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Metabolism Clinical and Experimental 54 (Suppl 1) (2005) 33–38

Metabolism
Clinical and Experimental

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Depression, cytokines, and glial function

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Abstract

It has been known for some time that cytokines made and released during systemic illness can result in a constellation of symptoms strikingly similar to those observed in depression. The overlap of the symptoms of depression and systemic illness raises the intriguing possibility that cytokines may be involved in the development and maintenance of mood disorders. Cytokines are small ubiquitous pleiotropic molecules that are made and released in response to a variety of stimuli. They have a multitude of actions throughout the body, including actions on the central and peripheral nervous systems. Alterations in the levels of circulating cytokines, especially the key proinflammatory cytokines, interleukin 6 and tumor necrosis factor α, have been linked to a variety of disease states including those involving central nervous system depression. In this brief review, epidemiological and clinical data on depression, as well as findings from relevant animal models, are examined for links between cytokine expression and depression. We suggest that glial cells, both as a source and target of cytokines, represent the overlooked targets involved in the etiology of depression.

1. Introduction

Winston Churchill's [1] lifelong battle with his metaphoric "black dog" eloquently describes the misery of depression. The multifaceted negative symptoms of depression include feelings of abject sadness, loss in all things pleasurable, feelings of hopelessness, worthlessness, dejection, and fatigue, problems in concentration, memory, sleep and appetite, and often suicidal thoughts or actions. The persistent presence of these symptoms for several weeks can denote clinical depression also referred to as major depressive disorder (MDD) [2]. Major depressive disorder is a lifelong disorder affecting as many as 21% of the general population [3]. Both genetic and environmental factors appear to be important. Having a close family member with the disease increases one's risk, and an emotional or stressful event can serve as a trigger for onset or relapse [4-7]. Major depressive disorder is 1 of the 5 leading causes of disability throughout the world and it also is associated with increased mortality [8]. This disease presents a great cost to the individual, to the family, and to society at large, accounting for 4.4% of the global disease burden with an estimated loss of 65 million disability-adjusted life years [9]. The sheer enormity of this public health issue suggests that a clearer understanding of the genesis of this disease would greatly benefit society as well as the individual sufferer.

Modern medicine has come a long way from Galen's belief that melancholic personality is caused by an excess of black bile [10]. Depression is now recognized as a brain disease; it can be managed and treated effectively with a wide range of options, but its biological basis is still far from clear. Thus, although several classes of antidepressant drugs are available, at least 30% of patients are resistant and do not show complete remission. Patients resistant to pharmacotherapy have the recourse of turning to more controversial but effective treatments such as electroconvulsive therapy [11]. Exercise, specific diets, transcranial magnetic stimulation, and vagus nerve stimulation also have been shown to be at least partially effective [12-14]. Although attempts at biochemical characterization of depression have been extensive, its diagnosis is still largely symptom based; definitive biochemical markers or neuroanatomical or neuropathological hallmarks of this condition are not yet available. The reliance on a symptom-based approach to diagnosis also has engendered and sustained the use of animal models of depression for the strategic development

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doi:10.1016/j.metabol.2005.01.011

of antidepressant drugs. Initially, animal models attempted to recapitulate the entire syndrome of depression, but more recent efforts have been directed to those modeling one or a limited number of the symptoms of the disorder. Obviously, symptoms like feelings of worthlessness, suicidal ideation, or preoccupation with death are uniquely human, and as such, they are not likely to be modeled successfully in animals. Despite such limitations, the widely used animal models, such as the forced swim test and its modifications, are able to detect antidepressant action. These tests likely will be further refined in light of the advances in the development of genetically altered rodents. Such refinements ensure that animal models will continue to play a crucial role in the preclinical selection of compounds for further development [3].

