalian brain and neural tissues (Yamada et al. 2003).

A large body of evidence has established a link between stressful life events and development or exacerbation of depression. Recent studies suggest that stress-induced atrophy and loss of hippocampal neurons may contribute to the pathophysiology of depression. At the cellular level, evidence has emerged indicating neuronal atrophy and cell loss in response to stress and in depression. At the molecular level, it has been suggested that these cellular deficiencies, mostly detected in the hippocampus, result from decreased expression of BDNF associated with elevation of glucocorticoids. However, as also revealed by converging lines of evidence, high levels of glucocorticoids down-regulate hippocampal synaptic connectivity ('negative' metaplasticity), whereas an increase in expression of BDNF up-regulates connectivity in the hippocampus ('positive' metaplasticity) (Garcia 2002). Stress hormones and 5-HT may act in an opposite manner – stress hormones decrease BDNF levels while 5-HT increases them. The reduction of BDNF could be the result of the decrease in CREB as shown in animal studies (Trentani et al. 2002). The loss of BDNF in chronic stress leads to an altered

output from areas such as the hippocampus to the pre-frontal cortex. It is well known that the glucocorticoid and mineralocorticoid hormones, released from the adrenal glands during stress, contribute to depression by acting on the hippocampus. They bind to specific receptors in this region and thus cause a drop in both BDNF mRNA and protein in neurons. In view of the opposite effects of stress and antidepressants on hippocampal neurogenesis, it is quite plausible that alterations in hippocampal neurogenesis are fundamental to the clinical syndrome of depression (Jacobs et al. 2000; Manev et al. 2001; D'Sa and Duman 2002; Kempermann 2002).

A growing body of evidence suggests that antidepressants may regulate neurotrophic signalling cascades. Different classes of long-term antidepressant treatments – including norepinephrine (NE) reuptake inhibitors, selective serotonin reuptake inhibitors (SSRIs), and electroconvulsive therapy – up-regulate CREB and BDNF expression, which indicates that CREB and BDNF are common postreceptor targets of these therapeutic agents (Nibuya et al. 1995; Nibuya et al. 1996). More evidence that links up-regulation of these pathways and antidepressant activity comes from behavioural models (Duman et al. 1999). It was observed that CREB overexpression in the dentate gyrus or BDNF injection results in an antidepressant-like effect in behavioural models of depression and antidepressant efficacy in rats (Siuciak et al. 1997; Chen et al. 2001a; Shirayama et al. 2002). Chronic, but not acute, antidepressant treatment also increases the neurogenesis of dentate gyrus granule cells (Jacobs et al. 2000; Manev et al. 2001; D'Sa and Duman 2002). Lithium, one of the most effective antidepressant potentiating agents, also increases neurogenesis in the dentate gyrus (Chen et al. 2000). In contrast, increased neurogenesis is not observed in response to long-term administration of non-antidepressant psychotropic drugs.

New research in animals is beginning to change radically our understanding of the biology of stress and the effects of antidepressant agents. Stress and antidepressants have reciprocal actions on neuronal growth and vulnerability (mediated by the expression of neurotrophins) and synaptic plasticity (mediated by excitatory amino acid neurotransmission) in the hippocampus and other brain structures. Antidepressant treatments might not only restore cell density but also regulate higher-order synaptic plasticity in the hippocampus by abolishing 'negative' metaplasticity, and thus restore hippocampal cognitive processes that are altered by stress and in depressed patients (Garcia 2002). Stressors have the capacity to progressively disrupt both the activities of individual cells and the operating characteristics of networks of neurons throughout the life cycle, while antidepressant treatments act to reverse such injurious effects. A central role for the regulation of synaptic connectivity in the pathophysiology of depressive disorder is thus proposed (Reid and Stewart 2001). Chronic administration of several different classes of antidepressant, but not non-antidepressant, agents was found to increase BrdU-labelled (bromodeoxyuridine, a marker of cell division) cell number, indicating that this is a common and selective action of antidepressants. These findings raise the possibility that increased cell proliferation and increased neuronal number may be a mechanism by which antidepressant treatment overcomes the stress-induced atrophy and loss of hippocampal neurons and may contribute to the therapeutic actions of antidepressant treatment (Malberg et al. 2000). Disrupting antidepressant-induced neurogenesis blocks behavioural responses to antidepressants, seen in a study, in which X-irradiation of mouse hippocampus prevented the neurogenesis and behavioural effects of two classes of antidepressants. These findings suggest that the behavioural effects of chronic antidepressants may be mediated by the stimulation of neurogenesis in the hippocampus (Santarelli et al. 2003).

Several studies with contradicting results suggest that these changes occur in the context of broader impairments of cellular plasticity and resilience, rather than in that of a limited neurogenesis model (van der Hart et al. 2002; Morcuende et al. 2003; Vollmayr et al. 2003).

BDNF as a biological marker in depression. In post-mortem studies of depressed patients with or without antidepressive treatment it was shown that there are abnormalities in the cAMP signalling pathway, and its downstream neurotrophic factor BDNF, which are major targets of antidepressant medications (Chen et al. 2001b). Increased BDNF expression was found in dentate gyrus, hilus and supragranular regions in subjects treated with antidepressant medications at the time of death, compared with antidepressant-untreated subjects. Furthermore, there was a trend toward increased BDNF expression in hilar and supragranular regions in depressed subjects treated with antidepressants, compared with the subjects not on these medications at the time of death. These findings are consistent with recent studies measuring CREB levels in this same subject sample, and support current animal and cellular models of antidepressant function.

Several lines of research show that the BDNF molecule is probably the "final common pathway"

for different antidepressant approaches. These include antidepressants (Nibuya et al. 1995), ECT (Nibuya et al. 1995; Duman and Vaidya 1998; Altar et al. 2003), exercise (Oliff et al. 1998; Garcia et al. 2003) and rTMS (repetitive transcranial magnetic stimulation) (Müller et al. 2000). All of these treatments increase BDNF at least in rats, and likely in humans, as supported by multiple threads of evidence, e.g., direct measurements of BDNF in the bloodstream (Karege et al. 2002, 2005; Shimizu et al. 2003). Treatment of depressed patients with antidepressants increases the reduced pretreatment serum BDNF levels close to the levels of normal controls (Aydemir et al. 2005; Gervasoni et al. 2005; Gonul et al. 2005). Some results suggest that the combination of exercise and antidepressant treatment may have significant neurochemical and behavioural effects. In addition, they support the possibility that the enhancement of BDNF expression may be an important element in the clinical response to antidepressant treatment (Russo-Neustadt et al. 2001). The results suggest that noradrenergic activation via β-adrenergic receptors may be essential for both exercise- and antidepressant-induced BDNF regulation. 5-HT (1A) and 5-HT(2A/C) receptor activation, on the other hand, appear to be most important for antidepressant-induced BDNF regulation, but may also participate significantly in exercise-induced regulation in the CA4 region of the hippocampus (Ivy et al. 2003).

Studies on human blood levels show that BDNF is low in depressed patients (Karege et al. 2002). These results suggest that major depression is characterized by low serum BDNF levels and support the hypothesis of neurotrophic factor involvement in affective disorders. In another study, serum BDNF was found significantly lower in antidepressant-naive patients with major depression than in the treated group or in the control group. A significant negative correlation was found between serum BDNF and HAM-D scores in all patients. In a preliminary examination, reduced BDNF values of three drug-naive patients recovered to basal levels after antidepressant treatment. This study suggests that low BDNF levels may play a pivotal role in the pathophysiology of depression and that antidepressants may increase BDNF in depressed patients (Shimizu et al. 2003). Low serum BDNF could thus be a marker of depression if the results are replicated in larger studies.

Recent findings from animal studies have suggested a possible role for BDNF in depression. BDNF protects against stress-induced neuronal damage, and it might affect neurogenesis in the hippocampus, which is thought to be involved in the pathogenesis of mood disorders (Hashimoto et al. 2004). Expression of CAMKII-α and TBR1 mRNAs was significantly increased in bipolar patients but not in major depressed patients, and there was a trend toward reduced BDNF expression in both groups (Molnar et al. 2003).

Exogenous delivery of BDNF or neurotrophin-3 (NT-3) promotes the function, sprouting and regrowth of 5-HT-containing neurons in the brains of adult rats. Antidepressants increase BDNF mRNA in the brain, via 5-HT2A and β-adrenoceptor subtypes and prevent the stress-induced decreases in BDNF mRNA. So, the existing treatments of depression might work by increasing endogenous brain levels of BDNF or NT-3, which in turn could promote monoamine-containing neurons growth and function (Altar 1999).

BDNF exerts direct antidepressant activity in animal models of depression (Shirayama et al. 2002). Other studies demonstrate that chronic antidepressant treatment increases the rate of neurogenesis in the adult hippocampus. They also show that antidepressants up-regulate the cyclic adenosine monophosphate (cAMP) and the neurotrophin signalling pathways involved in plasticity and survival. *In vitro* and *in vivo* data provide direct evidence that the transcription factor, cAMP response element-binding protein (CREB) and BDNF are key mediators of the therapeutic response to antidepressants (Nibuya et al. 1996). These results suggest that depression may be associated with a disruption of mechanisms that govern cell survival and neural plasticity in the brain. Antidepressants could mediate their effects by increasing neurogenesis and modulating the signalling pathways involved in plasticity and survival (D'Sa and Duman 2002).

Allelic variation of BDNF expression. Genetic abnormalities in BDNF and CREB may also occur in depression. Recent findings from family-based association studies have suggested that the BDNF gene is a potential risk locus for the development of bipolar disorder. They suggest that BDNF plays a critical role in the pathophysiology of mood disorders and in the activity of therapeutic agents in patients with mood disorders (Hashimoto et al. 2004). Sequence variations in the CREB1 gene have been reported to cosegregate with depressive disorders in women (Zubenko et al. 2003). A BDNF coding variant may be associated with the personality trait of neuroticism, which is a risk factor for depression (Sen et al. 2003). This polymorphism has been associated with alterations in BDNF trafficking and secretion *in vitro* and with alterations in hippocampal working memory in humans (Egan et al. 2003). Endogenous levels of BDNF protein

were measured in serum samples of healthy volunteers. A negative correlation between BDNF serum concentration and the depression related factor neuroticism was found. Low BDNF levels in healthy humans with depressive personality traits might constitute a risk marker, reflecting a personality profile, which is linked to vulnerability to mood disorders. These results provide further support for the hypothesis that BDNF may be central to the development of depressive mood states (Lang et al. 2004). In addition, two studies (Neves-Pereira et al. 2002; Sklar et al. 2002) suggest that the BDNF locus is associated with bipolar disorder.

Other neurotrophic factors: fibroblast growth factors. Many studies show us that BDNF is not the sole neurotrophin engaged in depression. Several data show the importance of fibroblast growth factors (FGFs). FGFs are a family of molecules that stimulate cell growth in many areas of the body, and are involved in the growth of multiple tissues and in growth that takes place at various stages of life. They have potent effects during embryonic, foetal and child development, and can modify the size and structure of particular brain regions. They are also involved in the repair of adult tissues after injury and may mediate the cross-talk between different cell types in the brain. As a result, they can be seen as mediators of the property that neuroscientists call "neural plasticity" – the ability of the brain to adapt to stress, experience, disease and the effects of drugs. Dysregulation of several fibroblast growth factor (FGF) system transcripts may occur in frontal cortical regions of brains from human subjects with major depression (Evans et al. 2004). This altered gene expression was discovered by microarray analysis of frontal cortical tissue from major depression, bipolar, and nonpsychiatric control subjects and was verified by quantitative real-time PCR analysis and, importantly, in a separate cohort of major depression subjects. Furthermore, it was shown, through a separate analysis of selective serotonin reuptake inhibitor (SSRI)-treated and non-SSRI-treated major depression subjects that the observed changes in expression of FGF transcripts are not secondary to drug treatment. Rather, changes in specific FGF transcripts are attenuated by SSRIs and may thus be partially responsible for the mechanism of action of these drugs (Evans et al. 2004). The most significant differences were in levels of mRNA for one of the FGFs, called FGF1, and for the two receptors, FGFR2 and FGFR3 (Evans et al. 2004). The brains of bipolar patients in the study did not show the decreased FGF gene activity, although both groups were severely depressed at the time of death. This is yet another indication that bipolar illness, though classified with depression as a mood disorder, is biologically a very different disease (Evans et al. 2004). Thus if these results are confirmed in the future by other investigators, we can gain access to a marker, differentiating between unipolar and bipolar depression.

Serotonergic markers in depression

Imipramine binding

One of the most robust biological markers in psychiatry is the binding of imipramine to blood platelets. Imipramine binds to the high-affinity serotonin transporter (5-HTT) on platelets, which represent a model system for serotonergic neurons. Imipramine binding to blood platelets is generally decreased in depression, as indicated by a decreased maximal binding capacity (B_{max}). Similarly, 5-HT uptake in blood platelets (V_{max}) is decreased. These findings correspond to a decrease of maximal binding capacity of imipramine to brain tissue. A meta-analysis by Ellis and Salmond (1994) has shown that imipramine binding to platelets is indeed a robust biological marker of depression.

5-HT receptors

5-HT1A receptor. Due to the efficacy of serotonergically acting drugs in major depression, some 5-HT receptors have been extensively studied in major depression. Of the 18 different types and subtypes of 5-HT receptors, the most extensively studied 5-HT receptor is the 5-HT1A receptor. Table I gives an overview of 5-HT1A receptor levels in major depression. As can be seen, almost all the studies point to a decreased or unchanged expression of the 5-HT1A receptor. These studies have employed a number of different methods. Only one study found an increased 5-HT1A receptor expression. Thus, a trend of decreased 5-HT1A receptor expression appears to be a robust finding in major depression. A functional genetic variant of the 5-HT1A receptor, the C-1019G promoter polymorphism, has been investigated in major depression. The −1019G allele was more frequent in major depression (Lemonde et al. 2003). Replication studies are eagerly awaited.

5-HT1B receptor. Among the genetic variants of the 5-HT1B receptor, the G861C polymorphism is the most frequently investigated variant. G861C, or most likely a variant in linkage disequilibrium with G861C, exhibits functional effects. Investigating variants of the 5-HT1B receptor in major depression, most of the studies do not find an association between the 5-HT1B receptor and major depression

Table I. 5-HT1A receptor levels in major depression.

Investigated region	Method	Change	Author
Prefrontal cortex	mRNA	Decreased	Lopez-Figueroa et al. (2004)
Prefrontal cortex	Binding	Unchanged	Arranz et al. (1994)
Prefrontal cortex	Binding	Unchanged	Stockmeier et al. (1997)
Prefrontal cortex	PET	Unchanged	Meltzer et al. (2004)
Cortex	Binding	Unchanged	Lowther et al. (1997b)
Cortex	PET	Decreased	Bhagwagar et al. (2004)
Cortex	PET	Decreased	Sargent et al. (2000)
Cortex	PET	Decreased	Drevets et al. (2000)
Hippocampus	mRNA	Decreased	Lopez-Figueroa et al. (2004)
Hippocampus	Binding	Unchanged	Lowther et al. (1997b)
Hippocampus	Binding	Unchanged	Stockmeier et al. (1997)
Raphe	Binding	Increased	Stockmeier et al. (1998)
Raphe	Binding	Decreased	Arango et al. (2001)
Raphe	PET	Decreased	Drevets et al. (2000)
Raphe	PET	Unchanged	Bhagwagar et al. (2004)
Raphe	PET	Decreased	Meltzer et al. (2004)

(Huang et al. 1999; Fehr et al. 2000; Tsai et al. 2004). A single postmortem study investigating prefrontal cortical 5-HT1B receptor binding did not find differences between major depression and controls (Huang et al. 1999). A cofactor of the 5-HT1B receptor, S100A10 (also termed p11) has been suggested to play a role in depression (Svenningsson et al. 2006); however, its effect may also relate to anxiety.

5-HT1D receptor. In a single postmortem study, a higher number of 5-HT1D receptors was found in globus pallidus (Lowther et al. 1997a). No 5-HT1D receptor variants have been investigated in major depression. In suicide victims, the frequency of a synonymous 5-HT1D receptor variant was similar to controls (Turecki et al. 2003).

5-HT1E and 1F receptor. Investigations of the 5-HT1E and 1F receptors have generally yielded negative results (Lowther et al. 1997a; Turecki et al. 2003).

5-HT2A receptor. 5-HT2A receptor polymorphisms are generally not associated with major depression (Zhang et al. 1997; Frisch et al. 1999; Tsai et al. 1999; Minov et al. 2001; Oswald et al. 2003; Choi et al. 2004; Khait et al. 2005; Levinson 2005).

5-HT2C receptor. A polymorphism of the 5-HT2C receptor, the Cys23Ser variant, has been investigated in a number of studies. Two out of four studies found an increased frequency of the serine variant, indicating that this variant may be associated with major depression (Frisch et al. 1999; Lerer et al. 2001; Holmes et al. 2003; Köks et al. 2006). 5-HT2C receptor RNA undergoes adenosine-to-inosine RNA modification. This results in amino acid changes in the second intracellular loop of the receptor protein. No consistent RNA editing changes of the 5-HT2C receptor were observed in major depression (Niswender et al. 2001; Gurevich et al. 2002; Iwamoto and Kato 2003).

Other 5-HT receptors. Variants of the 5-HT3 receptor and the 5-HT4 receptor have not been investigated in major depression. However, 5-HT4 receptor binding was assessed in depressed suicide victims (Rosel et al. 2004). A significantly higher number of 5-HT4 receptors was found in frontal cortex and caudate nucleus, compared to controls. No variants of the 5-HT5 receptor have been investigated in major depression, and no association of a common 5-HT5 receptor polymorphism was found in suicide victims (Turecki et al. 2003). A variant of the 5-HT6 receptor was assessed in major depression, with negative results (Hong et al. 1999; Lee et al. 2005). No investigations of the 5-HT7 receptor have been performed in major depression.

Overview of serotonergic polymorphisms in major depression

Table II gives an overview of serotonergic polymorphisms in major depression. In addition to 5-HT receptors, the serotonin transporter (Levinson 2005) and monoamine oxidase A are also shown. Findings concerning the recently discovered 5-HT-synthesizing enzyme of the brain, tryptophan hydroxylase 2 (TPH2) (Walther and Bader 2003; Walther et al. 2003) are currently under intense investigation and controversial. However, functional variants of TPH2 have been shown to be important in the pathogenesis of obsessive-compulsive disorder (Mössner et al. 2006), making it unlikely that TPH2 variants will yield biological markers of depression.

Table II. Serotonergic polymorphisms in major depression.

