Review
http://dx.doi.org/10.9758/cpn.2013.11.3.107
Clinical Psychopharmacology and Neuroscience 2013;11(3):107-117
pISSN 1738-1088 / eISSN 2093-4327

The Neuroimmunology of Schizophrenia

Annya M. Smyth, Stephen M. Lawrie
Department of Psychiatry, Royal Edinburgh Hospital, University of Edinburgh, Edinburgh, United Kingdom

Schizophrenia (SCZ) is a polygenic, multi-factorial disorder and a definitive understanding of its pathophysiology has been lacking since it was first described more than a century ago. The predominant pharmacological approach used to treat SCZ is the use of dopamine receptor antagonists. The fact that many patients remain symptomatic, despite complying with medication regimens, emphasises the need for a more encompassing explanation for both the causes and treatment of SCZ. Recent neuroanatomical, neurobiological, environmental and genetic studies have revived the idea that inflammatory pathways are involved in the pathogenesis of SCZ. These new insights have emerged from multiple lines of evidence, including the levels of inflammatory proteins in the central nervous system of patients with SCZ and animal models. This review focuses on aberrant inflammatory mechanisms present both before and during the onset of the psychotic symptoms that characterise SCZ and discusses recent research into adjunctive immune system modulating therapies for its more effective treatment.

KEY WORDS: Schizophrenia; Inflammation; Immune based therapies.

INTRODUCTION

Schizophrenia (SCZ) is a severe psychotic disorder affecting approximately 1% of the adult population worldwide over the average lifetime.[1,2] This debilitating illness is characterised by the presence of delusions and hallucinations (positive symptoms), social withdrawal and loss of motivation (negative symptoms) and cognitive deficits.[3] Historically thought of as a culmination of 'a number of conditions which may lead to a severe disturbance of the ego',[4] SCZ is now understood to arise from a complex interplay of genetic and environmental risk factors acting across many stages of brain development.[5-11] Several neurochemical and neuropathological theories have been proposed to explain the pathological processes intrinsic to SCZ, including impairments in dopaminergic,[12] glutamatergic[13,14] and GABAergic signalling,[15,16] impaired prefrontal cortex function,[17-19] aberrant neurodevelopment,[11,20] stress vulnerability[21] and variations in the inflammatory response.[22,23]

Considering the sheer number of physiological systems implicated in the development of SCZ, it is perhaps unsurprising that decades of intense scientific and clinical investigation have only partially resolved the complex mechanisms driving the disease process. Recently, attention has increasingly focussed on the impact of a dysregulated inflammatory system on downstream cellular and molecular pathways previously implicated in the pathogenesis of SCZ.[24-26] This review article focuses on the increasingly popular role of various inflammatory mediators and how a more comprehensive understanding of their contribution could improve both our understanding and treatment of SCZ.

Received: November 8, 2013 / Revised: November 22, 2013
Accepted: November 25, 2013
Address for correspondence: Stephen M. Lawrie, MD
Department of Psychiatry, Royal Edinburgh Hospital, University of Edinburgh, Edinburgh EH10 5HF, United Kingdom
Tel: +44-131-537-6220, Fax: +44-131-537-6802
E-mail: S.Lawrie@ed.ac.uk

MAIN SUBJECTS

Inflammation and the central nervous system (CNS)

A connection between inflammatory factors and the development of 'mental maladies' was first voiced by Esquirol upon the epidemic appearance of psychiatric disorders in 1845.[23] Since then, a steady stream of patients have been described displaying symptoms suggestive of acute SCZ but also presented with, or later developed, the clinical hallmarks of multisystem encephalitis.[27-32] Following the publication of a number of experimental studies over the last three decades, interest in activated inflammatory processes in SCZ has once again gained momentum.[24-26,33-37] Inflammation is a complex homeo-

Table 1. Key research questions

- How specific are cytokine alterations to schizophrenia?
- When do immunological changes occur and how do they correlate to the clinical course of schizophrenia?
- Can certain immune factors act as markers for relapse?
- Should anti-inflammatory augmentation therapies be introduced into normal clinical practice?