2. The symptoms of depression, "sickness behavior," and cytokines

The extensive focus on symptoms of depression and the search for its cause(s) also have prompted an interest in examining other conditions that elicit these same symptoms. For example, symptoms of depression can accompany excessive exercise or overtraining [15]. Striking similarities also have been noted between the behaviors displayed during infectious illness, referred to as sickness behavior, and those apparent in MDD [16]. Sickness behavior, first investigated several decades ago by Neal Miller [17], has been found in all organisms studied to date and is considered a normal response, rather than a debilitated state, that allows an organism to cope with infection in a regulated fashion. The similarities between sickness behavior, namely lethargy, somnolence and fatigue, lack of interest in the surroundings, lack of appetite and anorexia, problems with concentration, et cetera, and the more vegetative symptoms of MDD, suggest a link between the immune system and depression.

It is now widely recognized that bidirectional communication exists between the immune and nervous systems via a cytokine-based signaling network. Cytokines are polypeptide messengers that coordinate complex immune responses often termed *proinflammatory* in nature, although some of them can have antiinflammatory actions [18]. Dysregulated cytokine signaling can result in debilitating immune-related disease states such as rheumatoid arthritis. In the case of the central nervous system (CNS), cytokines have been implicated in neuroinflammatory diseases (eg, multiple sclerosis) as well, but more complex roles in physiological interactions between neurons and glia are just now being appreciated [19,20]. Although cytokines have difficulty entering the brain, it is now known that there are several routes of communication: (1) passive entry in areas where the blood-brain barrier is not intact, (2) active transport, and (3) binding to cytokine receptors on peripheral afferents (eg, vagus nerve) [21]. The discovery of cytokine receptors on neurons and glia was suggestive of a role for these systemic messengers in communicating information from the periphery (eg, the onset of infections) to the CNS. The more recent observation that brain cells themselves can synthesize cytokines [22] suggested even more complex roles for these diverse groups of peptide messengers. Indeed, the involvement of cytokines in "cross talk" between glia and neurons in compromised or injured states implicates cytokines in a much broader communication role within the brain than was first suspected [23].

Several sets of observations support the supposition that cytokines, and proinflammatory cytokines in particular, are involved in MDD [16,24-32]. First, as noted above, there is an overlap between certain symptoms of MDD and those occurring in a variety of other conditions shown to involve proinflammatory cytokines, including infectious disease, allergies, excessive athletic training, and autoimmune inflammatory diseases like multiple sclerosis [33]. Second, exposing human beings or experimental animals to proinflammatory cytokines such as interleukin 1 (IL-1), IL-6, tumor necrosis factor α (TNF-α), or interferon γ (IFN-γ), or stimulating their production by treatment with endotoxin, will induce sickness behavior [22,33]. IFN-α and IL-2 are potent immunostimulators and have antiviral actions, partly because they can induce the production of proinflammatory cytokines. In their recombinant forms, they are used clinically to treat hepatitis C and various cancers (eg, melanoma) [26,34]. Importantly, cytokine therapy often has to be discontinued because of the incidence of depression as an adverse effect. For example, 50% of those receiving IFN-α are sufficiently symptomatic to be diagnosed with major depression [25]. The depression induced by these cytokines resolves when treatment is terminated. Third, depression sufferers have elevated blood levels of proinflammatory cytokines, and increases, albeit not consistent ones, in IL-1, IL-6, and TNF-α all have been reported [16,25,35]. The relationship between cytokines and depression is, however, more striking in the medically ill, where inflammation is more likely to occur than in the medically healthy. A more consistent finding in depressed individuals is an elevation of acute phase reactants (haptoglobin, C-reactive protein, etc), proteins manufactured by the liver in response to proinflammatory cytokines [18,25]. Finally, antidepressant treatments, including electroconvulsive therapy, effectively reduce the elevated levels of proinflammatory cytokines in MDD patients [26,36]. Prophylactic treatment with an antidepressant also is able to prevent the depressive episodes in those receiving recombinant cytokines for cancer or other diseases [26,33].