Gene	Polymorphism	Functional	Association
5HT1A	C-1019G	Yes	Yes (replication required) binding mostly decreased in depression
5HT1B	Several	Yes	No
5HT1D	Several	Not known	Binding increased in depression No association in suicide
5HT1E	C117T	Not known	No association in suicide
5HT1F	C-78T	Not known	No association in suicide
5HT2A	T102C	Yes	No
5HT2B		Not known	No
5HT2C	Cys23Ser	Yes	Probably yes
5HT3	Pro16Ser	Yes	Not assessed
5HT4			Binding increased in depression
5HT5	G-19C	Not known	No association in suicide
5HT6	C267T	Not known	No
5HT7		Not known	Not assessed
MAOA	MAOA-LPR	Yes	No
5HTT	5HTTLPR	Yes	No

Biochemical markers

Lipids

The search for biochemical markers of depression has been particularly intense. Several studies have searched for lipids as biological markers of depression. Hypocholesterolemia has been associated with depression, suicide and affective disorders. Rapidly accumulating evidence suggests that low or lowered cholesterol may be associated with increases of suicides and accidents. Lipid-induced changes in brain chemistry affect the lipid environment of the brain and modulate neurotransmitter action and function of neuronal proteins. The tertiary and quaternary structures of neuronal proteins as receptors, ion channels and protein kinases depend upon the electrical and fluidity parameters determined by electrolytes and the lipid environment of the brain. Lipid and electrolyte abnormalities have a marked impact on neuronal disturbance and ultimately, mood and behaviour. The biochemistry of depression is often characteristic in the blood chemistry as low levels of cholesterol, iron, potassium, albumin and nitrogen markers and elevation of triglycerides. Cholesterol is the substrate for all steroidal and gonadal hormones. There is virtually no system of the body that does not require attenuation of specific fatty acid substrates and coenzymes to maintain health and repair of bodily tissues. Cholesterol levels were identified as a blood marker for depression and anxiety in a normal population in a primary care setting (Rafter 2001). People with low cholesterol scored significantly higher on the Hamilton depression scale. A hypertriglyceridemia-driven metabolic cause of depression has also been demonstrated in controlled clinical trials**,** showing that triglyceride lowering alleviates the symptoms of depression. The connection of hypertriglyceridemia and depression involves insulin resistance, as the ingestion of high glycemic food releases insulin which immobilizes the modulation of essential fatty acid metabolism, negatively impacting the production of prostaglandins, cytokines, hormones, membrane traffic and brain chemistry (Glueck et al. 1993). Examination of red cell membrane fatty acid profiling is reflective of long-term insufficiencies and imbalances in fatty acid metabolism. Plasma fatty acids reflect dietary intake of a few days' duration rather than metabolic conversion observed in fatty acids incorporated into red cell membranes. Examination of patients with affective disorders, depression, schizophrenia, anxiety, autism, seizure disorders, aggression, attention deficit disorder as well as physically oriented acute and chronic illness reveal characteristic patterns that may be addressed with lipid manipulation with targeted fatty acids through competitive inhibition. Brain function depends on the organic metal constituents of the central nervous system as well as lipids but the convergence of these systems occurs in the case of depression for cholesterol. Thus, for example, manganese is required to stimulate the synthesis of cholesterol. A large part of the brain, especially the membranes of the nerves, is made up of essential fatty acids. Roles for fish oil in various brain-related disorders including Alzheimer's disease, ADHD, autism, schizophrenia, hostility, anxiety, borderline, and bipolar disorders are observed. It has been proposed that the Omega 6 to Omega 3 ratio should be 1:1 (Simopoulos et al. 1999). Recent evidence has suggested an important role for lipids in the aetiology and treatment of depression (Ross et al. 2004): methylnicotinate-induced vasodilation

was used to investigate lipid-dependent signalling mechanisms involving the phospholipase A2–cyclooxygenase pathway, an important signalling system, involved in the action of several neurotransmitters including serotonin. Methylnicotinate-induced erythema was reduced in subjects with unipolar depression compared to controls at 5 min after application and it returned to normal after 15 min. Thus, although the maximal response to methylnicotinate appears normal, patients with unipolar depression exhibit an apparently delayed response. In that study, all unipolar patients were medicated at the time of testing. The results support the hypothesis that unipolar depression may be associated with abnormalities in lipid-associated signalling systems, and may provide insight into how lipid intake may modulate depressive symptoms.

Nitrogen

Macronutrients such as consumption of high quality proteins and the supplementation of creatine, ammonium chloride, urea, glutamine, and niacin, as indicated in the patient's blood chemistry will attenuate nitrogen retention. Nitrogen markers are blood urea nitrogen (BUN), creatinine, and uric acid. It is interesting to remember that the inhalation of nitrous oxide (laughing gas) may evoke the emotion of pleasure with the increase in nitrogen, while exposure to high altitudes, atmospheric low pressure or a full moon, where a downward nitrogen shift is created, may evoke feelings of depression or exacerbate mood disorders. Nitrogen retention is dependent upon dietary consumption of nitrogen rich foods along with lipid consumption, electrolyte stability, and mineral density.

Analysis of polymorphisms of nitric oxide synthases have not yielded any conclusive evidence for their involvement in the pathogenesis of major depression (Yu et al. 2003; Reif et al. 2006). In a small sample of 15 subjects with major depression, decreased plasma nitric oxide metabolite levels and platelet endothelial nitric oxide synthase activity were observed (Chrapko et al. 2004). Conversely, however, increased nitric oxide metabolite levels in plasma were suggested to be associated with suicide attempt, especially in major depressive patients (Lee et al. 2006).

Electrolytes and trace metals

Acute and chronically ill patients frequently become severely depressed and lose their will to live when serum potassium levels drop to below the low end of the laboratory reference range. Subnormal levels of zinc are associated with treatment resistant depression (Maes et al. 1997b). Deficiencies of magnesium can provoke a wide range of psychiatric symptoms related to depression, ranging from apathy to psychosis (Rasmussen et al. 1989). Research on manic patients, on the other hand, has revealed elevated vanadium in the hair, significantly higher levels than those measured in both a control group and a group of recovered manic patients (Naylor et al. 1984). Numerous studies have found long-term chronic low doses of mercury cause neurological, memory, behaviour, sleep, and mood problems (Smith 1978; Kishi et al. 1994; Siblerud et al. 1994; Bittner et al. 1998; Echeverria et al. 1998). Mercury has been found to strongly inhibit the activity of dipeptyl peptidase (DPP IV), which is required in the digestion of the milk protein casein. Studies involving a large sample of psychiatric patients found that a large part of those tested had high levels of the milk protein β-casomorphin-7 in their blood and urine and defective enzymatic processes for digesting milk protein. Elimination of milk products from the diet has been found to improve the condition. As mercury levels are reduced the protein binding is reduced and improvement in the enzymatic process occurs. Additional enzymatic effects at the cellular level via the binding of mercury to proteins include the blockade of sulphur oxidation processes and neurotransmitters (Stefanovic et al. 1998), enzymatic processes involving vitamins B6 and B12 (Srikantaiah and Radhakrishnan 1970), effects on the cytochrome-C energy processes, along with mercury's adverse effects on cellular mineral levels of calcium, magnesium, zinc, chromium, and lithium (Chetty et al. 1990; Rajanna et al. 1995; Freitas et al. 1996). Mercury causes decreased lithium levels, and lithium is an important treatment option for depression. Lithium protects brain cells against excess glutamate and calcium (Rossi et al. 1993; Nonaka et al. 1998). Mercury inhibits macrophage and neutrophil defense against candida by affecting Th1 and Th2 cytokine effects (Perlingeiro and Queiroz 1994; Mathieson 1995; Hua et al. 1996). Candida overgrowth results in production of the highly toxic canditoxin and ethanol which are known to cause fatigue, toxicity, and depressive symptoms (Crook 1984; Edwards 1985). There is also evidence that mercury affects neurotransmitter levels which have effects on conditions such as depression. There is evidence that mercury can block the dopamine–β-hydroxylase (DBH) enzyme (Manzo et al. 1996). This enzyme synthesizes noradrenaline, and low noradrenaline can cause fatigue and depression. Mercury molecules can block all copper-catalysed dithiolane oxidases, such as coproporphyrin oxidase and DBH. Mercury and other toxic metals have been

found to accumulate in the pineal gland and reduce melatonin levels, which is thought to be a significant factor in mercury's toxic effects (Baccarelli et al. 2000).

Vitamins: folic acid

Several cross-sectional studies have focused on the low blood folate levels of depressed patients. Folate is a cofactor in 1-carbon metabolism, during which it promotes the remethylation of homocysteine (a cytotoxic sulfur-containing amino acid, that can induce DNA strand breakage, oxidative stress and apoptosis). Dietary folate is required for normal development of the nervous system and plays important roles in regulating neurogenesis and programmed cell death. Recent epidemiological and experimental studies have linked folate deficiency and resultant increased homocysteine levels with several neurodegenerative conditions, including Alzheimer's disease, Parkinson's disease, and stroke. Genetic and clinical data suggest roles for folate and homocysteine in the pathogenesis of psychiatric disorders (Mattson and Shea 2003). In a large Finnish study, depressed patients in the general population with energy-adjusted folate intake below the median had a higher risk of getting a discharge diagnosis of depression during the follow-up period than those who had a folate intake above the median. A low dietary intake of folate may be a risk factor for severe depression (Tolmunen et al. 2004). There has been some discussion in the recent literature regarding the possible relationship between peripheral levels of folate and serotonin deficiency in the CNS. At the same time, such a serotonin deficiency has been implicated in the biology of suicidal behaviour. Thus, decreased peripheral folate levels may be expected in patients who commit violent suicide. In this respect, the red-cell and serum folate levels in nine persons who later committed suicide were compared with those in age- and sex-matched control groups. However, no significant difference between the groups was found (Wolfersdorf et al. 1995). Although one of the first biological treatments of a major psychiatric disorder was the dietary treatment of pellagra, the use of diet and dietary components in the study of psychopathology has not aroused much interest in recent years (Young 1993). Folic acid deficiency causes a lowering of brain serotonin in rats, and of cerebrospinal fluid 5-hydroxyindoleacetic acid in humans. There is a high incidence of folate deficiency in depression, and there are indications in the literature that some depressed patients who are folate deficient respond to folate administration. Folate deficiency is known to lower levels of *S*-adenosylmethionine, which is an antidepressant that raises brain serotonin levels. These data suggest that low levels of serotonin in some depressed patients may be a secondary consequence of low levels of *S*-adenosylmethionine. They also suggest that the dietary intake and psychopharmacological action of methionine, the precursor of *S*-adenosylmethionine, should be studied in patients with depression. The limited available evidence suggests folate may have a potential role as a supplement to other treatments for depression. It is currently unclear if this is the case both for people with normal folate levels, and for those with folate deficiency (Taylor et al. 2004). In the study of Botez et al. (1982), folate-deficient patients were classified according to whether they exhibited a neuropsychiatric syndrome, consisting of organic mental changes, polyneuropathy, and depression, which responded to folate administration. CSF 5-hydroxyindoleacetic acid (5-HIAA) was low in the vitamin B12-deficient patients and in those folate-deficient patients whose symptoms were not related to folate deficiency. CSF 5-HIAA returned to normal with folate treatment in the patients exhibiting folate-responsive neuropsychiatric signs. The data indicated a close association between folate-responsive neuropsychiatric symptoms and changes in serotonin metabolism in the central nervous system (Botez et al. 1982). Similarly, in another study, a subgroup of severely depressed patients with red-cell folate deficiency had significantly lower CSF 5-HIAA compared to neurological controls. For all depressed patients red-cell folate was significantly correlated with CSF 5-HIAA and homovanillic acid (HVA). CSF tetrahydrobiopterin was significantly correlated with CSF 5-HIAA and HVA and red-cell folate. These observations provided further evidence of the links between folate, biopterin and monoamine metabolism in depression (Bottiglieri et al. 1992). Folate deficiency, or inborn errors of folate metabolism, cause reduced turnover of serotonin, and perhaps dopamine, in the central nervous system. It has been concluded that the mechanism by which deficiency of 5-methyltetrahydrofolate causes reduced 5-hydroxytryptamine and dopamine turnover is unlikely to be mediated by *S*-adenosylmethionine (Surtees et al. 1994). A consistent finding in major depression has been a low plasma and red cell folate, which has also been linked to poor response to antidepressants (Coppen and Bailey 2000). There was a significantly greater improvement in the fluoxetine plus folic acid group. Folic acid is a simple method of improving the antidepressant action of fluoxetine and probably other antidepressants. Folic acid should be given in doses sufficient

to decrease plasma homocysteine**.** Men require a higher dose of folic acid to achieve this than women, but more work is required to ascertain the optimum dose of folic acid. Subjects with low folate levels are more likely to have melancholic depression and are significantly less likely to respond to fluoxetine. The results of another study are consistent with findings linking low folate levels to poorer response to antidepressant treatment. Folate levels should be considered in the evaluation of depressed patients who do not respond to antidepressant treatment (Fava et al. 1997).

Low folate is associated with poorer response to selective serotonin reuptake inhibitors (SSRIs) in major depressive disorder. Folate supplementation in major depressive disorder has been studied in other settings with promising results (Alpert et al. 2002). Folic acid (leucovorin) appears to be modestly effective as an adjunct among SSRI-refractory depressed individuals with normal folate levels. The application of leucovorin as an adjunct in the setting of refractory depression deserves further study. In a study of patients with acute psychiatric disorders (DSM-III diagnosis of major depression or schizophrenia), 33% of patients had borderline or definite folate deficiency. Among both depressed and schizophrenic patients methylfolate significantly improved clinical and social recovery. The differences in outcome scores between methylfolate and placebo groups became greater with time. These findings add to the evidence implicating disturbances of methylation in the nervous system in the biology of some forms of mental illness (Procter 1991). Unmedicated outpatients with a major depressive illness had blood drawn for measurement of serum folate, red cell folate, and vitamin B12 within 24 h of completion of ratings of severity of depression at the beginning and ending of a 5-week trial of desmethylimipramine (Wesson et al. 1994). As compared with nonresponders, responders had a significantly higher mean serum folate at baseline, and red cell folate showed a significant inverse correlation with severity of depression and a significant positive correlation with age of onset of illness. At week 5, change in severity of depression was significantly correlated with change in red cell folate, and significantly more responders than nonresponders had an increase in red cell folate. Lee et al. (1998) have demonstrated that depressed patients of Asian origin had a significantly lower mean serum folate level but a higher mean erythrocyte folate level than control subjects. Folate levels were not related to patients' demographic and clinical characteristics (Lee et al. 1998). Culturally patterned health beliefs and dietary practices can influence the connection between folate status and depression in different societies. Folate deficiency and low folate status have been linked to depression, persistent depressive symptoms, and poor antidepressant response. In another study, 31% of all examined psychiatric patients had red cell folate below 200 ng/ml and 12% had concentrations below 150 ng/ml. The mean red cell folate in the depressed patients was significantly lower than in the euthymic, manic and schizophrenic groups. Alcoholics had a similar mean red cell folate to depressed patients, which was not quite significantly lower than the other groups. The mean serum B12 level in the alcoholics was, however, significantly raised. There were no significant differences in red cell folate or serum B12 between lithium-treated and untreated euthymic patients. The highest proportions of values below 200 and 150 ng/ml were found in depressed and alcoholic patients. Endogenous depressives had the highest percentage of values below 150 ng/ml (folate-deficient) of all psychiatric groups and alcoholic patients (Carney et al. 1990). In another study, patients with depressive disorder had lower serum folate levels than healthy controls, but showed no differences in red cell folate levels. Patients with schizophrenia also had lower serum folate levels than age- and sex-matched controls, while red cell folate levels did not differ (Herran et al. 1999). Another investigation also showed that patients with major depressive disorder had significantly lower serum and red cell folate concentrations than normal controls. Lower serum folate concentrations were associated with greater severity of depression. There was no association between serum and red cell folate concentrations and endogenicity of depression or the presence of weight loss (Abou-Saleh and Coppen 1989). Another study in the same year found that the duration of the current depressive episode was significantly inversely correlated with folate levels, age at onset of illness was significantly correlated with B12 and in a subgroup of recurrent depressives, current age and age at onset of depressive illness were positively correlated with folate (Levitt and Joffe 1989). Depressed geriatric patients have lower levels of folate than controls and folate supplement can reduce depressive morbidity (Alpert et al. 2003). Higher folate levels at baseline predicted greater improvement with antidepressant treatment, especially for SSRI response, based on a self-rating depression scale. A relation between low folate status and depression has been recognized since the 1960s. Since 1998, flour in the United States has been fortified with folic acid, and the prevalence of folate deficiency has decreased dramatically (Ramos et al. 2004). The data indicate that, despite folic acid fortification, low folate status is associated with depressive symptoms in elderly Latino women (but

not elderly Latino men). Recently, a review of the effectiveness, adverse effects and acceptability of folate in the treatment of depression was performed. Electronic databases (Cochrane Controlled Trials Register and the Cochrane Collaboration Depression, Anxiety and Neurosis Controlled Trials Register) and reference lists were searched, and authors, experts and pharmaceutical companies contacted to identify randomized controlled trials that compared treatment with folic acid or 5′-methyltetrahydrofolic acid to an alternative treatment, for patients with a diagnosis of depressive disorder (Taylor et al. 2004). The identified trials did not find evidence of any problems with the acceptability or safety of folate. The limited evidence available suggests folate may have a potential role as a supplement to other treatments for depression. The relationship between serum folate, vitamin B12, and homocysteine levels and the rate of relapse in outpatients with remitted major depressive disorder during a 28-week continuation phase of treatment with fluoxetine was assessed (Papakostas et al. 2004a). The presence of low serum folate levels, but not low B12 or elevated homocysteine levels, was associated with relapse during continuation treatment with fluoxetine. The relapse rates for patients with and without low folate levels were 42.9 versus 3.2%, respectively. Low serum folate levels were found to place patients with remitted major depression at risk for relapse during the continuation phase of treatment with fluoxetine. Those patients who previously failed to respond to open treatment with fluoxetine 20 mg/day were enrolled in a 4-week, double-blind trial of either (1) fluoxetine dose increase, (2) lithium augmentation of fluoxetine, or (3) desipramine augmentation of fluoxetine (Papakostas et al. 2004b). Low serum folate levels, but not elevated homocysteine or low vitamin B12 levels, were associated with poorer response to treatment. The response rates for patients with and without low folate levels were 7.1 versus 44.7%, respectively. Low serum folate levels were found to be associated with further treatment resistance among patients with fluoxetine-resistant major depression.