static cellular response designed to protect an organism from a potentially harmful environmental stimuli, such as infection.[38,39] Immunomodulatory mechanisms regulating the type, extent and outcome of any inflammatory response exist both in the periphery and CNS and involves either the up- or down-regulation of pro- and/or anti-inflammatory cytokines and their receptors.[38] Cytokines are a super-family of low-molecular weight proteins secreted by a variety of cell types and have wide-ranging functions within the innate and adaptive inflammatory response.[40,41] Cytokines are capable of penetrating the blood-brain barrier (BBB) to permit cross-talk between the CNS and immune system[42] in order to regulate neuronal migration, synaptic maturation and dopaminergic and GABAergic neuronal differentiation.[43-46] However, when the balance of these inflammatory mediators is disrupted, cytokines can induce neuronal inflammation, damage and degeneration, thus implicating them in several neuropsychiatric disorders.[47-49]

Immune System Genetics and SCZ

SCZ is highly heritable, making genetic predisposition the most sought after risk factor for its development. As with a number of common diseases however, the inheritance pattern is complex, the penetrance of all but a small number of genes is low and a reliable biological marker is lacking. Recent, suitably large genome-wide association studies identified seven significant loci in SCZ, with the strongest association in the extended major histocompatibility complex region (MHC) on chromosome 6.[50] Earlier meta-analytic studies have also documented significant associations between sequence variants previously linked to SCZ with the MHC,[51-53] making MHC genes one of the most replicated genetic risk factors for the disorder. The MHC encodes more than 200 genes, many of which have essential roles for both CNS and immune function.[54] This region of chromosome 6 has also been linked with an increased risk of autoimmune disorders,[55,56] some of which have been associated with as much as a 45% increased risk of developing SCZ.[34] Furthermore, a recent study identified 144 differentially expressed genes related to immune response and inflammation in the hippocampus of patients with SCZ,[57] providing additional evidence that abnormal inflammatory responses underlie the pathophysiology of SCZ.

Single nucleotide polymorphism (SNP) based genome-wide association studies have implicated a number of genes of the immune system and their respective underlying biological pathways in psychiatric disorders.[52,58] Linkage studies have identified a SNP in the interferon γ gene, a gene involved in regulating both the innate and adaptive immune response, and recently associated it with a 2 fold higher risk of paranoid SCZ.[59] Differences in allele frequencies of interleukin (IL)12[60] and IL10[61] gene promoter variants and IL1 gene expression[62] have been found between patients with SCZ and healthy controls. Genetic studies have also found that the IL1B gene may increase the risk for SCZ[63-65] and two immune response genes; colony-stimulating factor receptor-α (CSF1R-α) and IL-3-α have also been linked to SCZ.[66-68] Significant upregulation of inflammatory markers IL-6, IL-8 and IL-β were found in the dorsolateral prefrontal cortex (DLPFC) of individuals with SCZ.[69] Future work must focus on directly examining the additive effects of these specific immune-related SNPs as the genetic contribution and mechanisms remain far from clear.

Inflammatory Cytokine Alterations and SCZ

Two recent meta-analyses of over 100 studies provide *in vivo* evidence that SCZ can be, in part, explained by an inflammatory imbalance[25,70] Potvin *et al*.[25] found an increase in IL-1 receptor antagonist (IL-1RA), soluble IL-2 receptor (sIL-2R) and IL-6 in either the plasma or serum of patients with SCZ, regardless of clinical presentation. Conversely, Miller *et al*.[70] found that cytokine alterations in SCZ vary with clinical status, potentially labelling specific cytokines as either 'state' or 'trait' markers. IL-1β, IL-6, and transforming growth factor-β (TGF-β) were found to be elevated in first episode and acutely exacerbated patients and normalised with medication whereas IL-12, interferon gamma (IFNG), TNF, and sIL-2R levels remained elevated following antipsychotic treatment in acutely relapsed patients.[70] These disparate findings could reflect varying patient groups, medication effects or major 'pro-inflammatory' confounds such as smoking, diet, stress and obesity, previously shown to significantly impact on the immune system.[71-75] Considering the inflammatory impact of lifestyle, medication and environmental variables, along with the added complication of other immune-mediated comorbidities,[26,76] it is therefore

essential to determine how inflammation specially operates within the confines of SCZ.