All of the above observations are consistent with the view that the cytokine network can be activated during MDD. There is no general agreement, however, regarding the role cytokines may play in the pathophysiology of depression [18,28]. Thus, although it is clear that strong evidence exists to associate cytokines with symptoms of depression, a causal link cannot be attributed to any specific aspect of cytokine signaling and the development or maintenance of clinical depression.

3. Regional and cellular aspects of depression

Depression often is referred to as a neurochemical disease because the effective antidepressant drugs have potent actions on monoamine neurotransmitter systems [37,38]. The monoamine theory of depression has led to a concerted effort to characterize extensively the disease- and treatment-associated changes in monoamine levels, and monoamine receptor-related interactions, in an effort to understand the etiology of mood disorders. The clinically effective antidepressant agents, including the selective serotonin reuptake inhibitors, tricyclics, and monoamine oxidase inhibitors, have immediate and potent monoaminergic effects. Nevertheless, their clinical effectiveness usually requires a number of weeks of treatment, suggesting that alterations in monoamine function cannot constitute the central mechanism underlying the therapeutic action of these compounds. Recent experimental work has raised the possibility that depression is a disease of diminished neurogenesis and that effective antidepressant treatments enhance this structural remodeling, but a number of questions have been raised about the viability of this hypothesis [6,38-40].

Characteristic molecular and cellular changes, such as those found in Alzheimer's and Parkinson's diseases (eg, neurofibrillary tangles, amyloid plaques, synuclein inclusions), not only provide hallmarks for diagnosis but also provide useful avenues to pursue in searching for the causes of these disorders. Unfortunately, MDD is not accompanied by such striking molecular or cellular signatures. Despite this handicap, recent structural neuroimaging studies of depressed patients, as well postmortem evaluations, have directed attention to the presence of more subtle neuropathological abnormalities in a specific neuroanatomical circuit, the limbic-cortical-striatal-pallidal-thalamic (LCSPCT) tract. Altered metabolism and blood flow, volume reductions, as well as the loss of neurons and glia have been found in various structures of this highly interconnected circuit [41-49]. For example, positron emission tomography imaging of MDD patients has repeatedly demonstrated altered brain flow and metabolism in cortical, limbic-paralimbic, and subcortical areas, with consistent resolution of these abnormalities in prefrontal and anterior cingulate by varied treatments [50,51]. As noted by Sheline [44], many magnetic resonance imaging studies also have revealed volume changes in structures of the LCSPCT tract, including the frontal cortex, hippocampus, amygdala, and basal ganglia of depressed individuals. For certain areas, like the hippocampus, the degree of volume loss is directly related to the lifetime duration of depression, and effective treatment can protect against this decline [44]. Magnetic resonance imaging studies find both increases and decreases in amygdala volume in MDD, but long disease duration appears related to a reduction whereas an increased volume is more apparent in the early stages [46,52]. Rather than an outright reduction in number, neuronal changes, when found, involve neuronal shrinkage or enlargement (although some synaptic pathology has been noted as well) [53]. Whether any of these decrements reflect actual loss of neuropil, or in contrast, are indicative of compromised development has not been determined [54].

4. Is depression a glial disorder?

The region-specific changes in brain volume found to be associated with clinical depression fostered a more detailed examination of specific cytoarchitectural alterations, using postmortem tissue obtained from individuals diagnosed with MDD. The consensus emerging from these comprehensive neuroanatomical examinations is surprising. Although neuronal changes are reported, glial abnormalities are a much more apparent and consistent characteristic of MDD [43,48,54,55]. In contrast to the neuronal findings in MDD, striking and consistent decreases in the density and number of glial cells in frontal cortex have been independently reported by a number of laboratories [41,48,55]. In familial cases of MDD, the loss of glial numbers was as great as 24% [43]. Reduced glial numbers are found in amygdala as well [56]. In some instances, the decrease in glial number was accompanied by an increase in the size of the nuclei of the remaining glia and may reflect a compensatory response to an increased demand [54]. Although the results of these studies define *glia* as potential neural substrates underlying depression, the subtype(s) of glia involved remain to be determined.