Vitamins B6 and B12

A group of Danish investigators have suggested that a low level of vitamin B6 is associated with symptoms of depression. A low level of vitamin B6 might theoretically cause depression as vitamin B6 is a cofactor in the tryptophan–serotonin pathway. A low plasma level of the vitamin B6 derivative, pyridoxal phosphate (PLP) was significantly associated with the depression score. That study suggested that a low level of plasma PLP is associated with symptoms of depression (Hvas et al. 2004a). However, a recent systematic review did not find a meaningful treatment effect of vitamin B6 for depression in general (Williams et al. 2005).

In a study of the 6-month treatment outcome in patients with major depressive disorder, higher vitamin B12 levels were significantly associated with a better outcome. The association between the folate level and treatment outcome was weak and probably not independent. The vitamin B12 level and the probability of recovery from major depression may thus be positively associated (Hintikka et al. 2003).

An association between depression and folate status has been demonstrated in clinical studies, whereas data are sparse on the relationship between depression and other components of 1-carbon metabolism such as vitamin B12, homocysteine, and the methylenetetrahydrofolate reductase 677C→T polymorphism. Overall, hyperhomocysteinemia and TT methylenetetrahydrofolate reductase genotype, but not low plasma folate or vitamin B12 levels, are significantly related to depression without comorbid anxiety disorder. Plasma folate level were inversely associated with depression only in the subgroup of middle-aged women (Bjelland et al. 2003). In a large group of elderly people (3884 probands), hyperhomocysteinemia, vitamin B12 deficiency, and, to a lesser extent, folate deficiency were all related to depressive disorders (Tiemeier et al. 2002). For folate deficiency and hyperhomocysteinemia, the association with depressive disorders was substantially reduced after adjustment for functional disability and cardiovascular disease, but for vitamin B12 this appeared independent. The association of vitamin B12 and folate with depressive disorders may have different underlying mechanisms. Vitamin B12 may be causally related to depression, whereas the relation with folate could be due to physical comorbidity (Tiemeier et al. 2002). Vitamin B12 and folic acid play a major role, since deficiency of both vitamins is associated with the pathogenesis of different diseases such as declining neurocognitive function and atherosclerotic lesions (Wolters et al. 2004). Vitamin B12 and folic acid act as coenzymes and show a close molecular interaction on the basis of the homocysteine metabolism. In addition to the serum concentrations of the vitamins, the metabolites homocysteine and methylmalonic acid are sensitive markers of cobalamin and folate status. A high prevalence of poor cobalamin status is caused by the increasing prevalence of atrophic gastritis type B in the elderly, occurring with a frequency of approximately 20–50% in elderly subjects. Atrophic gastritis results in declining gastric acid and pepsinogen secretion, and reduced absorption of vitamin

B12. Folic acid intake among elderly subjects is generally well below the recommended dietary reference values. Even moderately increased homocysteine levels or poor folate and vitamin B12 status are associated with vascular disease and neurocognitive disorders. Results of a meta-analysis of prospective studies revealed that lowering homocysteine level by 25% was associated with lowering ischemic heart disease risk by 11% and lowering stroke risk by 19%. Homocysteine initiates different proatherogenic mechanisms such as the formation of reactive oxygen species and an enhanced fibrin synthesis. Supplementation of folic acid reduces the homocysteine concentration by 25%. Additional vitamin B12 induces further reduction by 7%. In secondary prevention, supplementation has already led to clinical improvements. Depression, dementia, and mental impairment are often associated with folate and vitamin B12 deficiency. The biochemical reason of this finding may be the importance of folic acid and vitamin B12 for the transmethylation of neuroactive substances (myelin, neurotransmitters), which is impaired in vitamin deficiency ("hypomethylation hypothesis") (Wolters et al. 2004). In contrast to other studies that have found folate deficiency in 10–50% of psychiatric patients, one study observed that less than 2% of the patients had serum folate levels below 3 ng/ml, while low vitamin B12 levels (below 200 pg/ml) were seen in about 12% of the patients (Wolfersdorf and Konig 1995).

In one study, 28% of all depressed subjects were deficient in B2 (riboflavin), B6 (pyridoxine), and/or B12 (cobalamin), but none in B1 (thiamine) or folate. The geriatric sample had significantly higher serum folate levels. Psychotic depressive patients had lower B12 than did non-psychotic depressives. The data support the hypothesis that poorer status in certain B vitamins is present in major depression, but blood measures may not reflect central nervous system vitamin function or severity of affective syndromes (Bell et al. 1991). In another study of geriatric patients by the same research group, only 3.7% of patients were B12 deficient and 1.3% were folate deficient; 4% were anemic (Bell et al. 1990b). Nevertheless, those with below-median values of both vitamins had significantly lower Mini-Mental State scores than patients higher in one or both vitamins. These data suggest that biochemically interrelated vitamins such as B12 and folate may exert both a separate and a concomitant influence on affect and cognition and that poorer vitamin status may contribute to certain geriatric psychiatric disorders that lack a familial predisposition. Similarly, in a study examining whether community-dwelling older women with metabolically significant vitamin B12 or folate deficiency are particularly prone to depression, serum homocysteine levels, folate levels, and the prevalences of folate deficiency and anemia were not associated with depression status (Penninx et al. 2000). However, the depressed subjects, especially those with severe depression, had a significantly higher serum methylmalonic acid level and a nonsignificantly lower serum vitamin B12 level than the nondepressed subjects. After adjustment for sociodemographic characteristics and health status, the subjects with vitamin B12 deficiency were twice as likely to be severely depressed as were the non-deficient subjects. In another study, a psychotic depression subgroup demonstrated numerous significant positive correlations between vitamin B12 level and cognitive subtests not seen in other diagnostic subgroups, especially those of IQ, and verbal and visual memory (Bell et al. 1990a). The last study of this research group is an augmentational open one with tricyclic antidepressants combined with 10 mg each of vitamins B1, B2, and B6 in geriatric inpatients with depression (Bell et al. 1992). The active vitamin group demonstrated a trend toward greater improvement in scores on ratings of depression and cognitive function, as well as in serum nortriptyline levels compared with placebo-treated subjects. Without specific supplementation, B12 levels increased in the subjects receiving B1/B2/B6 and decreased in those on placebo. These findings implicate a possible role of B complex vitamin augmentation in the treatment of geriatric depression.

Detection of cobalamin deficiency is clinically important for a better understanding of neuropsychiatric diseases, and why the deficiency occurs more frequently than previously anticipated. However, serum cobalamin measurements have a limited ability to diagnose a deficiency state (Gultepe et al. 2003). However, a good correlation exists between urinary methylmalonic acid (MMA) and serum vitamin B12 determinations. When cobalamin deficiency is suspected in neuropsychiatric patients, urinary MMA determination analysis can be the first diagnostic test used. If the MMA concentration is above the reference value, serum cobalamin levels can be determined for further diagnosis.

Vitamin B12 deficiency is a common problem in elderly subjects (Wolters et al. 2004). An already moderately reduced vitamin B12 level is associated with vascular disease and neurocognitive disorders such as depression and impaired cognitive performance. Furthermore, a poor vitamin B12 status is presumed to be involved in the development and progression of dementia. This is especially observable if the folic acid status is reduced as well. Due to the insecure supply, the cobalamin status of elderly

persons should be regularly controlled and a general supplementation with vitamin B12 should be considered (Wolters et al. 2004). Associations between vitamin B12 deficiency and impaired cognitive function and depression have been reported. In a randomized placebo controlled study of depressed patients with vitamin B12, no improvement was found in cognitive function comparing the treatment and placebo group, nor among individuals with only slightly impaired cognitive function (Hvas et al. 2004b). Finally, an open trail of treatment resistant major depression found a response rate of 50% and a remission rate of 43% following augmentation of antidepressive therapy with *S*-adenosyl-1-methionine (Alpert et al. 2004).

G-proteins

Abnormal signal transduction pathways have been implicated in the pathogenesis of major depression and bipolar disorder (Zill et al. 2000). G-proteins are key elements of these pathways in the regulation of cellular responses by transmission of signals from receptors to effector proteins. In recent years several studies have reported altered levels and activities of G-protein subunits in depressive patients. A polymorphism of a G-protein β3 subunit (C825T) has been shown to be associated with increased signal transduction and ion transport activity. A significantly higher frequency of the T allele was found in depressive patients than in healthy controls. Moreover, a significant association between TT homozygosity and response to antidepressant treatment after 4 weeks was observed. Thus, the G-protein β3 subunit appears to be a susceptibility factor for major depression (Zill et al., 2000). In a Korean sample, significantly more carriers of the 825T allele were found in major depressive disorder patients than in normal controls (Lee et al. 2004). The T-allele carriers showed higher scores than those with the CC genotype in the baseline total and in some subcategories of the Hamilton Depression Rating Scale. A statistically significant association between T-allele carriers and antidepressant treatment response was found. These results suggest that the T allele of the C825T polymorphism is associated with major depressive disorder. It was also demonstrated that major depressive disorder patients bearing the T allele had a more severe symptomatology and a better response to antidepressant treatment than patients without the T allele. Subjects with TT variants showed better response to treatment and this effect was independent from analysed demographic and clinical variables (Serretti et al. 2003). 825T allele carriers displayed higher levels of depression, as measured by questionnaire (Exton et al. 2003). Regression analysis demonstrated that allele type was the single predictor of depression. The G protein β3 subunit 825T allele is predictive of depressive mood in a young, healthy population.

For depressed patients under the age of 25 years, the T allele of the G protein β3 subunit was associated with a markedly poorer response to nortriptyline, while serotonin transporter polymorphisms did not predict antidepressant response (Joyce et al. 2003). However, in patients 25 years or older, the G protein β3 polymorphisms did not predict antidepressant response, while the short/short genotype of the serotonin transporter promotor polymorphism was associated with a poorer response to both fluoxetine and nortriptyline. These differential pharmacogenetic predictors of antidepressant response by age may provide clues to understanding the discontinuities in pharmacological responsiveness of child/adolescent and adult depressive disorders.

Although it is well established that depression is a major risk factor for the development of coronary artery disease and that cerebrovascular disease can be a major contributing factor for the development of depression, the information about the interplay between the central nervous system and cardiovascular disease is still limited. In an investigation of the G-protein β3-subunit C825T polymorphism and the angiotensin I converting enzyme (ACE) ID polymorphism, analysis of both genes showed that the combined actions of ACE and C825T genotypes accumulate in carriers of the ACE D allele (ID and DD) and C825T TT homozygotes with ID/DD–TT carriers showing a more than five-fold increase in risk for major depression (Bondy et al. 2002). As the study was carried out with depressive patients without serious cardiac impairment at the time of the investigation, it was impossible to predict whether this combined action of the ID/DD– TT genotype is increasing the risk for both disorders. Nevertheless that study reports for the first time that the same allelic combination of two genes that have been shown to increase the risk for myocardial infarction (Naber et al. 2000) increase the vulnerability for depressive disorder. The C825T polymorphism was associated with seasonal affective disorder in another study sample (Willeit et al. 2003). This finding strengthens the evidence for the involvement of G protein-coupled signal transduction in the pathogenesis of affective disorders.

Hypothalamic-pituitary-adrenal axis

Cortisol hypersecretion, non-suppression or the dexamethasone suppression test (DST) and a

blunted thyrotropin response to protirelin are factors which have been studied extensively (Roy et al. 1987; Joyce and Paykel 1989). None of these tests, however, is positive or diagnostic in the majority of all depressed patients.

The dexamethasone/CRH test is one of the most reliable neuroendocrine function tests for hypothalamic–pituitary–adrenocortical (HPA) system dysregulation in depression. Persistent overdrive of HPA system activity after successful antidepressant treatment predicts an enhanced risk for relapse of a depressive episode. As the renin–angiotensin system influences the HPA axis, a study investigated the angiotensin-converting enzyme gene insertion (I)/deletion (D) polymorphism. This polymorphism determines ACE plasma concentrations. The DD genotype showed a higher cortisol stimulation during the first dexamethasone/CRH test after admission than the II genotype. After successful antidepressive treatment and attenuation of HPA system overdrive these differences were no more detectable. The HPA axis stimulating properties of higher ACE and consecutively higher angiotensin and lower substance P concentrations may be crucial factors for the HPA system hyperactivity during major depressive episodes (Baghai et al. 2002, 2006).

Regarding an animal model of dysregulation of the HPA axis and the stress-response system, corticotropin-releasing hormone receptor-2 (CRHR2)-deficient mice display a stress-sensitive and anxiety-like phenotype suggesting that the CRHR2 is a plausible functional candidate gene influencing the reactivity of the HPA axis and therefore the liability to develop affective disorders. However, a SNP analysis of the CRHR2 gene did not reveal consistent changes in major depression patients (Villafuerte et al. 2002). The availability of free corticotropin releasing hormone in the central nervous system is tightly regulated by the expression of corticotropin-releasing hormone binding protein. Therefore, the gene encoding corticotropin releasing hormone binding protein is a functional candidate gene for major depression. Two single nucleotide polymorphisms within the corticotropin-releasing hormone binding protein gene were significantly associated with the disease (Claes et al. 2003). The corticotropin-releasing hormone binding protein gene is likely to be involved in the genetic vulnerability for major depression. Moreover, variants in a glucocorticoid receptor-regulating protein, FKBP5, have been found associated with increased recurrence of depressive episodes (Binder et al. 2004).

Neuroimaging markers

Positron emission tomography (PET) imaging studies have revealed multiple abnormalities of regional cerebral blood flow (CBF) and glucose metabolism in limbic structures and the prefrontal cortex (PFC) in mood disorders. Although disagreement exists regarding the specific locations and the direction of some of these abnormalities, in unmedicated subjects with major depression, regional CBF and metabolism are consistently increased in the amygdala, orbital cortex, and medial thalamus, and decreased in the dorsomedial/dorsal anterolateral PFC and anterior cingulate cortex ventral to the genu of the corpus callosum (subgenual PFC) relative to healthy controls (Drevets 2001; Manji et al. 2001). These abnormalities implicate limbic–thalamic–cortical and limbic–cortical–striatal–pallidal–thalamic circuits, involving the amygdala, orbital and medial PFC, and anatomically related parts of the striatum and thalamus in the pathophysiology of major depression. These circuits have also been implicated more generally in emotional behaviour by the results of electrophysiological, lesion analysis, and brain mapping studies of humans and experimental animals. Structural imaging studies have demonstrated reduced gray-matter volumes in areas of the orbital and medial PFC, ventral striatum, and hippocampus, and enlargement of the third ventricle in individuals with mood-disorders relative to healthy control samples (Drevets 2001). Complementary postmortem neuropathological studies have shown abnormal reductions in cortex volume, and either glial cell counts, neuron size, or both, in the subgenual PFC, orbital cortex, dorsal anterolateral PFC, and amygdala (Ongur et al. 1998; Rajkowska 2000; Manji et al. 2003). It is not known whether these deficits constitute developmental abnormalities that may confer vulnerability to abnormal mood episodes, compensatory changes to other pathogenic processes, or the sequelae of recurrent affective episodes per se. Nevertheless, the marked reduction in glial cells in these regions has been particularly intriguing, in view of the growing appreciation that glia play critical roles in regulating synaptic glutamate concentrations and central nervous system energy homeostasis and in releasing trophic factors that participate in the development and maintenance of synaptic networks formed by neuronal and glial processes (Coyle and Schwarcz 2000; Ullian et al. 2001). Abnormalities of glial function could thus prove integral to the impairment of structural plasticity and overall pathophysiology of major depression. Taken together with other clinical and preclinical data regarding these structures' specific roles in emotional processing, the neuroimaging and

neuropathological abnormalities in major depression suggest that major depression is associated with activation of regions that putatively mediate emotional and stress responses (for example, amygdala), whereas areas that appear to inhibit emotional expression (such as posterior orbital cortex) contain histological abnormalities that may interfere with the modulation of emotional or stress responses (Drevets 2001). For example, in major depression, the elevation of CBF and metabolism in the amygdala is positively correlated with depression severity, consistent with this structure's role in organizing the autonomic, neuroendocrine, and behavioural manifestations of some types of emotional responses. In contrast, some of the medial and orbital PFC areas, where metabolism is abnormal in major depression, appear to play roles in reducing autonomic and endocrine responses to stressors or threats and in extinguishing behavioural responses to fear-conditioned stimuli that are no longer reinforced (Drevets 2001). Activation of the orbital cortex during depressive episodes may thus reflect endogenous attempts to interrupt unreinforced, aversive thoughts and emotions. However, the histopathological abnormalities identified in these areas in major depression post-mortem suggest that the ability to mediate these functions may be impaired. The hypothesis that dysfunction of these regions may contribute to the development of depression is consistent with evidence that lesions (such as strokes or tumours) involving either the PFC or the striatum (a major target of efferent projections from the PFC), as well as degenerative diseases affecting the striatum (for instance, Parkinson's and Huntington's diseases), are associated with an increased risk for developing depression.

PET imaging of 5-HT1A receptor binding in the dorsal raphe nucleus and prefrontal cortex may be assessed with the radioligand [^{11}C]WAY 100635. Significantly diminished binding in the dorsal raphe nucleus in elderly depressived patients was observed relative to control subjects (Meltzer et al. 2004). These findings support evidence of altered 5-HT1A autoreceptor function in depression. In a PET study in healthy volunteers, a preferential occupancy by pindolol of 5-HT1A autoreceptors as compared to postsynaptic receptors was demonstrated (Rabiner et al. 2004). This preferential occupancy was attenuated in depressed patients. A possible mechanism underlying this preferential occupancy and the attenuation of this phenomenon in depressed patients on SSRIs may include changes in the proportion of high affinity autoreceptor 5-HT1A sites in the midbrain raphe.

Another study investigated changes of the 5-HT2A receptor in older depressed patients, employing the PET ligand [^{18}F]altanserin. Depressed subjects had significantly less hippocampal 5-HT2A receptor binding than controls. Moreover, depressed patients not previously treated for depression had significantly less hippocampal 5-HT2A receptor binding than previously treated subjects. It may be that prior medication leads to a partial compensatory upregulation of the 5-HT2A receptor. In a PET study employing a selective serotonin transporter (5-HTT) ligand ([^{11}C]McN5652), 5-HTT sites were increased in the frontal and cingulate cortices of depressed patients (Reivich et al. 2004). These alterations in 5-HTT sites may be of pathophysiological significance in the pathophysiology of depression.