Imaging Neuronal Inflammation and SCZ

Dilatation of the lateral ventricles in the brains of people with SCZ was first documented in the landmark study of Johnstone *et al*.[77] Following this revelation more sophisticated neuroimaging studies using techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) consistently showed abnormalities in several brain structures in SCZ.[78-83] It has been repeatedly shown that a population at high risk of developing SCZ display structural brain abnormalities and deficits in a number of schizotypal features that precede the onset of psychosis, for example, social withdrawal, anxiety and executive function.[84-90] These studies therefore exclude the possibility that structural and functional variations are merely a result of chronic illness or treatment.[91] It has also been shown that patients with a diagnosis of SCZ and previously exposed to high levels of IL-8 *in utero* have significant increases in their ventricular cerebrospinal fluid (CSF) and decreases in left entorhinal cortex and right posterior cingulate volumes, structural modifications that have been highly reproducible in SCZ research.[92]

Functional neuroimaging has also been employed to investigate whether systemic inflammation alters neural activity associated with SCZ and other psychiatric disorders. Recent genome-wide linkage studies have started to pinpoint a number of common genetic denominators upstream of neurotransmitter release.[93] For example, *NRG1*, encoding neuregulin 1, is involved in nervous system development and plasticity[94] and has been associated with decreased activation of frontal and temporal lobe regions, increased development of psychotic symptoms and decreased premorbid IQ.[95] The onset of SCZ has also been shown to be partly associated with polymorphisms in *NRG1* and their interactions with variants of IL-1 β.[96] A recent functional imaging study demonstrated that genetic variability at a particular locus of the IL-1 β gene correlates with differential neuronal activation in the bilateral frontal region of patients with SCZ.[97] PET imaging has also revealed that a functional polymorphism of the IL-1 β gene is associated with decreased neuronal activity in the left DLPFC of SCZ patients during an attention task.[98] These findings suggest that the altered expression of immune-related genes and the impact on downstream cytokines might contribute to both structural and functional brain abnormalities documented in people with SCZ.

Prenatal Infection and the Risk of Adult SCZ

A neurodevelopmental origin for at least some aspects of SCZ has received strong support in the literature over the past twenty years.[11,20] Two major lines of evidence support the view that SCZ may be, in part, caused or exacerbated by inflammation triggered at an early age. First, events affecting the course of *in utero* neurodevelopment can have significant effects on long-term health and functioning. An inflammatory insult experienced *in utero* can lead to an enhanced expression of pro-inflammatory cytokines that have been previously shown to interfere with neonatal white matter development[99-101] during the middle trimester of intrauterine life.[102] A significant association has been found between high maternal levels of the pro-inflammatory cytokines TNF- α [103] and IL-8[104] during pregnancy and an increased risk of the progeny developing the clinical features associated with SCZ. Epidemiological evidence suggests immune activation triggered by prenatal exposure to a range of infectious agents, such as herpes simplex virus (HSV-1), cytomegalovirus or influenza, is also associated with a heightened risk of SCZ.[33,105-114] Exposure to HSV-1 has been linked to the presence of various structural abnormalities well documented in the brains of patients with SCZ[114-116] and in those at high risk of developing psychosis.[117] Voxel-based morphometric analyses has revealed that patients with SCZ who tested positive for antibodies to HSV-1 displayed grey matter reductions in the thalamus,[115] cerebellum,[115] pallidum,[115] prefrontal cortex (PFC)[118] and anterior cingulate cortex (ACC).[114,115] These patients also performed significantly worse in neuropsychological measures of psychomotor speed, executive functioning and verbal memory.[115,116] Prenatal infection and subsequent inflammatory attack on a background of genetic liability serves to further increase the risk of developing SCZ, consistent with the idea that genetic factors are necessary for inflammation to affect *in utero* brain development.[119]