In the CNS, the glial population consists of oligodendroglia, astrocytes, and microglia. Together, glia, by far, constitute the greatest percentage of all cells in the CNS, outnumbering neurons by at least 5 to 1 [41]. Although the functional roles for individual glial cell types have hardly been as well defined as any given type of neuron, glia-specific markers long have been available to differentiate glial changes associated with a variety of disease states [57]. Such markers have been used to examine glial alterations associated with depression. One prominent example is glial fibrillary acidic protein (GFAP), the major protein component of the astrocyte cytoskeleton. Increases in GFAP, and the attendant astrocytic hypertrophy, reflect the widely recognized response of astrocytes to all types of injury, often referred to as gliosis or astrogliosis. Decreases in GFAP, although rare in occurrence, can be used as an indicator of decreased astrocytic volume or number. Immunostaining for GFAP in brain tissue prepared from depressed individuals has not revealed evidence for astrogliosis (ie, increases in GFAP), findings that appear to confirm the lack of significant neural degeneration in this disorder [58-60]. Indeed, proteomic analysis of brain tissue obtained from individuals with MDD revealed reductions in several isoforms of GFAP in prefrontal cortex [61]. Moreover, GFAP levels in prefrontal cortex

determined by immunoblot analysis also were lower in those with MDD than age-matched controls, and these decreases were more prominent in younger depressives [60]. These decreases in GFAP are consistent with previous observations (see previous sections) of decreased glial number/volume associated with depression. Nevertheless, these results, which focus largely on a single marker associated with astrocytes, may tell only a part of the story. The recent results from a genomewide survey of transcriptional profiles in temporal cortex from patients with MDD show a remarkable constellation of gene expression decreases associated with oligodendroglial-related genes [62]. This comprehensive profile of decrements related to oligodendroglia is similar to the results of transcript profiling studies in schizophrenia and bipolar disorder, findings suggestive of an involvement of oligodendroglia in these complex depressive disorders [57,63,64]. Together, these findings point to the potential key role astrocytes, and perhaps more importantly, oligodendroglia, may play in the etiology of depression.

5. Depression, glia, and cytokines

We have presented the case for the association of cytokines with sickness behavior and depression and have briefly reviewed the evidence for a role of glia in depression. Can the case be made for a link among cytokines, glia, and depression? With the limited amount of data available, the question remains open, but avenues of investigation have emerged based on the results of recent studies. A glial-cytokine relationship needs no defense. An action of cytokines on glia or an elaboration of cytokines from glia has been established for years based on both in vivo and in vitro test systems. Both beneficial and detrimental aspects of cytokine and glial relationships have been documented. One widely held view suggests that proinflammatory cytokines activate astrocytes and lead to gliosis, a reaction that can be viewed as either trophic or degenerative [65,66]. As depression is associated with peripheral elevations in cytokines, this might be expected to result in astrogliosis as a consequence of systemic-CNS cytokine signaling. The lack of gliosis in depression would seem to argue against this reasoning. The fact remains, however, that animal models of sickness behavior and depression (eg, administration of lipopolysaccharide), which result in systemic and central elevations in cytokines, do not exhibit astrogliosis [67]. The function of CNS elevations in cytokines under these conditions has yet to be defined. One possibility that remains, and that is consistent with a role of cytokines in depression, is a detrimental action of cytokines on oligodendroglia. A number of cytokines have a suppressive or cytotoxic effect on oligodendroglia [66]. Key among these are members of the TNF-α and IL-2 superfamilies, cytokines elevated systemically in depression that also are increased systemically and centrally in animal models of sickness behavior and depression. Although research on cytokine expression in the CNS remains focused on a role in astrogliosis and neurodegenerative conditions, attention needs to be directed toward characterizing the effects of chronic elevations of these key signaling molecules in disease conditions where gliosis is not a feature, such as depression.