PET studies have reported altered resting regional brain glucose metabolism in mood disorders. Unlike healthy male subjects who have significant increases in regional glucose metabolism in prefrontal and parietal cortical regions after receiving the serotonin-releasing agent fenfluramine, depressed male subjects have no significant increases in regional glucose metabolism. This blunting is consistent with the serotonin hypothesis of depression (Anderson et al. 2004). Two other articles provide intriguing data on the functional neuroanatomy of depression (Brody et al. 2001; Martin et al. 2001). Using single-photon emission computed tomography (SPECT) and [^{18}F]fluorodeoxyglucose PET neuroimaging methods, outpatients with major depressive disorder were studied before and after treatment. What distinguishes these reports from earlier neuroimaging investigations using pretreatment and posttreatment designs is that both studies compared the effects of pharmacotherapy with those of interpersonal psychotherapy, one of the better studied psychosocial treatments of depression. Results indicate that both treatments were associated with increased blood flow to the left temporal or right basal ganglia regions.

There is growing evidence from neuroimaging and postmortem studies that severe mood disorders, which have traditionally been conceptualized as neurochemical disorders, are associated with impairments of structural plasticity. Both first- and multiple-episode depressed groups have hippocampal dysfunction apparent on several tests of recollection memory. However, only depressed subjects with multiple depressive episodes have hippocampal volume reductions, with an association between illness duration and hippocampal volume. Reductions in hippocampal volume may not antedate illness onset, but volume may decrease at the greatest rate in the early years after illness onset (MacQueen et al. 2003). Remitted patients with a history of depression have smaller hippocampal

volumes bilaterally than controls. These "post-depressives" also have smaller amygdala core nuclei volumes, and these volumes correlate with hippocampal volumes. In addition, post-depressives score lower in verbal memory, a neuropsychological measure of hippocampal function, suggesting that the volume loss is related to an aspect of cognitive functioning. In the absence of a significant correlation between hippocampal volume and age in either post-depressive or control subjects, a significant correlation with total lifetime duration of depression was found. This suggests that repeated stress during recurrent depressive episodes may result in cumulative hippocampal injury as reflected in volume loss (Sheline et al. 1999). Longer durations during which depressive episodes went untreated with antidepressant medication were associated with reductions in hippocampal volume. There was no significant relationship between hippocampal volume loss and time depressed while taking antidepressant medication or with lifetime exposure to antidepressants. Thus, antidepressants may have a neuroprotective effect during depression (Sheline et al. 2003).

Depression is associated with interpersonal difficulties related to abnormalities in affective facial processing. Average activation (capacity) and differential response to variable affective intensity (dynamic range) were estimated in fMRI time series (Fu et al. 2004). Over time, depressed subjects showed reduced capacity for activation in the left amygdala, ventral striatum, and frontoparietal cortex and a negatively correlated increase of dynamic range in the prefrontal cortex. Symptomatic improvement was associated with reduction of dynamic range in the pregenual cingulate cortex, ventral striatum, and cerebellum. Thus, antidepressant treatment reduces left limbic, subcortical, and neocortical capacity for activation in depressed subjects and increases the dynamic range of the left prefrontal cortex. Changes in anterior cingulate function associated with symptomatic improvement indicate that fMRI may be a useful surrogate marker of antidepressant treatment response. Biological markers of treatment response may include structural brain changes seen on neuroimaging. Depressed patients with small right-sided and total hippocampal volumes were less likely to achieve remission (Hsieh et al. 2002). Thus, left-right hippocampal volume differences appear to exist in depression. Neuroimaging technology has provided unprecedented opportunities for elucidating the anatomical correlates of major depression (Drevets 2001). The knowledge gained from imaging research is catalysing a paradigm shift in which primary mood disorders are conceptualized as illnesses that involve abnormalities of brain structure, as well as of brain function. Dysfunction within the prefrontal cortical and striatal systems that normally modulate limbic and brainstem structures involved in mediating emotional behaviour is postulated to be of particular importance in the pathogenesis of depression.

Finally, a very recent PET study demonstrated MAOA (monoamine oxidase A) levels elevated by 34% throughout the brain in untreated depressed patients (Meyer et al. 2006). This promising finding will certainly be assessed in confirmatory studies, since analyses of functional MAOA polymorphisms in depression have generally yielded negative results.

Immunological markers in major depression

Immune cells

Early studies showed an increase of T-helper cells ($CD4^+$ cells) and an increased $CD4^+/CD8^+$ ratio in depressive disorders (Syvalähti et al. 1985; Maes et al. 1992; Müller et al. 1993). Further investigations of the cellular components of the immune system focussed on monocytes and macrophages. Increased numbers of peripheral mononuclear cells have been described by different groups of researchers (Herbert and Cohen 1993; Seidel et al. 1996; Rothermundt et al. 2001). Neopterin is a sensitive marker of cell-mediated immunity. The main source of neopterin is monocytes/macrophages. In agreement with the findings of increased monocytes/macrophages, an increased secretion of neopterin has been described in patients suffering from major depression by several groups of researchers (Duch et al. 1984; Dunbar et al. 1992; Maes et al. 1994; Bonaccorso et al. 1998).

Interleukin-6

As a product of monocytes and macrophages, interleukin-6 (IL-6) is one of the most frequently investigated immune parameters in major depression patients. Most publications report a marked increase of *in vitro* IL-6 production (Maes et al. 1993) or serum IL-6 levels in depressed patients (Maes et al. 1995b, 1997a; Sluzewska et al. 1995, 1996; Berk et al. 1997; Frommberger et al. 1997; Song et al. 1998). Most of these studies also report elevated plasma levels of acute phase proteins – markers of the unspecific (innate) immune system. Contradictory results are very few, indicating reduced (Katila et al. 1989), or unchanged serum IL-6 levels (Maes et al. 1995b; Brambilla and Maggioni 1998). An age-related increase of IL-6 serum values was reported in patients with major depression (Ershler et al. 1993). From a methodological point of view, the potential influence of possibly interfering

variables such as smoking, gender, recent infections and prior medication on IL-6 release and concentration must be considered (Haack et al. 1999).

Prostaglandin E_2 (PGE_2) stimulates IL-6. Therefore an increased secretion of PGE_2 would be expected in depressive disorders, too. Early studies described increased PGE_2 both in the cerebrospinal fluid and in the serum of depressed patients (Linnoila et al. 1983; Calabrese et al. 1986). Increased concentrations of PGE_2 in saliva of depressed patients have been repeatedly described (Ohishi et al. 1988; Nishino et al. 1989). Moreover, *in vitro* studies show an increased PGE_2 secretion from lymphocytes of depressed patients compared to healthy controls (Song et al. 1998).

Data on IL-6 and the IL-6 system in the CSF are still rare. Markedly decreased levels of IL-6 and its soluble receptor subunit IL-6Rα in elderly patients with major depression compared to matched healthy control persons have been described (Stübner et al. 1999). IL-6 is a highly important inducer of antibody production (Th2 immune response) and indeed, some data show increased antibody titres in major depression. As in schizophrenia, a great heterogeneity of antigen-specificity of the antibodies, such as anti-nuclear anti-phospholipid, antithyroidal or anti-viral antibodies was found (Haggerty et al. 1987; Maes et al. 1991; Amsterdam and Hernz 1993).

There is no doubt that IL-6 is involved in modulation of the hypothalamic–pituitary–adrenal (HPA) axis (Plata-Salaman 1991). Activation of the HPA axis is one of the best-documented changes in major depression (Roy et al. 1987). Furthermore, the relationship between psychological or physical stress and an enhanced IL-6 secretion in the peripheral immune system seems to be well established (LeMay et al. 1990; Salas et al. 1990; Zhou et al. 1993; Miyahara et al. 2000). An impaired ability to cope with stress is often observed in depressed patients. Thus, the high number of reports showing elevated peripheral IL-6 levels in major depression patients may be related to psychological stress. On the other hand, there is evidence for a relationship between high peripheral IL-6 levels and elevated central nervous system serotonin availability. Intravenous or intraperitoneal administration of IL-6 in an animal model induced not only an activation of the HPA axis, but also an increase in brain tryptophan and serotonin metabolism, whereas norepinephrine metabolism was unaffected (Wang and Dunn 1998). Accordingly, IL-6 may be a mediator of activation of the HPA axis and of the central nervous serotonin system after administration of the endotoxin LPS (Wang and Dunn 1999). Thus, elevated plasma levels of IL-6 do not fit with the hypothesis of a serotonin deficiency in major depression. On the other hand, there is also a report showing a correlation between increased IL-6 production in culture supernatants of mitogen-stimulated peripheral leukocytes *in vitro* and decreased tryptophan levels in depressed patients that emphasizes the influence of IL-6 on serotonin metabolism (Maes et al. 1993). Serotonin synthesis in the CNS is at least partly dependent on the availability of tryptophan in the blood (Fernstrom 1977).

Interleukin-2

Data on IL-2 in major depression are mainly restricted to measurements of its soluble receptor in peripheral blood. The blood levels of sIL-2R were repeatedly found to be increased in major depression patients (Maes et al. 1995b,a; Sluzewska et al. 1996). One single study investigated CSF levels of sIL-2R and reported a highly significant reduction in major depression patients compared to healthy control subjects (Levine et al. 1999). Production of both IL-2 and IFN-γ is the typical marker of a type-1 immune response. IFN-γ is produced in higher amounts by lymphocytes of patients with major depression than in healthy controls (Seidel et al. 1996). Higher plasma levels of IFN-γ in depressed patients, accompanied by lower plasma tryptophan availability, have been described (Maes et al. 1994). Mendlovic et al. (1999) discriminated between suicidal and non-suicidal major depression patients in a small study. They found distinct associations between suicidality and type-1 immune response on the one hand and a predominance of type-2 immune parameters in non-suicidal patients on the other hand (Mendlovic et al. 1999).

Tryptophan metabolism

The essential amino acid tryptophan is the precursor of two distinct metabolic pathways, leading to the products serotonin or kynurenine. The enzyme indoleamine 2,3-dioxygenase (IDO) metabolizes tryptophan to kynurenine, which is then converted to quinolinic acid by the enzyme kynurenine hydroxylase. Both IDO and kynurenine hydroxylase are induced by IFN-γ. The activity of IDO is an important regulatory component in the control of lymphocyte proliferation (Mellor and Munn 1999). It induces a halt in the lymphocyte cell cycle due to the catabolism of tryptophan (Munn et al. 1999). The type-2 cytokines IL-4 and IL-10 inhibit the IFN-γ-induced tryptophan catabolism by IDO (Weiss et al. 1999). The enzyme IDO is located in several cell types including monocytes, microglial

cells and astrocytes (Alberati-Giani et al. 1996; Schwarcz and Pellicciari 2002). An IFN-γ-induced, IDO-mediated decrease of central nervous tryptophan availability may lead to a serotonergic deficiency. While in schizophrenia the further metabolism of kynurenine to kynurenic acid may be an important factor infuencing the dopaminergic neurotransmission via type-2 immune response, in depression the defiency of serotonin via activation of the type-1 immune response, especially IFN-γ, seems to be the link between immunity, inflammation, and serotonergic or dopaminergic neurotransmission, respectively.

Neurophysiological findings

Generally, electrophysiological measurements like event-related potentials (ERPs) are suitable as biological markers of physiological and pathological brain function, as they allow to measure neuronal activity related to distinct cognitive and emotional processes. The basic idea behind this method is to repeatedly present a subject with different classes of stimuli, which are supposed to activate distinct brain processes while the ongoing electrical activity in the brain is measured by means of scalp electrodes. The occurrence of each stimulus is marked in the ongoing EEG. This procedure allows to average all behaviourally correct, sufficiently artefact-free EEG epochs locked to one class of stimuli, which results in an event-related potential (ERP). This ERP is dominated by the specific neuronal response of the brain to the stimulus while the background EEG activity is diminished by the averaging process. ERPs have the clear advantage of an optimal resolution in the time domain. This means that neuronal activity associated with emotional or cognitive processes can be assessed with accuracy in the order of milliseconds, which is far superior to metabolic measurements like the blood oxygen level dependent (BOLD) effect in functional magnetic resonance imaging (fMRI). However, the precision of the ERPs in terms of spatial resolution is hampered by the so-called inverse problem, which makes a mathematically exact and unique source localisation impossible for a given distribution of ERP-amplitudes measured at scalp electrodes. In comparison, the spatial resolution of the BOLD response in fMRI investigations is far superior. Other features which make ERPs attractive in the search for biological markers in psychiatric diseases like depressions are that they are absolutely non-invasive, repeatable, easy to apply, very cheap, and, most importantly, well accepted also by psychiatric patients.

Since the first description of the P300 component elicited in an acoustic odd-ball paradigm (Sutton et al. 1965), numerous studies aimed at measuring event-related potentials (ERPs) as biological markers of diagnosis, therapeutic response and outcome in all major psychiatric diseases including depressive disorders. Due to limitations in space, we have to focus on four ERP measures reflecting information processing in the brain, which are possibly relevant in depressive disorders: These are the classical P300 amplitude in the acoustic oddball paradigm (Sutton et al. 1965), the loudness dependence of the auditory evoked N1/P2-response (LDAEP) (Hegerl et al. 2001), the error negativity (Ne/ERN) (Falkenstein et al. 1997) elicited by a visual Erikson flanker task, and the NoGo-anteriorisation (NGA) (Fallgatter et al. 1997) provoked by a visual Go–NoGo paradigm. Other electroencephalographic approaches that cannot be dealt with here particularly comprise frequency-analytic approaches, such as studies on the frontal α asymmetry in depression that are based on Davidson's concept of cerebral asymmetry and emotion/affective style (Davidson 1998).

In the classical acoustic P300 paradigm, the subject is presented in random order via headphones with higher frequency, rare target tones (typically 2000 Hz, 20% probability) or lower frequency, more frequent distractor tones (1000 Hz, 80%). The subject has to respond to each target tone either with a button press or with silent counting. Averaging of the correct and artefact-free EEG-epochs typically reveals significantly higher P300 amplitudes at parietal electrode leads for the rare target as compared to the frequent distractor tones, which is commonly interpreted as an indication of stronger neuronal activity in the target condition. This P300 component has been repeatedly shown to have reduced amplitudes and prolonged latencies in patients with depressive disorders as compared to healthy age- and gender-matched controls (Roth et al. 1981; Pfefferbaum et al. 1984; Blackwood et al. 1987; Urretavizcaya et al. 2003; Kawasaki et al. 2004). Although altered P300 amplitudes and latencies are reported quite robustly across studies, the problem of these measures is their low specificity. Identical findings have been reported for all major psychiatric disorders, including schizophrenias, dementias and addictions (Polich and Herbst 2000).

The loudness dependence of the auditory evoked N1/P2-response (LDAEP; slope of amplitude increases with louder tones) is associated with the serotonergic neurotransmission in the primary auditory cortex. A pronounced LDAEP is supposed to reflect low serotonergic neurotransmission and vice versa (Hegerl et al. 2001). A diminished serotonergic neurotransmission is considered as one biological basis of depressive disorders and is the

rationale for treatments with serotonergic antidepressants. Consequently, strong loudness dependence in depressive patients indicative for a weak serotonergic neurotransmission has been shown to predict a favourable response to selective serotonin reuptake inhibitors (SSRI) (Hegerl et al. 2001; Linka et al. 2004). Furthermore, in withdrawn alcohol-dependent patients a highly significant inverse correlation was found between the loudness dependence and the personality trait "Harm Avoidance" from Cloninger's Temperament and Character Inventory, which is supposed to be associated with both a low serotonergic neurotransmission and an increased risk to develop depressive disorders and alcohol dependence (Herrmann et al. 2001).

The error negativity (Ne, ERN) is another interesting ERP parameter, which occurs within 100 ms after an erroneous response and is supposed to reflect response monitoring processes within prefrontal brain areas (Herrmann et al. 2004). As perceived failure is reported to have harmful effects on subsequent performance in patients with depressive disorders, the Ne/ERN is a potentially interesting ERP parameter in this patient group. Interestingly, another study showed a less negative Ne/ERN in patients with major depressive disorders as compared to healthy controls (Ruchsow et al. 2004). This finding was interpreted as a sign of impaired response monitoring processes in this group of patients.

The NoGo-anteriorisation (NGA) (Fallgatter et al. 1997) is another interesting ERP measure, which is calculated as the spatial difference between the centre of gravity of the electrical P300-field in the NoGo- as compared to the Go-condition of a cued Go/NoGo-task. The NGA has been shown to be a very stable (Fallgatter et al. 1997, 2000; Fallgatter and Strik 1999), reliable (Fallgatter et al. 2001) and age-independent (Fallgatter et al. 1999) ERP phenomenon, which reflects pronounced activity in medial prefrontal brain areas including the anterior cingulate cortex (ACC) during a response inhibition process (Fallgatter et al. 2002). Positron emission tomography (PET) studies suggest that depressive patients might be heterogeneous regarding the level of activity in such medial prefrontal brain areas including the ACC during the acute depressive state with one group being hyperactive while others display a normal or even reduced metabolism. Interestingly, an initial hypermetabolism in these medial prefrontal brain areas predicted a favourable therapeutic response to antidepressive medication (Mayberg et al. 1997) as well as sleep deprivation (Wu et al. 1999), whereas those patients with low initial metabolism in this brain region tended to respond worse. Corresponding results were obtained in another study (Pizzagalli et al. 2001) with a three-dimensional EEG source location analysis (low resolution electromagnetic tomography, LORETA) (Pascual-Marqui et al. 1994) aiming on Theta-EEG activity in the ACC. Based on these findings we investigated the NGA as an ERP-marker of prefrontal brain function in 28 depressive in-patients (18 female, 10 male, mean age 42.8 ± 12.0 years) of the Department of Psychiatry and Psychotherapy at the University of Würzburg, Germany. The NGA was measured at two time-points, shortly after admission to the hospital (t1) and again after about 4 weeks (26.4 ± 9.1 days) of an antidepressive treatment (t2) in a naturalistic design consisting of individually chosen psychopharmacological treatment and supportive psychotherapy. The hypotheses were (1) that the variance of the NGA in acutely depressive patients would be higher than in a healthy control sample matched for sex, age, and handedness (pooled from Fallgatter et al. 1997, 2000; Fallgatter and Strik 1999) and (2) that the therapeutic response as measured by improvements of the depressive symptomatology in terms of investigator- (21-item version of the Hamilton Depression Rating Scale, HDRS) (Hamilton 1967) and patient-ratings (Becks Depression Inventory, BDI) (Beck et al. 1961) would be predicted by the initial NGA. The first hypothesis was supported by the data, since the variance of the NGA at t1 was significantly higher in the group of depressive patients compared to the healthy control sample as indicated by Levene's test for the equality of variances (mean NGA 0.87 ± 0.34 vs. 0.77 ± 0.68 for healthy controls versus depressive patients; $F = 7.61$, $P < 0.01$) (Figure 1). The second hypothesis was not supported by the data, since there was no significant correlation between initial NGA and therapeutic outcome (Pearson coefficients of $r = 0.009$ and 0.024 for the correlation between the initial NGA and changes in the BDI and HDRS score, respectively; n.s.). However, a classification of the patient sample based on the initial NGA revealed subgroup-specific treatment effects in the direction of normalisation: both the patients with initial high and with initial low NGA tended to have an NGA in the normal range after 4 weeks of treatment, whereas the group with a normal initial NGA did not change notably (Figure 2). However, further studies with bigger and less heterogeneous patient samples and more standardized treatment protocols are necessary, to further clarify the usefulness of the NGA as a predictor of therapeutic response in depressive patients.

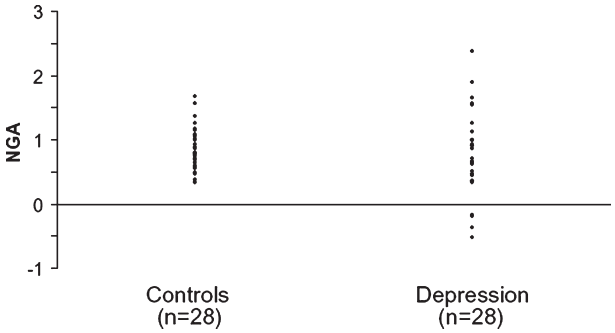

Figure 1. Variance of the NGA. Values of the Nogo-Anteriorisation (NGA) in 28 depressive in-patients and 28 healthy controls matched for gender, age, and handedness.

In summary, there are several ERP measures of information processing which are suitable candidates for biological markers of depressive disorders. However, their value in this respect has to be further established, before a useful clinical application is possible. Moreover, some of these measures (LDAEP, NGA) might have the potential for a prediction of therapeutic response of different antidepressive therapies.

Cognitive deficits in major depression

There is growing evidence that several cognitive domains are significantly impaired in patients with major depression, including attention, memory and executive functioning. Patients with major depression manifest significant impairments in their ability to maintain attention on tasks requiring effortful mental operations, i.e. tasks that require selective and sustained attention, or which imply great resources allocation capacities (Tancer et al. 1990). Contrary to schizophrenia and bipolar disorder, sustained attention (evaluated by Continuous Performance Task) deficits seem state-dependent indicators for major depression (Liu et al. 2002). Patients with major depression also are particularly impaired on verbal learning and episodic memory tasks (Austin et al. 1999; Sweeney et al. 2000), while

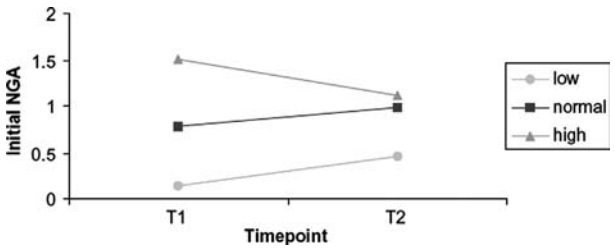

Figure 2. Changes of the NGA over the course of the treatment. Mean NGA on admittance to the psychiatric hospital (T1) and after approximately 4 weeks of antidepressant treatment (T2) in depressive patients with an initially low ($n=11$; green, circles), normal ($n=8$; blue, squares) or high ($n=9$; red, triangles) NGA.

implicit memory performances seem spared (Danion et al. 1995; Ilsley et al. 1995). However, no memory deficit was observed in drug-free major depression (Schatzberg et al. 2000; Porter et al. 2003). This could suggest that deficits are related to antidepressant medications. Conversely, memory deficits could persist after remission (Neu et al. 2005), even in euthymic state (Kessing 1998). Thus, memory impairment may be linked to other factors than medication, such as other illness characteristics. Indeed, pronounced deficits in verbal learning, recall and recognition were found only in major depression patients with melancholia compared both with controls and major depression patients without melancholia (Austin et al. 1999). Patients with major depression also have widespread executive dysfunctions, including working memory, set-shifting and inhibition processes, even during the euthymic state (Elliott et al. 1998; Murphy et al. 2001; Harvey et al. 2004). Several studies have reported that depressed patients are impaired on verbal fluency tasks (Landro et al. 2001; Moritz et al. 2002; Ravnkilde et al. 2002), Trail Making Tests (Austin et al. 1999; Grant et al. 2001; Moritz et al. 2002), Wisconsin Card Sorting Test (Ilonen et al. 2000; Grant et al. 2001; Moritz et al. 2002), and on the Tower of London task (Beats et al. 1996; Elliott et al. 1996). There is, however, some inconsistency, the deficit appearing only in endogenous cases in some studies (Austin et al. 1999; Rogers et al. 2004), while other authors failed to evidence executive functioning deficits in major depression regardless of the severity (Ravnkilde et al. 2002). These discrepancies may reflect a number of methodological issues, including variation in diagnostic criteria, test selection and strategies used to perform this task. Executive processes are also likely to contribute to impairments in memory performance (Baudic et al. 2004), as depressed participants have been found to show greater impairment in recalling information that benefits from semantic organisation compared to information that does not (Channon et al. 1993).

Cognitive deficits appear particularly pronounced in elderly patients and among major depression patients with severe illness, or with melancholic/psychotic features (Beats et al. 1996; Schatzberg et al. 2000). However, the relationship between cognitive performances and major depression melancholic subtype disappeared after covarying for Hamilton score (Austin et al. 1999) and could thus implicate severity itself rather than subtype. On the other hand, while one study failed to observe cognitive differences between unipolar and bipolar patients (Neu et al. 2001), other studies suggest greater cognitive impairment during an acute depressive episode (Borkowska and Rybakowski 2001)

and greater time course deterioration in patients with bipolar compared to patients with unipolar disorder (Burt et al. 2000). Several factors could explain these discrepancies, and among them psychotic features. Indeed, it was observed that patients with first episode of psychotic unipolar depression had a pattern of neuropsychological dysfunction similar to but less severe than that of patients with schizophrenia (Hill et al. 2004). This suggests that these psychotic disorders may have common pathophysiological features.

Because of widely reported but generally modest correlations between symptom severity and neuropsychological deficits in depressed patients, as well as studies showing improvement in function after treatment (Calev et al. 1986; Goldberg et al. 1993), it has traditionally been accepted that cognitive deficits in mood disorders are related to the acute state of illness. However, this point is considered controversial since some authors found cognitive disabilities in euthymic depressive patients which led to the hypothesis that cognitive deficits might persist late after the period of illness. Indeed, some studies have failed to demonstrate any residual memory impairment after clinical recovery, whereas others show persistent impairment, particularly in aspects of executive functioning (Beats et al. 1996; Paradiso et al. 1997). Thus, executive deficits could represent a relatively stable trait marker, whereas mnemonic impairment seems to be related to clinical state. This view is not supported by some studies reporting impaired verbal memory in unipolar depressive patients in remission (Tham et al. 1997; Kessing 1998). This discrepancy could be explained by the number of previous depressive episodes. Indeed, in one of the studies (Tham et al. 1997), cognitive dysfunctions were observed in a subgroup of patients with more frequent relapses and episodes of hospitalization, even when euthymic.

Cognitive functioning in general might be disturbed rather than distinct abilities. However, not all major depression patients show cognitive deficits and there is marked disagreement about the reasons why certain patients develop more severe cognitive problems than others. These discrepancies may

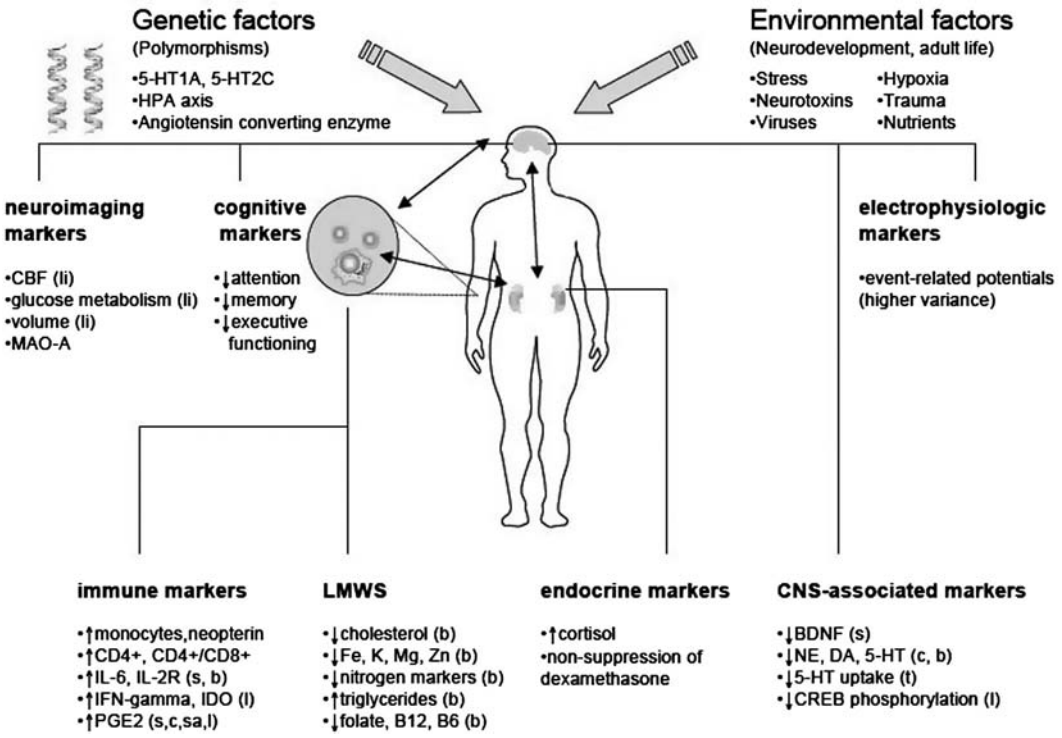

Figure 3. Biological markers of depression. Both genetic and environmental factors during neurodevelopment or later in life influence nervous system function and plasticity and modulate immune and endocrine cascades associated with pathophysiology of depression. Nervous, immune and endocrine systems have feedback regulations and are linked to each other. For example: an increase of cortisol may activate monocytes to increase pro-inflammatory cytokines which may lead to a deficiency of 5-HT due to the favoured metabolism of tryptophan by increased activity of IDO to the neurotoxins kynurenine and quinolinic acid. Such regulations can be measurable and may be used as indicators (robust, good or weak) of the presence, severity and prognosis of depression as well as prediction of drug/other treatment and are characterized as biological markers of depression. Li, limbic areas; ↑, increase; ↓, decrease; s, serum; c, CSF; sa, saliva; l, lymphocytes; b, blood; t, thrombocytes.

reflect a number of methodological problems. We suggest that cognitive deficits may depend on age, illness severity and psychotic or melancholic features. Furthermore, these deficits have not been well characterized in younger patients with mild to moderate depression. The cognitive deficits in depression may be associated with both trait and state factors and raise questions about the long-term cognitive functioning of patients with major depression. These deficits may be explained by structural or functional changes associated with illness severity, aging effects, or a possible cumulative pathologic effect of depression on brain structure and function across recurrent episodes of illness.

Summary

In summary, amongst the plethora of potential biological markers of major depression including neurotrophic factors, serotonergic markers, biochemical markers, immunological markers, neuroimaging, neurophysiological findings, and neuropsychological markers (Figure 3), some stand out as more robust. These are:

- decreased platelet imipramine binding (5-HTT expression);
- decreased 5-HT1A receptor expression;
- increase of sIL-2R and IL-6 in serum
- decreased BDNF and FGF-1 in serum
- hypocholesterolemia
- low blood folate levels
- cortisol hypersecretion; non-suppression of the dexamethasone suppression test

However, none of these markers have been shown to be sufficiently specific to allow inclusion into diagnostic manuals of major depression.

Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

References

Abou-Saleh MT, Coppen A. 1989. Serum and red blood cell folate in depression. Acta Psychiatr Scand 80:78–82.

Akin D, Manier DH, Sanders-Bush E, Shelton RC. 2004. Decreased serotonin 5-HT2A receptor-stimulated phosphoinositide signaling in fibroblasts from melancholic depressed patients. Neuropsychopharmacology 29:2081–2087.

Akin D, Manier DH, Sanders-Bush E, Shelton RC. 2005. Signal transduction abnormalities in melancholic depression. Int J Neuropsychopharmacol 8:5–16.

Alberati-Giani D, Ricciardi-Castagnoli P, Kohler C, Cesura AM. 1996. Regulation of the kynurenine metabolic pathway by interferon-gamma in murine cloned macrophages and microglial cells. J Neurochem 66:996–1004.

Alpert JE, Mischoulon D, Rubenstein GE, Bottonari K, Nierenberg AA, Fava M. 2002. Folinic acid (Leucovorin) as an adjunctive treatment for SSRI-refractory depression. Ann Clin Psychiatry 14:33–38.

Alpert JE, Papakostas G, Mischoulon D, et al. 2004. S-adenosyl-L-methionine (SAMe) as an adjunct for resistant major depressive disorder: an open trial following partial or non-response to selective serotonin reuptake inhibitors or venlafaxine. J Clin Psychopharmacol 24:661–664.

Alpert M, Silva RR, Pouget ER. 2003. Prediction of treatment response in geriatric depression from baseline folate level: interaction with an SSRI or a tricyclic antidepressant. J Clin Psychopharmacol 23:309–313.

Altar CA. 1999. Neurotrophins and depression. Trends Pharmacol Sci 20:59–61.

Altar CA, Whitehead RE, Chen R, Wortwein G, Madsen TM. 2003. Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. Biol Psychiatry 54:703–709.

Amsterdam JD, Hernz WJ. 1993. Serum antibodies to herpes simplex virus types I and II in depressed patients. Biol Psychiatry 34:417–420.

Anderson AD, Oquendo MA, Parsey RV, Milak MS, Campbell C, Mann JJ. 2004. Regional brain responses to serotonin in major depressive disorder. J Affect Disord 82:411–417.

Angelucci F, Aloe L, Vasquez PJ, Mathe AA. 2000. Mapping the differences in the brain concentration of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in an animal model of depression. Neuroreport 11:1369–1373.

Arango V, Underwood MD, Boldrini M, et al. 2001. Serotonin 1A receptors, serotonin transporter binding and serotonin transporter mRNA expression in the brainstem of depressed suicide victims. Neuropsychopharmacology 25:892–903.

Arranz B, Eriksson A, Mellerup E, Plenge P, Marcusson J. 1994. Brain 5-HT1A, 5-HT1D, and 5-HT2 receptors in suicide victims. Biol Psychiatry 35:457–463.

Austin MP, Mitchell P, Wilhelm K, et al. 1999. Cognitive function in depression: a distinct pattern of frontal impairment in melancholia? Psychol Med 29:73–85.

Aydemir O, Deveci A, Taneli F. 2005. The effect of chronic antidepressant treatment on serum brain-derived neurotrophic factor levels in depressed patients: a preliminary study. Prog Neuropsychopharmacol Biol Psychiatry 29:261–265.

Baccarelli A, Pesatori AC, Bertazzi PA. 2000. Occupational and environmental agents as endocrine disruptors: experimental and human evidence. J Endocrinol Invest 23:771–781.

Baghai TC, Schule C, Zwanzger P, et al. 2002. Hypothalamic-pituitary-adrenocortical axis dysregulation in patients with major depression is influenced by the insertion/deletion polymorphism in the angiotensin I-converting enzyme gene. Neurosci Lett 328:299–303.

Baghai TC, Binder EB, Schule C, et al. 2006. Polymorphisms in the angiotensin-converting enzyme gene are associated with unipolar depression, ACE activity and hypercortisolism. Mol Psychiatry.

Baudic S, Tzortzis C, Barba GD, Traykov L. 2004. Executive deficits in elderly patients with major unipolar depression. J Geriatr Psychiatry Neurol 17:195–201.

Beats BC, Sahakian BJ, Levy R. 1996. Cognitive performance in tests sensitive to frontal lobe dysfunction in the elderly depressed. Psychol Med 26:591–603.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. 1961. An inventory for measuring depression. Arch Gen Psychiatry 4:561–571.

Bell IR, Edman JS, Miller J, et al. 1990a. Relationship of normal serum vitamin B12 and folate levels to cognitive test performance in subtypes of geriatric major depression. J Geriatr Psychiatry Neurol 3:98–105.

Bell IR, Edman JS, Marby DW, et al. 1990b. Vitamin B12 and folate status in acute geropsychiatric inpatients: affective and cognitive characteristics of a vitamin nondeficient population. Biol Psychiatry 27:125–137.

Bell IR, Edman JS, Morrow FD, et al. 1991. B complex vitamin patterns in geriatric and young adult inpatients with major depression. J Am Geriatr Soc 39:252–257.

Bell IR, Edman JS, Morrow FD, et al. 1992. Brief communication. Vitamin B1, B2, and B6 augmentation of tricyclic antidepressant treatment in geriatric depression with cognitive dysfunction. J Am Coll Nutr 11:159–163.

Berk M, Wadee AA, Kuschke RH, O'Neill-Kerr A. 1997. Acute phase proteins in major depression. J Psychosom Res 43:529–534.

Bhagwagar Z, Rabiner EA, Sargent PA, Grasby PM, Cowen PJ. 2004. Persistent reduction in brain serotonin1A receptor binding in recovered depressed men measured by positron emission tomography with [11C]WAY-100635. Mol Psychiatry 9:386–392.

Binder EB, Salyakina D, Lichtner P, et al. 2004. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nat Genet 36:1319–1325.

Bittner AC Jr, Echeverria D, Woods JS, et al. 1998. Behavioral effects of low-level exposure to Hg0 among dental professionals: a cross-study evaluation of psychomotor effects. Neurotoxicol Teratol 20:429–439.

Bjelland I, Tell GS, Vollset SE, Refsum H, Ueland PM. 2003. Folate, vitamin B12, homocysteine, and the MTHFR 677C- > T polymorphism in anxiety and depression: the Hordaland Homocysteine Study. Arch Gen Psychiatry 60:618–626.

Blackwood DH, Whalley LJ, Christie JE, Blackburn IM, St Clair DM, McInnes A. 1987. Changes in auditory P3 event-related potential in schizophrenia and depression. Br J Psychiatry 150:154–160.