6. Summary

In the preceding analysis, we have highlighted the potential role of cytokines and glia in depression. Given the complexity of this disorder and the diverse array of at least partially effective therapies, it seems likely that a variety of cell-cell signaling events may underlie the depressed condition. Clues to the etiology of depression have emerged from genomic and proteomic profiling studies. The results of such studies need to be broadly verified and extended if we are to determine the biological basis of depression with the ultimate goal of developing effective treatments.

References

[1] Storr A. Churchill's black dog, Kafka's mice, and other phenomena of the human mind. New York (NY): Ballantine Books; 1990.
[2] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington (DC): American Psychiatric Association; 1994.
[3] Cryan JF, Markou A, Lucki I. Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol Sci 2002;23:238-45.
[4] Caspi A, Sugen K, Moffitt TE, et al. Influence of life stress on depression; moderation by a polymorphism in the 5-HTT gene. Science 2003;301:386-9.
[5] Kendler KS, Thornton LM, Gardner CO. Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. Am J Psychiatry 2001;158:582-6.
[6] McEwen BS. Glucocorticoids, depression and mood disorders: structural remodeling in the brain. Metabolism 2005;54(Suppl):20-3.
[7] Hamet P, Tremblay J. Genetics of depression. Metabolism 2005.
[8] Penninx BWJH, Geerlings SW, Deeg DJH, et al. Minor and major depression and the risk of death in older persons. Arch Gen Psychiatry 1999;56:889-95.
[9] Chisholm D, Sanderson K, Ayuso-Mateos JL, et al. Reducing the global burden of depression: population-level analysis of intervention cost-effectiveness in 14 world regions. Br J Psychiatry 2004; 184:393-401.
[10] Jackson S. Galen—on mental disorders. J Hist Behav Sci 1969;5: 365-84.
[11] Paus T, Barrett J. Transcranial magnetic stimulation (TMS) of the human frontal cortex: implications for repetitive TMS treatment of depression. J Psychiatry Neurosci 2004;29:268-79.
[12] Maes M, Smith RS. Fatty acids, cytokines, and major depression. Biol Psychiatry 1998;43:313-4.
[13] Marangell LB, Rush AJ, George MS, et al. Vagus nerve stimulation (VNS) for major depressive episodes: longer-term outcome. Biol Psychiatry 2002;51:280-7.
[14] Tiemeier H, Ruud van Tuijl HR, Hofman A, et al. Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam Study. Am J Clin Nutr 2003;78:40-6.
[15] Smith LL. Cytokine hypothesis of overtraining: a physiological adaptation to excessive stress? Med Sci Sports Exerc 2000;32:317-31.