Bonaccorso S, Lin AH, Verkerk R, et al. 1998. Immune markers in fibromyalgia: comparison with major depressed patients and normal volunteers. J Affect Disord 48:75–82.

Bondy B, Baghai TC, Zill P, et al. 2002. Combined action of the ACE D- and the G-protein beta3 T-allele in major depression: a possible link to cardiovascular disease? Mol Psychiatry 7:1120–1126.

Bonni A, Brunet A, West AE, Datta SR, Takasu MA, Greenberg ME. 1999. Cell survival promoted by the Ras-MAPK signaling pathway by transcription-dependent and -independent mechanisms. Science 286:1358–1362.

Borkowska A, Rybakowski JK. 2001. Neuropsychological frontal lobe tests indicate that bipolar depressed patients are more impaired than unipolar. Bipolar Disord 3:88–94.

Botez MI, Young SN, Bachevalier J, Gauthier S. 1982. Effect of folic acid and vitamin B12 deficiencies on 5-hydroxyindoleacetic acid in human cerebrospinal fluid. Ann Neurol 12:479–484.

Bottiglieri T, Hyland K, Laundy M, et al. 1992. Folate deficiency, biopterin and monoamine metabolism in depression. Psychol Med 22:871–876.

Brambilla F, Maggioni M. 1998. Blood levels of cytokines in elderly patients with major depressive disorder. Acta Psychiatr Scand 97:309–313.

Breier A, Kelsoe JR Jr, Kirwin PD, Beller SA, Wolkowitz OM, Pickar D. 1988. Early parental loss and development of adult psychopathology. Arch Gen Psychiatry 45:987–993.

Brody AL, Saxena S, Stoessel P, et al. 2001. Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. Arch Gen Psychiatry 58:631–640.

Burt T, Prudic J, Peyser S, Clark J, Sackeim HA. 2000. Learning and memory in bipolar and unipolar major depression: effects of aging. Neuropsychiatry Neuropsychol Behav Neurol 13:246–253.

Calabrese JR, Skwerer RG, Barna B, et al. 1986. Depression, immunocompetence, and prostaglandins of the E series. Psychiatry Res 17:41–47.

Calev A, Korin Y, Shapira B, Kugelmass S, Lerer B. 1986. Verbal and non-verbal recall by depressed and euthymic affective patients. Psychol Med 16:789–794.

Carney MW, Chary TK, Laundy M, et al. 1990. Red cell folate concentrations in psychiatric patients. J Affect Disord 19:207–213.

Channon S, Baker JE, Robertson MM. 1993. Effects of structure and clustering on recall and recognition memory in clinical depression. J Abnorm Psychol 102:323–326.

Chen AC, Shirayama Y, Shin KH, Neve RL, Duman RS. 2001a. Expression of the cAMP response element binding protein (CREB) in hippocampus produces an antidepressant effect. Biol Psychiatry 49:753–762.

Chen B, Dowlatshahi D, MacQueen GM, Wang JF, Young LT. 2001b. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 50:260–265.

Chen DF, Tonegawa S. 1998. Why do mature CNS neurons of mammals fail to re-establish connections following injury – functions of bcl-2. Cell Death Differ 5:816–822.

Chen DF, Schneider GE, Martinou JC, Tonegawa S. 1997. Bcl-2 promotes regeneration of severed axons in mammalian CNS. Nature 385:434–439.

Chen G, Rajkowska G, Du F, Seraji-Bozorgzad N, Manji HK. 2000. Enhancement of hippocampal neurogenesis by lithium. J Neurochem 75:1729–1734.

Chetty CS, McBride V, Sands S, Rajanna B. 1990. Effects in vitro of mercury on rat brain Mg(++)-ATPase. Arch Int Physiol Biochim 98:261–267.

Choi MJ, Lee HJ, Ham BJ, Cha JH, Ryu SH, Lee MS. 2004. Association between major depressive disorder and the -1438A/G polymorphism of the serotonin 2A receptor gene. Neuropsychobiology 49:38–41.

Chrapko WE, Jurasz P, Radomski MW, Lara N, Archer SL, Le Melledo JM. 2004. Decreased platelet nitric oxide synthase activity and plasma nitric oxide metabolites in major depressive disorder. Biol Psychiatry 56:129–134.

Claes S, Villafuerte S, Forsgren T, et al. 2003. The corticotropin-releasing hormone binding protein is associated with major depression in a population from Northern Sweden. Biol Psychiatry 54:867–872.

Coppen A, Bailey J. 2000. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. J Affect Disord 60:121–130.

Cotman CW, Berchtold NC. 2002. Exercise: a behavioral intervention to enhance brain health and plasticity. Trends Neurosci 25:295–301.

Coyle JT, Schwarcz R. 2000. Mind glue: implications of glial cell biology for psychiatry. Arch Gen Psychiatry 57:90–93.

Crook WG. 1984. Depression associated with Candida albicans infections. Jama 251:2928–2929.

D'Sa C, Duman RS. 2002. Antidepressants and neuroplasticity. Bipolar Disord 4:183–194.

Danion JM, Kauffmann-Muller F, Grange D, Zimmermann MA, Greth P. 1995. Affective valence of words, explicit and implicit memory in clinical depression. J Affect Disord 34:227–234.

Davidson RJ. 1998. Anterior electrophysiological asymmetries, emotion, and depression: conceptual and methodological conundrums. Psychophysiology 35:607–614.

Drevets WC. 2001. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional features of mood disorders. Curr Opin Neurobiol 11:240–249.

Drevets WC, Frank E, Price JC, Kupfer DJ, Greer PJ, Mathis C. 2000. Serotonin type-1A receptor imaging in depression. Nucl Med Biol 27:499–507.

Duch DS, Woolf JH, Nichol CA, Davidson JR, Garbutt JC. 1984. Urinary excretion of biopterin and neopterin in psychiatric disorders. Psychiatry Res 11:83–89.

Duman RS, Vaidya VA. 1998. Molecular and cellular actions of chronic electroconvulsive seizures. J Ect 14:181–193.

Duman RS, Malberg J, Thome J. 1999. Neural plasticity to stress and antidepressant treatment. Biol Psychiatry 46:1181–1191.

Duman RS, Malberg J, Nakagawa S. 2001. Regulation of adult neurogenesis by psychotropic drugs and stress. J Pharmacol Exp Ther 299:401–407.

Dunbar PR, Hill J, Neale TJ, Mellsop GW. 1992. Neopterin measurement provides evidence of altered cell-mediated immunity in patients with depression, but not with schizophrenia. Psychol Med 22:1051–1057.

Dwivedi Y, Rizavi HS, Conley RR, Roberts RC, Tamminga CA, Pandey GN. 2003a. Altered gene expression of brain-derived neurotrophic factor and receptor tyrosine kinase B in postmortem brain of suicide subjects. Arch Gen Psychiatry 60:804–815.

Dwivedi Y, Rao JS, Rizavi HS, et al. 2003b. Abnormal expression and functional characteristics of cyclic adenosine monophosphate response element binding protein in postmortem brain of suicide subjects. Arch Gen Psychiatry 60:273–282.

Echeverria D, Aposhian HV, Woods JS, et al. 1998. Neurobehavioral effects from exposure to dental amalgam Hg(o): new distinctions between recent exposure and Hg body burden. Faseb J 12:971–980.

Edwards DA. 1985. Depression and Candida. J Am Med Assoc 253:3400.

Egan MF, Kojima M, Callicott JH, et al. 2003. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell 112:257–269.

Elliott R, Sahakian BJ, Michael A, Paykel ES, Dolan RJ. 1998. Abnormal neural response to feedback on planning and guessing tasks in patients with unipolar depression. Psychol Med 28:559–571.

Elliott R, Sahakian BJ, McKay AP, Herrod JJ, Robbins TW, Paykel ES. 1996. Neuropsychological impairments in unipolar depression: the influence of perceived failure on subsequent performance. Psychol Med 26:975–989.

Ellis PM, Salmond C. 1994. Is platelet imipramine binding reduced in depression? A meta-analysis. Biol Psychiatry 36:292–299.

Ershler WB, Sun WH, Binkley N, et al. 1993. Interleukin-6 and aging: blood levels and mononuclear cell production increase with advancing age and in vitro production is modifiable by dietary restriction. Lymphokine Cytokine Res 12:225–230.

Evans SJ, Choudary PV, Neal CR, et al. 2004. Dysregulation of the fibroblast growth factor system in major depression. Proc Natl Acad Sci USA 101:15506–15511.

Exton MS, Artz M, Siffert W, Schedlowski M. 2003. G protein beta3 subunit 825T allele is associated with depression in young, healthy subjects. Neuroreport 14:531–533.

Falkenstein M, Hoormann J, Hohnsbein J. 1997. Event-related potential components related to errors]. Z Exp Psychol 44:117–138.

Fallgatter AJ, Strik WK. 1999. The NoGo-anteriorization as a neurophysiological standard-index for cognitive response control. Int J Psychophysiol 32:233–238.

Fallgatter AJ, Brandeis D, Strik WK. 1997. A robust assessment of the NoGo-anteriorisation of P300 microstates in a cued Continuous Performance Test. Brain Topogr 9:295–302.

Fallgatter AJ, Mueller TJ, Strik WK. 1999. Age-related changes in the brain electrical correlates of response control. Clin Neurophysiol 110:833–838.

Fallgatter AJ, Bartsch AJ, Herrmann MJ. 2002. Electrophysiological measurements of anterior cingulate function. J Neural Transm 109:977–988.

Fallgatter AJ, Esienack SS, Neuhauser B, Aranda D, Scheuerpflug P, Herrmann MJ. 2000. Stability of late event-related potentials: topographical descriptors of motor control compared with the P300 amplitude. Brain Topogr 12:255–261.

Fallgatter AJ, Bartsch AJ, Strik WK, et al. 2001. Test-retest reliability of electrophysiological parameters related to cognitive motor control. Clin Neurophysiol 112:198–204.

Fava M, Borus JS, Alpert JE, Nierenberg AA, Rosenbaum JF, Bottiglieri T. 1997. Folate, vitamin B12, and homocysteine in major depressive disorder. Am J Psychiatry 154:426–428.

Fehr C, Grintschuk N, Szegedi A, et al. 2000. The HTR1B 861G>C receptor polymorphism among patients suffering from alcoholism, major depression, anxiety disorders and narcolepsy. Psychiatry Res 97:1–10.

Fernstrom JD. 1977. Effects on the diet on brain neurotransmitters. Metabolism 26:207–223.

Freedman DA. 1981. The effects of sensory and other deficits in children on their experience of people. J Am Psychoanal Assoc 29:831–867.

Freitas AJ, Rocha JB, Wolosker H, Souza DO. 1996. Effects of Hg2+ and CH3Hg+ on Ca2+ fluxes in rat brain microsomes. Brain Res 738:257–264.

Friedland RP, Fritsch T, Smyth KA, et al. 2001. Patients with Alzheimer's disease have reduced activities in midlife compared with healthy control-group members. Proc Natl Acad Sci USA 98:3440–3445.

Frisch A, Postilnick D, Rockah R, et al. 1999. Association of unipolar major depressive disorder with genes of the serotonergic and dopaminergic pathways. Mol Psychiatry 4:389–392.

Frommberger UH, Bauer J, Haselbauer P, Fraulin A, Riemann D, Berger M. 1997. Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. Eur Arch Psychiatry Clin Neurosci 247:228–233.

Fu CH, Williams SC, Cleare AJ, et al. 2004. Attenuation of the neural response to sad faces in major depression by antidepressant treatment: a prospective, event-related functional magnetic resonance imaging study. Arch Gen Psychiatry 61:877–889.

Gale CR, Martyn CN. 2004. Birth weight and later risk of depression in a national birth cohort. Br J Psychiatry 184:28–33.

Garcia C, Chen MJ, Garza AA, Cotman CW, Russo-Neustadt A. 2003. The influence of specific noradrenergic and serotonergic lesions on the expression of hippocampal brain-derived neurotrophic factor transcripts following voluntary physical activity. Neuroscience 119:721–732.

Garcia R. 2002. Stress, metaplasticity, and antidepressants. Curr Mol Med 2:629–638.

Gervasoni N, Aubry JM, Bondolfi G, et al. 2005. Partial normalization of serum brain-derived neurotrophic factor in

remitted patients after a major depressive episode. Neuropsychobiology 51:234–238.
Glueck CJ, Tieger M, Kunkel R, et al. 1993. Improvement in symptoms of depression and in an index of life stressors accompany treatment of severe hypertriglyceridemia. Biol Psychiatry 34:240–252.
Goldberg TE, Gold JM, Greenberg R, et al. 1993. Contrasts between patients with affective disorders and patients with schizophrenia on a neuropsychological test battery. Am J Psychiatry 150:1355–1362.
Gonul AS, Akdeniz F, Taneli F, Donat O, Eker C, Vahip S. 2005. Effect of treatment on serum brain-derived neurotrophic factor levels in depressed patients. Eur Arch Psychiatry Clin Neurosci 255:381–386.
Grant MM, Thase ME, Sweeney JA. 2001. Cognitive disturbance in outpatient depressed younger adults: evidence of modest impairment. Biol Psychiatry 50:35–43.
Gultepe M, Ozcan O, Avsar K, Cetin M, Ozdemir AS, Gok M. 2003. Urine methylmalonic acid measurements for the assessment of cobalamin deficiency related to neuropsychiatric disorders. Clin Biochem 36:275–282.
Gurevich I, Tamir H, Arango V, Dwork AJ, Mann JJ, Schmauss C. 2002. Altered editing of serotonin 2C receptor pre-mRNA in the prefrontal cortex of depressed suicide victims. Neuron 34:349–356.
Haack M, Hinze-Selch D, Fenzel T, et al. 1999. Plasma levels of cytokines and soluble cytokine receptors in psychiatric patients upon hospital admission: effects of confounding factors and diagnosis. J Psychiatr Res 33:407–418.
Haggerty JJ Jr, Simon JS, Evans DL, Nemeroff CB. 1987. Relationship of serum TSH concentration and antithyroid antibodies to diagnosis and DST response in psychiatric inpatients. Am J Psychiatry 144:1491–1493.
Hamilton M. 1967. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 6:278–296.
Hartmann M, Heumann R, Lessmann V. 2001. Synaptic secretion of BDNF after high-frequency stimulation of glutamatergic synapses. EMBO J 20:5887–5897.
Harvey PO, Le Bastard G, Pochon JB, et al. 2004. Executive functions and updating of the contents of working memory in unipolar depression. J Psychiatr Res 38:567–576.
Hashimoto K, Shimizu E, Iyo M. 2004. Critical role of brain-derived neurotrophic factor in mood disorders. Brain Res Brain Res Rev 45:104–114.
Hegerl U, Gallinat J, Juckel G. 2001. Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? J Affect Disord 62:93–100.
Herbert TB, Cohen S. 1993. Depression and immunity: a meta-analytic review. Psychol Bull 113:472–486.
Herran A, Garcia-Unzueta MT, Amado JA, Lopez-Cordovilla JJ, Diez-Manrique JF, Vazquez-Barquero JL. 1999. Folate levels in psychiatric outpatients. Psychiatry Clin Neurosci 53:531–533.
Herrmann MJ, Weijers HG, Wiesbeck GA, Boning J, Fallgatter AJ. 2001. Alcohol cue-reactivity in heavy and light social drinkers as revealed by event-related potentials. Alcohol Alcohol 36:588–593.
Herrmann MJ, Rommler J, Ehlis AC, Heidrich A, Fallgatter AJ. 2004. Source localization (LORETA) of the error-related-negativity (ERN/Ne) and positivity (Pe). Brain Res Cogn Brain Res 20:294–299.
Hill SK, Keshavan MS, Thase ME, Sweeney JA. 2004. Neuropsychological dysfunction in antipsychotic-naive first-episode unipolar psychotic depression. Am J Psychiatry 161:996–1003.
Hintikka J, Tolmunen T, Tanskanen A, Viinamaki H. 2003. High vitamin B12 level and good treatment outcome may be associated in major depressive disorder. BMC Psychiatry 3:17.
Holm KH, Cicchetti F, Bjorklund L, et al. 2001. Enhanced axonal growth from fetal human bcl-2 transgenic mouse dopamine neurons transplanted to the adult rat striatum. Neuroscience 104:397–405.
Holmes C, Arranz M, Collier D, Powell J, Lovestone S. 2003. Depression in Alzheimer's disease: the effect of serotonin receptor gene variation. Am J Med Genet B Neuropsychiatr Genet 119:40–43.
Hong CJ, Tsai SJ, Cheng CY, Liao WY, Song HL, Lai HC. 1999. Association analysis of the 5-HT(6) receptor polymorphism (C267T) in mood disorders. Am J Med Genet 88:601–602.
Hsieh MH, McQuoid DR, Levy RM, Payne ME, MacFall JR, Steffens DC. 2002. Hippocampal volume and antidepressant response in geriatric depression. Int J Geriatr Psychiatry 17:519–525.
Hua MS, Huang CC, Yang YJ. 1996. Chronic elemental mercury intoxication: neuropsychological follow-up case study. Brain Inj 10:377–384.
Huang YY, Grailhe R, Arango V, Hen R, Mann JJ. 1999. Relationship of psychopathology to the human serotonin1B genotype and receptor binding kinetics in postmortem brain tissue. Neuropsychopharmacology 21:238–246.
Hvas AM, Juul S, Bech P, Nexo E. 2004a. Vitamin B6 level is associated with symptoms of depression. Psychother Psychosom 73:340–343.
Hvas AM, Juul S, Lauritzen L, Nexo E, Ellegaard J. 2004b. No effect of vitamin B-12 treatment on cognitive function and depression: a randomized placebo controlled study. J Affect Disord 81:269–273.
Ibanez CF. 1995. Neurotrophic factors: from structure-function studies to designing effective therapeutics. Trends Biotechnol 13:217–227.
Ilonen T, Taiminen T, Lauerma H, et al. 2000. Impaired Wisconsin card sorting test performance in first-episode schizophrenia: resource or motivation deficit? Compr Psychiatry 41:385–391.
Ilsley JE, Moffoot AP, O'Carroll RE. 1995. An analysis of memory dysfunction in major depression. J Affect Disord 35:1–9.
Ivy AS, Rodriguez FG, Garcia C, Chen MJ, Russo-Neustadt AA. 2003. Noradrenergic and serotonergic blockade inhibits BDNF mRNA activation following exercise and antidepressant. Pharmacol Biochem Behav 75:81–88.
Iwamoto K, Kato T. 2003. RNA editing of serotonin 2C receptor in human postmortem brains of major mental disorders. Neurosci Lett 346:169–172.
Jacobs BL, Praag H, Gage FH. 2000. Adult brain neurogenesis and psychiatry: a novel theory of depression. Mol Psychiatry 5:262–269.
Joyce PR, Paykel ES. 1989. Predictors of drug response in depression. Arch Gen Psychiatry 46:89–99.
Joyce PR, Mulder RT, Luty SE, et al. 2003. Age-dependent antidepressant pharmacogenomics: polymorphisms of the serotonin transporter and G protein beta3 subunit as predictors of response to fluoxetine and nortriptyline. Int J Neuropsychopharmacol 6:339–346.
Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM. 2002. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res 109:143–148.
Karege F, Bondolfi G, Gervasoni N, Schwald M, Aubry JM, Bertschy G. 2005. Low brain-derived neurotrophic factor (BDNF) levels in serum of depressed patients probably results

from lowered platelet BDNF release unrelated to platelet reactivity. Biol Psychiatry 57:1068–1072.
Katila H, Cantell K, Hirvonen S, Rimon R. 1989. Production of interferon-alpha and gamma by leukocytes from patients with schizophrenia. Schizophr Res 2:361–365.
Kaufman J. 1991. Depressive disorders in maltreated children. J Am Acad Child Adolesc Psychiatry 30:257–265.
Kawasaki T, Tanaka S, Wang J, Hokama H, Hiramatsu K. 2004. Abnormalities of P300 cortical current density in unmedicated depressed patients revealed by LORETA analysis of event-related potentials. Psychiatry Clin Neurosci 58:68–75.
Kempermann G. 2002. Regulation of adult hippocampal neurogenesis – implications for novel theories of major depression. Bipolar Disord 4:17–33.
Kessing LV. 1998. Cognitive impairment in the euthymic phase of affective disorder. Psychol Med 28:1027–1038.
Khait VD, Huang YY, Zalsman G, et al. 2005. Association of serotonin 5-HT2A receptor binding and the T102C polymorphism in depressed and healthy Caucasian subjects. Neuropsychopharmacology 30:166–172.
Kishi R, Doi R, Fukuchi Y, et al. 1994. Residual neurobehavioural effects associated with chronic exposure to mercury vapour. Occup Environ Med 51:35–41.
Koch JM, Kell S, Hinze-Selch D, Aldenhoff JB. 2002. Changes in CREB-phosphorylation during recovery from major depression. J Psychiatr Res 36:369–375.
Köks S, Nikopensius T, Koido K, et al. 2006. Analysis of SNP profiles in patients with major depressive disorder. Int J Neuropsychopharmacol 9:167–174.
Lai IC, Hong CJ, Tsai SJ. 2003. Expression of cAMP response element-binding protein in major depression before and after antidepressant treatment. Neuropsychobiology 48:182–185.
Landro NI, Stiles TC, Sletvold H. 2001. Neuropsychological function in nonpsychotic unipolar major depression. Neuropsychiatry Neuropsychol Behav Neurol 14:233–240.
Lang UE, Hellweg R, Gallinat J. 2004. BDNF serum concentrations in healthy volunteers are associated with depression-related personality traits. Neuropsychopharmacology 29:795–798.
Lauder JM. 1988. Neurotransmitters as morphogens. Prog Brain Res 73:365–387.
Laurin D, Verreault R, Lindsay J, MacPherson K, Rockwood K. 2001. Physical activity and risk of cognitive impairment and dementia in elderly persons. Arch Neurol 58:498–504.
Lee BH, Lee SW, Yoon D, et al. 2006. Increased plasma nitric oxide metabolites in suicide attempters. Neuropsychobiology 53:127–132.
Lee HJ, Cha JH, Ham BJ, et al. 2004. Association between a G-protein beta 3 subunit gene polymorphism and the symptomatology and treatment responses of major depressive disorders. Pharmacogenomics J 4:29–33.
Lee S, Wing YK, Fong S. 1998. A controlled study of folate levels in Chinese inpatients with major depression in Hong Kong. J Affect Disord 49:73–77.
Lee SH, Lee KJ, Lee HJ, Ham BJ, Ryu SH, Lee MS. 2005. Association between the 5-HT6 receptor C267T polymorphism and response to antidepressant treatment in major depressive disorder. Psychiatry Clin Neurosci 59:140–145.
LeMay LG, Vander AJ, Kluger MJ. 1990. The effects of psychological stress on plasma interleukin-6 activity in rats. Physiol Behav 47:957–961.
Lemonde S, Turecki G, Bakish D, et al. 2003. Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. J Neurosci 23:8788–8799.
Lerer B, Macciardi F, Segman RH, et al. 2001. Variability of 5-HT2C receptor cys23ser polymorphism among European populations and vulnerability to affective disorder. Mol Psychiatry 6:579–585.
Levine J, Barak Y, Chengappa KR, Rapoport A, Antelman SM, Barak V. 1999. Low CSF soluble interleukin 2 receptor levels in acute depression. Short communication. J Neural Transm 106:1011–1015.
Levinson DF. 2005. Meta-analysis in psychiatric genetics. Curr Psychiatry Rep 7:143–151.
Levitt AJ, Joffe RT. 1989. Folate, B12, and life course of depressive illness. Biol Psychiatry 25:867–872.
Linka T, Muller BW, Bender S, Sartory G. 2004. The intensity dependence of the auditory evoked N1 component as a predictor of response to Citalopram treatment in patients with major depression. Neurosci Lett 367:375–378.
Linnoila M, Whorton AR, Rubinow DR, Cowdry RW, Ninan PT, Waters RN. 1983. CSF prostaglandin levels in depressed and schizophrenic patients. Arch Gen Psychiatry 40:405–406.
Lipton ED. 1970. A perceptual-motor development program's effect on visual perception and reading readiness of first-grade children. Res Q 41:402–405.
Liu SK, Chiu CH, Chang CJ, Hwang TJ, Hwu HG, Chen WJ. 2002. Deficits in sustained attention in schizophrenia and affective disorders: stable versus state-dependent markers. Am J Psychiatry 159:975–982.
Lopez-Figueroa AL, Norton CS, Lopez-Figueroa MO, et al. 2004. Serotonin 5-HT1A, 5-HT1B, and 5-HT2A receptor mRNA expression in subjects with major depression, bipolar disorder, and schizophrenia. Biol Psychiatry 55:225–233.
Lowther S, Katona CL, Crompton MR, Horton RW. 1997a. 5-HT1D and 5-HT1E/1F binding sites in depressed suicides: increased 5-HT1D binding in globus pallidus but not cortex. Mol Psychiatry 2:314–321.
Lowther S, De Paermentier F, Cheetham SC, Crompton MR, Katona CL, Horton RW. 1997b. 5-HT1A receptor binding sites in post-mortem brain samples from depressed suicides and controls. J Affect Disord 42:199–207.
Lu B. 2003. BDNF and activity-dependent synaptic modulation. Learn Mem 10:86–98.
MacQueen GM, Campbell S, McEwen BS, et al. 2003. Course of illness, hippocampal function, and hippocampal volume in major depression. Proc Natl Acad Sci USA 100:1387–1392.
Maes M, Meltzer HY, Buckley P, Bosmans E. 1995a. Plasma-soluble interleukin-2 and transferrin receptor in schizophrenia and major depression. Eur Arch Psychiatry Clin Neurosci 244:325–329.
Maes M, Bosmans E, Suy E, Vandervorst C, Dejonckheere C, Raus J. 1991. Antiphospholipid, antinuclear, Epstein-Barr and cytomegalovirus antibodies, and soluble interleukin-2 receptors in depressive patients. J Affect Disord 21:133–140.
Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. 1997a. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 9:853–858.
Maes M, Stevens W, DeClerck L, et al. 1992. Immune disorders in depression: higher T helper/T suppressor-cytotoxic cell ratio. Acta Psychiatr Scand 86:423–431.
Maes M, Scharpe S, Meltzer HY, et al. 1993. Relationships between interleukin-6 activity, acute phase proteins, and function of the hypothalamic-pituitary-adrenal axis in severe depression. Psychiatry Res 49:11–27.
Maes M, Meltzer HY, Bosmans E, et al. 1995b. Increased plasma concentrations of interleukin-6, soluble interleukin-6, soluble interleukin-2 and transferrin receptor in major depression. J Affect Disord 34:301–309.
Maes M, Scharpe S, Meltzer HY, et al. 1994. Increased neopterin and interferon-gamma secretion and lower availability of L-

tryptophan in major depression: further evidence for an immune response. Psychiatry Res 54:143–160.

Maes M, Vandoolaeghe E, Neels H, et al. 1997b. Lower serum zinc in major depression is a sensitive marker of treatment resistance and of the immune/inflammatory response in that illness. Biol Psychiatry 42:349–358.

Malberg JE, Eisch AJ, Nestler EJ, Duman RS. 2000. Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 20:9104–9110.

Mamounas LA, Blue ME, Siuciak JA, Altar CA. 1995. Brain-derived neurotrophic factor promotes the survival and sprouting of serotonergic axons in rat brain. J Neurosci 15:7929–7939.

Manev H, Uz T, Smalheiser NR, Manev R. 2001. Antidepressants alter cell proliferation in the adult brain in vivo and in neural cultures in vitro. Eur J Pharmacol 411:67–70.

Manji HK, Drevets WC, Charney DS. 2001. The cellular neurobiology of depression. Nat Med 7:541–547.

Manji HK, Quiroz JA, Sporn J, et al. 2003. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. Biol Psychiatry 53:707–742.

Manzo L, Artigas F, Martinez E, et al. 1996. Biochemical markers of neurotoxicity. A review of mechanistic studies and applications. Hum Exp Toxicol 15(Suppl 1):S20–35.

Martin SD, Martin E, Rai SS, Richardson MA, Royall R. 2001. Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride: preliminary findings. Arch Gen Psychiatry 58:641–648.

Martinez A, Alcantara S, Borrell V, Del Rio JA, Blasi J, Otal R, et al. 1998. TrkB and TrkC signaling are required for maturation and synaptogenesis of hippocampal connections. J Neurosci 18:7336–7350.

Mathieson PW. 1995. Mercury: god of Th2 cells? Clin Exp Immunol 102:229–230.

Mattson MP, Shea TB. 2003. Folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. Trends Neurosci 26:137–146.

Mattson MP, Maudsley S, Martin B. 2004. BDNF and 5-HT: a dynamic duo in age-related neuronal plasticity and neurodegenerative disorders. Trends Neurosci 27:589–594.

Mayberg HS, Brannan SK, Mahurin RK, et al. 1997. Cingulate function in depression: a potential predictor of treatment response. Neuroreport 8:1057–1061.

Mellor AL, Munn DH. 1999. Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? Immunol Today 20:469–473.

Meltzer CC, Price JC, Mathis CA, et al. 2004. Serotonin 1A receptor binding and treatment response in late-life depression. Neuropsychopharmacology 29:2258–2265.

Mendlovic S, Mozes E, Eilat E, et al. 1999. Immune activation in non-treated suicidal major depression. Immunol Lett 67:105–108.

Meyer JH, Ginovart N, Boovariwala A, et al. 2006. Elevated monoamine oxidase a levels in the brain: an explanation for the monoamine imbalance of major depression. Arch Gen Psychiatry 63:1209–1216.

Minov C, Baghai TC, Schule C, et al. 2001. Serotonin-2A-receptor and -transporter polymorphisms: lack of association in patients with major depression. Neurosci Lett 303:119–122.

Miyahara S, Komori T, Fujiwara R, et al. 2000. Effects of repeated stress on expression of interleukin-6 (IL-6) and IL-6 receptor mRNAs in rat hypothalamus and midbrain. Life Sci 66:PL93–98.

Molnar M, Potkin SG, Bunney WE, Jones EG. 2003. MRNA expression patterns and distribution of white matter neurons in dorsolateral prefrontal cortex of depressed patients differ from those in schizophrenia patients. Biol Psychiatry 53:39–47.

Moore GJ, Bebchuk JM, Hasanat K, et al. 2000. Lithium increases N-acetyl-aspartate in the human brain: in vivo evidence in support of bcl-2's neurotrophic effects? Biol Psychiatry 48:1–8.

Morcuende S, Gadd CA, Peters M, et al. 2003. Increased neurogenesis and brain-derived neurotrophic factor in neurokinin-1 receptor gene knockout mice. Eur J Neurosci 18:1828–1836.

Moritz S, Birkner C, Kloss M, et al. 2002. Executive functioning in obsessive-compulsive disorder, unipolar depression, and schizophrenia. Arch Clin Neuropsychol 17:477–483.

Mössner R, Walitza S, Geller F, et al. 2006. Transmission disequilibrium of polymorphic variants in the tryptophan hydroxylase-2 gene in children and adolescents with obsessive-compulsive disorder. Int J Neuropsychopharmacol 9:437–442.

Müller MB, Toschi N, Kresse AE, Post A, Keck ME. 2000. Long-term repetitive transcranial magnetic stimulation increases the expression of brain-derived neurotrophic factor and cholecystokinin mRNA, but not neuropeptide tyrosine mRNA in specific areas of rat brain. Neuropsychopharmacology 23:205–215.

Müller N, Hofschuster E, Ackenheil M, Mempel W, Eckstein R. 1993. Investigations of the cellular immunity during depression and the free interval: evidence for an immune activation in affective psychosis. Prog Neuropsychopharmacol Biol Psychiatry 17:713–730.

Munn DH, Shafizadeh E, Attwood JT, Bondarev I, Pashine A, Mellor AL. 1999. Inhibition of T cell proliferation by macrophage tryptophan catabolism. J Exp Med 189:1363–1372.

Murphy FC, Rubinsztein JS, Michael A, et al. 2001. Decision-making cognition in mania and depression. Psychol Med 31:679–693.

Naber CK, Husing J, Wolfhard U, Erbel R, Siffert W. 2000. Interaction of the ACE D allele and the GNB3 825T allele in myocardial infarction. Hypertension 36:986–989.

Nakagawa S, Kim JE, Lee R, et al. 2002. Regulation of neurogenesis in adult mouse hippocampus by cAMP and the cAMP response element-binding protein. J Neurosci 22:3673–3682.

Naylor GJ, Smith AH, Bryce-Smith D, Ward NI. 1984. Elevated vanadium content of hair and mania. Biol Psychiatry 19:759–764.

Neu P, Kiesslinger U, Schlattmann P, Reischies FM. 2001. Time-related cognitive deficiency in four different types of depression. Psychiatry Res 103:237–247.

Neu P, Bajbouj M, Schilling A, Godemann F, Berman RM, Schlattmann P. 2005. Cognitive function over the treatment course of depression in middle-aged patients: correlation with brain MRI signal hyperintensities. J Psychiatr Res 39:129–135.

Neves-Pereira M, Mundo E, Muglia P, King N, Macciardi F, Kennedy JL. 2002. The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. Am J Hum Genet 71:651–655.

Newton SS, Thome J, Wallace TL, et al. 2002. Inhibition of cAMP response element-binding protein or dynorphin in the nucleus accumbens produces an antidepressant-like effect. J Neurosci 22:10883–10890.

Nibuya M, Morinobu S, Duman RS. 1995. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 15:7539–7547.

Nibuya M, Nestler EJ, Duman RS. 1996. Chronic antidepressant administration increases the expression of cAMP response