[16] Maes M. Evidence for an immune response in major depression: a review and hypothesis. Prog Neuropsychopharmacol Biol Psychiatry 1995;19:11-38.
[17] Miller NE. Some psychophysiological studies of motivation and of the behavioural effects of illness. Bull Br Psychol Soc 1964;17:1-21.
[18] Kronfol Z, Remick DG. Cytokines and the brain: implications for clinical psychiatry. Am J Psychiatry 2000;157:683-94.
[19] Newman EA, Volterr A. Glial control of synaptic function. Glia 2004;47:207-8.
[20] Rose CR, Blum R, Pichler B. Truncated TrkB-T1 mediates neurotrophin-evoked calcium signaling in glia cells. Nature 2003;426:74-8.
[21] Miller AH. Cytokines and sickness behavior: implications for cancer care and control. Brain Behav Immun 2003;17:S132-4.
[22] Kelley KW, Bluthe R-M, Dantzer R, et al. Cytokine-induced sickness behavior. Brain Behav Immun 2003;17:S112-8.
[23] Sriram K, Benkovic SA, Hebert MA, et al. Induction of gp130-related cytokines and activation of JAK2/STAT3 pathway in astrocytes precedes up-regulation of glial fibrillary acidic protein in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of neurodegeneration. J Biol Chem 2004;279:19936-47.
[24] Anisman H, Merali Z. Cytokines, stress and depressive illness: brain-immune interactions. Ann Med 2003;35:2-11.
[25] Capuron L, Miller AH. Cytokines and psychopathology: lessons from interferon-α. Biol Psychiatry 2004;56:819-24.
[26] Capuron L, Hauser P, Hinze-Selch D, et al. Treatment of cytokine-induced depression. Brain Behav Immun 2002;16:575-80.
[27] Dantzer R, Wollman EE, Yirmiya R. Cytokines, stress, and depression. New York (NY): Plenum, Kluwer Academic; 1999.
[28] De Beaurepaire R. Questions raised by the cytokine hypothesis of depression. Brain Behav Immun 2002;16:610-7.
[29] Maes M. Major depression and activation of the inflammatory response system. Adv Exp Med Biol 1999;461:25-46.
[30] Maes M. The depressogenic effects of cytokines: implications for the psychological and organic aetiology and treatment of depression. Int J Neuropsychopharmacol 2002;5:375-88.
[31] Smith RS. The macrophage theory of depression. Med Hypotheses 1991;35:298-306.
[32] Wichers M, Maes M. The psychoneuroimmuno-pathophysiology of cytokine-induced depression in humans. Int J Neuropsychopharmacol 2002;5:375-88.
[33] Pollak Y, Orion E, Goshen I, et al. Experimental autoimmune encephalomyelitis-associated behavioral syndrome as a model of 'depression due to multiple sclerosis'. Brain Behav Immun 2002;16:533-43.
[34] Capuron L, Dantzer R. Cytokines and depression: the need for a new paradigm. Brain Behav Immun 2003;17:S119-24.
[35] Hestad KA, Tonseth S, Stoen CD, et al. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. J ECT 2003;19:183-8.
[36] Castanon N, Leonard BE, Neveu PJ, et al. Effects of antidepressants on cytokine production and actions. Brain Behav Immun 2002;16:569-74.
[37] Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. Biol Psychiatry 2000;48:740-54.
[38] Sapolsky RM. Is impaired neurogenesis relevant to the affective symptoms of depression? Biol Psychiatry 2004;56:137-9.
[39] D'Sa C, Duman RS. Antidepressants and neuroplasticity. Bipolar Disord 2002;4:183-94.
[40] Sapolsky RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. Biol Psychiatry 2000;48:755-65.
[41] Cotter D, Mackay D, Landau S, et al. Reduced glial cell density and neuronal size in the anterior cingulated cortex in major depressive disorder. Arch Gen Psychiatry 2001;58:545-53.
[42] Cotter DR, Pariante CM, Everall IP. Glial cell abnormalities in major psychiatric disorders: the evidence and implications. Brain Res Bull 2001;55:585-95.
[43] Rajkowska G. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biol Psychiatry 2000;48:766-77.
[44] Sheline YI. Neuroimaging studies of mood disorder effects on the brain. Biol Psychiatry 2003;54:338-52.
[45] Sheline Y, Wany P, Gado M, et al. Hippocampal atrophy in recurrent major depression. Proc Natl Acad Sci U S A 1996;93:3908-13.
[46] Sheline YI, Gado MH, Price JL. Amygdala core nuclei volumes are decreased in recurrent major depression. Neuroreport 1998;9:2023-8.
[47] Sheline YI, Gado MH, Kraemer HC. Untreated depression and hippocampal volume loss. Am J Psychiatry 2003;160:1516-8.
[48] Stockmeier CA, Rajkowska G. Cellular abnormalities in depression: evidence from postmortem brain tissue. Dialogues Clin Neurosci 2004;6:185-97.
[49] Vythilingam M, Vermetten E, Anderson GM, et al. Hippocampal volume, memory, and cortisol status in major depressive disorder: effects of treatment. Biol Psychiatry 2004;56:101-12.
[50] Liotti M, Mayberg HS, McGinnis S, et al. Unmasking disease-specific cerebral blood flow abnormalities: mood challenge in patients with remitted unipolar depression. Am J Psychiatry 2002;159(11):1830-40.
[51] Mayberg HS, Silva JA, Brannan SK, et al. The functional neuroanatomy of the placebo effect. Am J Psychiatry 2002;159:728-37.
[52] Frodl T, Meisenzahl E, Zetzsche T, et al. Enlargement of the amygdala in patients with a first episode of major depression. Biol Psychiatry 2002;51:708-14.
[53] Eastwood SL, Harrison PJ. Synaptic pathology in the anterior cingulated cortex in schizophrenia and mood disorders. A review and a Western blot study of synaptophysin. GAP-43 and the complexins. Brain Res Bull 2001;55:569-78.
[54] Rajkowska G, Miguel-Hidalgo JJ, Wei J, et al. Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. Biol Psychiatry 1999;45:1085-98.
[55] Ongur D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci U S A 1998;95:13290-5.
[56] Bowley MP, Drevets WC, Ongur D, Price JL. Low glial numbers in the amygdala in major depressive disorder. Biol Psychiatry 2002;52:404-12.
[57] Coyle JT, Schwarcz R. Mind glue: implications of glial cell biology for psychiatry. Arch Gen Psychiatry 2000;57:90-3.
[58] Damadzic R, Bigelow LB, Krimer LS, et al. A quantitative immunohistochemical study of astrocytes in the entorhinal cortex in schizophrenia, bipolar disorder and major depression: absence of significant astrocytosis. Brain Res Bull 2001;55:611-8.
[59] Miguel-Hidalgo JJ, Baucom C, Dilley G, et al. Glial fibrillary acidic protein immunoreactivity in the prefrontal cortex distinguishes younger from older adults in major depressive disorder. Biol Psychiatry 2000;48:861-73.
[60] Si X, Miguel-Hidalgo JJ, O'Dwyer G, et al. Age-dependent reductions in the level of glial fibrillary acidic protein in the prefrontal cortex in major depression. Neuropsychopharmacol 2004 [advance online publication 7 July].
[61] Johnston-Wilson NL, Sims CD, Hofmann JP, et al. Disease-specific alterations in frontal cortex brain proteins in schizophrenia, bipolar disorder, and major depressive disorder. The Stanley Neuropathology Consortium. Mol Psychiatry 2000;5:142-9.
[62] Aston C, Jiang L, Sokolov BP. Transcriptional profiling reveals evidence for signaling and oligodendroglial abnormalities in the temporal cortex from patients with major depressive disorder. Mol Psychiatry 2004 [advance online publication, 10 August].

[63] Hakak Y, Walker JR, Li C, et al. Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia. Proc Natl Acad Sci U S A 2001;98:4746-51.
[64] Tkachev D, Mimmack ML, Ryan MM. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet 2003;362:798-805.
[65] Faulkner JR, Herrmann JE, Woo MJ, et al. Reactive astrocytes protect tissue and preserve function after spinal cord injury. J Neurosci 2004;24:2143-55.
[66] St Pierre BA, Merrill JE, Dopp JM. Effects of cytokines on CNS cells: glia. In: Ransohoff RM, Benveniste EN, editors. Cytokines and the CNS. Boca Raton (Fla): CRC Press, Inc; 1996. p. 152-68.
[67] Little AR, Benkovic SA, Miller DB, et al. Chemically-induced neuronal damage and gliosis: Enhanced expression of the proinflammatory chemokine, monocyte chemoattractant protein (MCP)-1, without a corresponding increase in proinflammatory cytokines. Neurosci 2002;115:307-20.