element binding protein (CREB) in rat hippocampus. J Neurosci 16:2365–2372.
Nibuya M, Takahashi M, Russell DS, Duman RS. 1999. Repeated stress increases catalytic TrkB mRNA in rat hippocampus. Neurosci Lett 267:81–84.
Nishino S, Ueno R, Ohishi K, Sakai T, Hayaishi O. 1989. Salivary prostaglandin concentrations: possible state indicators for major depression. Am J Psychiatry 146:365–368.
Niswender CM, Herrick-Davis K, Dilley GE, et al. 2001. RNA editing of the human serotonin 5-HT2C receptor. alterations in suicide and implications for serotonergic pharmacotherapy. Neuropsychopharmacology 24:478–491.
Nonaka S, Katsube N, Chuang DM. 1998. Lithium protects rat cerebellar granule cells against apoptosis induced by anticonvulsants, phenytoin and carbamazepine. J Pharmacol Exp Ther 286:539–547.
Ohishi K, Ueno R, Nishino S, Sakai T, Hayaishi O. 1988. Increased level of salivary prostaglandins in patients with major depression. Biol Psychiatry 23:326–334.
Oliff HS, Berchtold NC, Isackson P, Cotman CW. 1998. Exercise-induced regulation of brain-derived neurotrophic factor (BDNF) transcripts in the rat hippocampus. Brain Res Mol Brain Res 61:147–153.
Ongur D, An X, Price JL. 1998. Prefrontal cortical projections to the hypothalamus in macaque monkeys. J Comp Neurol 401:480–505.
Oswald P, Souery D, Massat I, et al. 2003. Lack of association between the 5HT2A receptor polymorphism (T102C) and unipolar affective disorder in a multicentric European study. Eur Neuropsychopharmacol 13:365–368.
Papakostas GI, Petersen T, Mischoulon D, et al. 2004a. Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 2: predictors of relapse during the continuation phase of pharmacotherapy. J Clin Psychiatry 65:1096–1098.
Papakostas GI, Petersen T, Mischoulon D, et al. 2004b. Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 1: predictors of clinical response in fluoxetine-resistant depression. J Clin Psychiatry 65:1090–1095.
Paradiso S, Lamberty GJ, Garvey MJ, Robinson RG. 1997. Cognitive impairment in the euthymic phase of chronic unipolar depression. J Nerv Ment Dis 185:748–754.
Pascual-Marqui RD, Michel CM, Lehmann D. 1994. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. Int J Psychophysiol 18:49–65.
Penninx BW, Guralnik JM, Ferrucci L, Fried LP, Allen RH, Stabler SP. 2000. Vitamin B(12) deficiency and depression in physically disabled older women: epidemiologic evidence from the Women's Health and Aging Study. Am J Psychiatry 157:715–721.
Perlingeiro RC, Queiroz ML. 1994. Polymorphonuclear phagocytosis and killing in workers exposed to inorganic mercury. Int J Immunopharmacol 16:1011–1017.
Perry BD, Pollard R. 1998. Homeostasis, stress, trauma, and adaptation. A neurodevelopmental view of childhood trauma. Child Adolesc Psychiatr Clin N Am 7:33–51, viii.
Pettmann B, Henderson CE. 1998. Neuronal cell death. Neuron 20:633–647.
Pfefferbaum A, Ford JM, Wenegrat BG, Roth WT, Kopell BS. 1984. Clinical application of the P3 component of event-related potentials. I. Normal aging. Electroencephalogr Clin Neurophysiol 59:85–103.
Pizzagalli D, Pascual-Marqui RD, Nitschke JB, et al. 2001. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. Am J Psychiatry 158:405–415.
Plata-Salaman CR. 1991. Immunoregulators in the nervous system. Neurosci Biobehav Rev 15:185–215.
Polich J, Herbst KL. 2000. P300 as a clinical assay: rationale, evaluation, and findings. Int J Psychophysiol 38:3–19.
Poo MM. 2001. Neurotrophins as synaptic modulators. Nat Rev Neurosci 2:24–32.
Porter RJ, Gallagher P, Thompson JM, Young AH. 2003. Neurocognitive impairment in drug-free patients with major depressive disorder. Br J Psychiatry 182:214–220.
Pozzo-Miller LD, Gottschalk W, Zhang L, et al. 1999. Impairments in high-frequency transmission, synaptic vesicle docking, and synaptic protein distribution in the hippocampus of BDNF knockout mice. J Neurosci 19:4972–4983.
Procter A. 1991. Enhancement of recovery from psychiatric illness by methylfolate. Br J Psychiatry 159:271–272.
Provence S. 1983. Struggling against deprivation and trauma. A longitudinal case study. Psychoanal Study Child 38:233–256.
Rabiner EA, Bhagwagar Z, Gunn RN, Cowen PJ, Grasby PM. 2004. Preferential 5-HT1A autoreceptor occupancy by pindolol is attenuated in depressed patients: effect of treatment or an endophenotype of depression? Neuropsychopharmacology 29:1688–1698.
Rafter D. 2001. Biochemical markers of anxiety and depression. Psychiatry Res 103:93–96.
Rajanna B, Chetty CS, Rajanna S, Hall E, Fail S, Yallapragada PR. 1995. Modulation of protein kinase C by heavy metals. Toxicol Lett 81:197–203.
Rajkowska G. 2000. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biol Psychiatry 48:766–777.
Ramos MI, Allen LH, Haan MN, Green R, Miller JW. 2004. Plasma folate concentrations are associated with depressive symptoms in elderly Latina women despite folic acid fortification. Am J Clin Nutr 80:1024–1028.
Rasmussen HH, Mortensen PB, Jensen IW. 1989. Depression and magnesium deficiency. Int J Psychiatry Med 19:57–63.
Ravnkilde B, Videbech P, Clemmensen K, Egander A, Rasmussen NA, Rosenberg R. 2002. Cognitive deficits in major depression. Scand J Psychol 43:239–251.
Reid IC, Stewart CA. 2001. How antidepressants work: new perspectives on the pathophysiology of depressive disorder. Br J Psychiatry 178:299–303.
Reif A, Strobel A, Jacob CP, et al. 2006. A NOS-III haplotype that includes functional polymorphisms is associated with bipolar disorder. Int J Neuropsychopharmacol 9:13–20.
Reivich M, Amsterdam JD, Brunswick DJ, Shiue CY. 2004. PET brain imaging with [11C](+)McN5652 shows increased serotonin transporter availability in major depression. J Affect Disord 82:321–327.
Riccio A, Ahn S, Davenport CM, Blendy JA, Ginty DD. 1999. Mediation by a CREB family transcription factor of NGF-dependent survival of sympathetic neurons. Science 286:2358–2361.
Rogers MA, Bellgrove MA, Chiu E, Mileshkin C, Bradshaw JL. 2004. Response selection deficits in melancholic but not nonmelancholic unipolar major depression. J Clin Exp Neuropsychol 26:169–179.
Rosel P, Arranz B, Urretavizcaya M, Oros M, San L, Navarro MA. 2004. Altered 5-HT2A and 5-HT4 postsynaptic receptors and their intracellular signalling systems IP3 and cAMP in brains from depressed violent suicide victims. Neuropsychobiology 49:189–195.
Ross BM, Ward P, Glen I. 2004. Delayed vasodilatory response to methylnicotinate in patients with unipolar depressive disorder. J Affect Disord 82:285–290.

Rossi AD, Larsson O, Manzo L, et al. 1993. Modifications of Ca2+ signaling by inorganic mercury in PC12 cells. Faseb J 7:1507–1514.

Roth WT, Pfefferbaum A, Kelly AF, Berger PA, Kopell BS. 1981. Auditory event-related potentials in schizophrenia and depression. Psychiatry Res 4:199–212.

Rothermundt M, Arolt V, Fenker J, Gutbrodt H, Peters M, Kirchner H. 2001. Different immune patterns in melancholic and non-melancholic major depression. Eur Arch Psychiatry Clin Neurosci 251:90–97.

Roy A, Pickar D, Paul S, Doran A, Chrousos GP, Gold PW. 1987. CSF corticotropin-releasing hormone in depressed patients and normal control subjects. Am J Psychiatry 144:641–645.

Ruchsow M, Herrnberger B, Wiesend C, Gron G, Spitzer M, Kiefer M. 2004. The effect of erroneous responses on response monitoring in patients with major depressive disorder: a study with event-related potentials. Psychophysiology 41: 833–840.

Russo-Neustadt A, Ha T, Ramirez R, Kesslak JP. 2001. Physical activity-antidepressant treatment combination: impact on brain-derived neurotrophic factor and behavior in an animal model. Behav Brain Res 120:87–95.

Rutter M. 1984. Psychopathology and development: II. Childhood experiences and personality development. Aust NZ J Psychiatry 18:314–327.

Salas MA, Evans SW, Levell MJ, Whicher JT. 1990. Interleukin-6 and ACTH act synergistically to stimulate the release of corticosterone from adrenal gland cells. Clin Exp Immunol 79:470–473.

Santarelli L, Saxe M, Gross C, et al. 2003. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301:805–809.

Sargent PA, Kjaer KH, Bench CJ, et al. 2000. Brain serotonin1A receptor binding measured by positron emission tomography with [11C]WAY-100635: effects of depression and antidepressant treatment. Arch Gen Psychiatry 57:174–180.

Scharfman HE, Maclusky NJ. 2005. Similarities between actions of estrogen and BDNF in the hippocampus: coincidence or clue? Trends Neurosci 28:79–85.

Schatzberg AF, Posener JA, DeBattista C, Kalehzan BM, Rothschild AJ, Shear PK. 2000. Neuropsychological deficits in psychotic versus nonpsychotic major depression and no mental illness. Am J Psychiatry 157:1095–1100.

Schwarcz R, Pellicciari R. 2002. Manipulation of brain kynurenines: glial targets, neuronal effects, and clinical opportunities. J Pharmacol Exp Ther 303:1–10.

Segal RA, Greenberg ME. 1996. Intracellular signaling pathways activated by neurotrophic factors. Annu Rev Neurosci 19:463–489.

Seidel A, Arolt V, Hunstiger M, Rink L, Behnisch A, Kirchner H. 1996. Major depressive disorder is associated with elevated monocyte counts. Acta Psychiatr Scand 94:198–204.

Sen S, Nesse RM, Stoltenberg SF, et al. 2003. A BDNF coding variant is associated with the NEO personality inventory domain neuroticism, a risk factor for depression. Neuropsychopharmacology 28:397–401.

Serretti A, Lorenzi C, Cusin C, et al. 2003. SSRIs antidepressant activity is influenced by G beta 3 variants. Eur Neuropsychopharmacol 13:117–122.

Sheline YI, Gado MH, Kraemer HC. 2003. Untreated depression and hippocampal volume loss. Am J Psychiatry 160:1516–1518.

Sheline YI, Sanghavi M, Mintun MA, Gado MH. 1999. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. J Neurosci 19:5034–5043.

Shimizu E, Hashimoto K, Okamura N, et al. 2003. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. Biol Psychiatry 54:70–75.

Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS. 2002. Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. J Neurosci 22:3251–3261.

Siblerud RL, Motl J, Kienholz E. 1994. Psychometric evidence that mercury from silver dental fillings may be an etiological factor in depression, excessive anger, and anxiety. Psychol Rep 74:67–80.

Simopoulos AP, Leaf A, Salem N Jr. 1999. Workshop on the Essentiality of and Recommended Dietary Intakes for Omega-6 and Omega-3 Fatty Acids. J Am Coll Nutr 18:487–489.

Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM. 1997. Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacol Biochem Behav 56:131–137.

Sklar P, Gabriel SB, McInnis MG, et al. 2002. Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor. Mol Psychiatry 7:579–593.

Sluzewska A, Rybakowski JK, Laciak M, Mackiewicz A, Sobieska M, Wiktorowicz K. 1995. Interleukin-6 serum levels in depressed patients before and after treatment with fluoxetine. Ann NY Acad Sci 762:474–476.

Sluzewska A, Rybakowski J, Bosmans E, et al. 1996. Indicators of immune activation in major depression. Psychiatry Res 64:161–167.

Smith DL Jr. 1978. Mental effects of mercury poisoning. South Med J 71:904–905.

Smith MA, Makino S, Kvetnansky R, Post RM. 1995. Stress and glucocorticoids affect the expression of brain-derived neurotrophic factor and neurotrophin-3 mRNAs in the hippocampus. J Neurosci 15:1768–1777.

Song C, Lin A, Bonaccorso S, et al. 1998. The inflammatory response system and the availability of plasma tryptophan in patients with primary sleep disorders and major depression. J Affect Disord 49:211–219.

Srikantaiah MV, Radhakrishnan AN. 1970. Studies on the metabolism of vitamin B6 in the small intestine. 3. Purification and properties of monkey intestinal pyridoxal kinase. Indian J Biochem 7:151–156.

Stefanovic V, Vlahovic P, Savic V, Ilic S, Mitic-Zlatkovic M. 1998. Kidney ectopeptidases in gentamicin and mercuric chloride-induced acute renal failure. Cell Physiol Biochem 8:278–284.

Stockmeier CA, Dilley GE, Shapiro LA, Overholser JC, Thompson PA, Meltzer HY. 1997. Serotonin receptors in suicide victims with major depression. Neuropsychopharmacology 16:162–173.

Stockmeier CA, Shapiro LA, Dilley GE, Kolli TN, Friedman L, Rajkowska G. 1998. Increase in serotonin-1A autoreceptors in the midbrain of suicide victims with major depression-postmortem evidence for decreased serotonin activity. J Neurosci 18:7394–7401.

Stübner S, Schon T, Padberg F, et al. 1999. Interleukin-6 and the soluble IL-6 receptor are decreased in cerebrospinal fluid of geriatric patients with major depression: no alteration of soluble gp130. Neurosci Lett 259:145–148.

Surtees R, Heales S, Bowron A. 1994. Association of cerebrospinal fluid deficiency of 5-methyltetrahydrofolate, but not S-adenosylmethionine, with reduced concentrations of the acid metabolites of 5-hydroxytryptamine and dopamine. Clin Sci (Lond) 86:697–702.

Sutton S, Braren M, Zubin J, John ER. 1965. Evoked-potential correlates of stimulus uncertainty. Science 150:1187–1188.

Svenningsson P, Chergui K, Rachleff I, et al. 2006. Alterations in 5-HT1B receptor function by p11 in depression-like states. Science 311:77–80.

Sweeney JA, Kmiec JA, Kupfer DJ. 2000. Neuropsychologic impairments in bipolar and unipolar mood disorders on the CANTAB neurocognitive battery. Biol Psychiatry 48:674–684.

Syvalähti E, Eskola J, Ruuskanen O, Laine T. 1985. Nonsuppression of cortisol in depression and immune function. Prog Neuropsychopharmacol Biol Psychiatry 9:413–422.

Tancer ME, Brown TM, Evans DL, et al. 1990. Impaired effortful cognition in depression. Psychiatry Res 31:161–168.

Taylor MJ, Carney SM, Goodwin GM, Geddes JR. 2004. Folate for depressive disorders: systematic review and meta-analysis of randomized controlled trials. J Psychopharmacol 18:251–256.

Tham A, Engelbrektson K, Mathe AA, Johnson L, Olsson E, Aberg-Wistedt A. 1997. Impaired neuropsychological performance in euthymic patients with recurring mood disorders. J Clin Psychiatry 58:26–29.

Thoenen H. 1995. Neurotrophins and neuronal plasticity. Science 270:593–598.

Tiemeier H, van Tuijl HR, Hofman A, Meijer J, Kiliaan AJ, Breteler MM. 2002. Vitamin B12, folate, and homocysteine in depression: the Rotterdam Study. Am J Psychiatry 159:2099–2101.

Tolmunen T, Hintikka J, Ruusunen A, et al. 2004. Dietary folate and the risk of depression in Finnish middle-aged men. A prospective follow-up study. Psychother Psychosom 73:334–339.

Trentani A, Kuipers SD, Ter Horst GJ, Den Boer JA. 2002. Selective chronic stress-induced in vivo ERK1/2 hyperphosphorylation in medial prefrontocortical dendrites: implications for stress-related cortical pathology? Eur J Neurosci 15:1681–1691.

Tsai SJ, Hong CJ, Yu YW, Chen TJ, Wang YC, Lin WK. 2004. Association study of serotonin 1B receptor (A-161T) genetic polymorphism and suicidal behaviors and response to fluoxetine in major depressive disorder. Neuropsychobiology 50:235–238.

Tsai SJ, Hong CJ, Hsu CC, et al. 1999. Serotonin-2A receptor polymorphism (102T/C) in mood disorders. Psychiatry Res 87:233–237.

Turecki G, Sequeira A, Gingras Y, et al. 2003. Suicide and serotonin: study of variation at seven serotonin receptor genes in suicide completers. Am J Med Genet B Neuropsychiatr Genet 118:36–40.

Tyler WJ, Alonso M, Bramham CR, Pozzo-Miller LD. 2002. From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. Learn Mem 9:224–237.

Ullian EM, Sapperstein SK, Christopherson KS, Barres BA. 2001. Control of synapse number by glia. Science 291:657–661.

Urretavizcaya M, Moreno I, Benlloch L, et al. 2003. Auditory event-related potentials in 50 melancholic patients: increased N100, N200 and P300 latencies and diminished P300 amplitude. J Affect Disord 74:293–297.

van der Hart MG, Czeh B, de Biurrun G, et al. 2002. Substance P receptor antagonist and clomipramine prevent stress-induced alterations in cerebral metabolites, cytogenesis in the dentate gyrus and hippocampal volume. Mol Psychiatry 7:933–941.

Villafuerte SM, Del-Favero J, Adolfsson R, et al. 2002. Gene-based SNP genetic association study of the corticotropin-releasing hormone receptor-2 (CRHR2) in major depression. Am J Med Genet 114:222–226.

Vollmayr B, Simonis C, Weber S, Gass P, Henn F. 2003. Reduced cell proliferation in the dentate gyrus is not correlated with the development of learned helplessness. Biol Psychiatry 54:1035–1040.

Walther DJ, Bader M. 2003. A unique central tryptophan hydroxylase isoform. Biochemical Pharmacology 66:1673–1680.

Walther DJ, Peter JU, Bashammakh S, et al. 2003. Synthesis of serotonin by a second tryptophan hydroxylase isoform. Science 299:76.

Wang J, Dunn AJ. 1998. Mouse interleukin-6 stimulates the HPA axis and increases brain tryptophan and serotonin metabolism. Neurochem Int 33:143–154.

Wang J, Dunn AJ. 1999. The role of interleukin-6 in the activation of the hypothalamo-pituitary-adrenocortical axis and brain indoleamines by endotoxin and interleukin-1 beta. Brain Res 815:337–348.

Weiss G, Murr C, Zoller H, et al. 1999. Modulation of neopterin formation and tryptophan degradation by Th1- and Th2-derived cytokines in human monocytic cells. Clin Exp Immunol 116:435–440.

Wilkinson AM, Anderson DN, Abou-Saleh MT, et al. 1994. 5-Methyltetrahydrofolate level in the serum of depressed subjects and its relationship to the outcome of ECT. J Affect Disord 32:163–168.

Willeit M, Praschak-Rieder N, Zill P, et al. 2003. C825T polymorphism in the G protein beta3-subunit gene is associated with seasonal affective disorder. Biol Psychiatry 54:682–686.

Williams AL, Cotter A, Sabina A, Girard C, Goodman J, Katz DL. 2005. The role for vitamin B-6 as treatment for depression: a systematic review. Fam Pract 22:532–537.

Wolfersdorf M, Konig F. 1995. Serum folic acid and vitamin B12 in depressed inpatients. A study of serum folic acid with radioimmunoassay in 121 depressed inpatients]. Psychiatr Prax 22:162–164.

Wolfersdorf M, Keller F, Maier V, Froscher W, Kaschka WP. 1995. Red-cell and serum folate levels in depressed inpatients who commit violent suicide: a comparison with control groups. Pharmacopsychiatry 28:77–79.

Wolters M, Strohle A, Hahn A. 2004. Age-associated changes in the metabolism of vitamin B(12) and folic acid: prevalence, aetiopathogenesis and pathophysiological consequences]. Z Gerontol Geriatr 37:109–135.

Wu J, Buchsbaum MS, Gillin JC, et al. 1999. Prediction of antidepressant effects of sleep deprivation by metabolic rates in the ventral anterior cingulate and medial prefrontal cortex. Am J Psychiatry 156:1149–1158.

Yamada S, Yamamoto M, Ozawa H, Riederer P, Saito T. 2003. Reduced phosphorylation of cyclic AMP-responsive element binding protein in the postmortem orbitofrontal cortex of patients with major depressive disorder. J Neural Transm 110:671–680.

Young SN. 1993. The use of diet and dietary components in the study of factors controlling affect in humans: a review. J Psychiatry Neurosci 18:235–244.

Yu YW, Chen TJ, Wang YC, Liou YJ, Hong CJ, Tsai SJ. 2003. Association analysis for neuronal nitric oxide synthase gene polymorphism with major depression and fluoxetine response. Neuropsychobiology 47:137–140.

Zhang HY, Ishigaki T, Tani K, et al. 1997. Serotonin2A receptor gene polymorphism in mood disorders. Biol Psychiatry 41:768–773.

Zhou D, Kusnecov AW, Shurin MR, DePaoli M, Rabin BS. 1993. Exposure to physical and psychological stressors elevates plasma interleukin 6: relationship to the activation of hypothalamic-pituitary-adrenal axis. Endocrinology 133:2523–2530.

Zill P, Baghai TC, Zwanzger P, et al. 2000. Evidence for an association between a G-protein beta3-gene variant with depression and response to antidepressant treatment. Neuroreport 11:1893–1897.

Zubenko GS, Hughes HB 3rd, Stiffler JS, et al. 2003. Sequence variations in CREB1 cosegregate with depressive disorders in women. Mol Psychiatry 8:611–618.