Second, animal models of maternal immune activation directly complements evidence suggesting that *in utero* infections are associated with an increased risk of developing SCZ. Experimental animal work shows that prenatal exposure to pro-inflammatory agents can be sufficient to cause apoptotic, necrotic and behavioural alterations consistent with what is observable in SCZ.[120-122] Prenatal administration of polycytidylic acid (poly-I:C), an agent capable of mimicking RNA virus exposure and immune challenge, has been shown to induce hallmark

SCZ-like abnormalities in rodent offspring. A recent systematic review found that studies published between May 2001 and October 2011 consistently reported the development of the positive and negative dimensions of SCZ in animals treated with poly-I:C.[123] In support of the neurodevelopmental model of SCZ, the progression of these symptoms were dependent on the specific gestation time window of the immune challenge.[123] A more recent study reported an increase in the expression of interferon-induced transmembrane protein 3 (IFITM3) in astrocytes and notable neurodevelopmental impairments in mice following exposure to poly-I:C.[124] Elevated mRNA expression levels of IFITM3 have also been routinely reported in the brains of neuropsychiatric diseases[125] and IFITM proteins can be strongly induced by a number of viruses.[126] Taken together, these findings serve to strengthen the argument that early, long-lasting immune insults contribute to the pathophysiology of neuronal dysfunction and SCZ. It is conceivable that maternal infection may impact negatively on later neurodevelopmental processes such as neuronal/glial cell maturation, signalling, differentiation, proliferation, and survival. The disruption of such crucial processes can lead to the thinning of cortical areas, reduced grey and white matter, and accelerated grey matter loss, potentially thereby facilitating the development of neuropsychological and neuropathological deficits associated with SCZ. It still remains unclear whether genes implicated in SCZ and environmental insults interact with pre- and postnatal levels of pro-inflammatory cytokines to increase the risk of SCZ and associated brain alterations.

Glial Cell Activation and SCZ

The release of cytokines in the CNS is mediated by glial cells - the 'house-keeping' cells of the brain. Microglia, supportive glial cells acting as resident macrophages and antigen-presenting cells within the CNS, are involved in the clearance of infection or cellular debris, thus playing a critical role in both neuronal repair and protection.[127,128] One approach used in the study of the neuropathology of SCZ has involved examination of microglial and astrocytic activity. It has recently emerged that microglia may play a part in mediating and modulating inflammatory processes in the CNS of patients with SCZ.[127-130] Increased densities of immunoreactive microglia have been reported in the brains of SCZ patients,[131-136] findings recently confirmed in temporolimbic grey matter using PET imaging and an activated microglial ligand.[135,136] However, this finding is not consistent and cannot be replicated in affected individuals using post-mortem immunohistochemical techniques.[137-141] Perhaps microglial activation associated with active psychosis is short-lived and therefore difficult to detect. Other complicating factors relate to the inclusion of older patients within such studies, as aging is known to lead to increased microglial activity.

Abnormal astrocyte functions have also been implicated in the pathogenesis of SCZ. Analogous to microglia, astrocytes serve as immunocompetent cells and secrete a wide array of chemokines and cytokines to maintain CNS homeostasis.[142] The proliferation of astrocytes (gliosis) can be considered a normal cellular process within the CNS, but can also serve as an indicator of a pathological process if persistent and present without explanation. In order to evaluate the functionality of astrocytes, astrocytic markers detected in the CSF and serum have been measured. A reliable indicator used in a number of studies is S100B, a small calcium binding astrocytic protein implicated in the regulation of both neuronal/glial proliferation and innate immune response.[143-146] It has been demonstrated that the levels of serum S100B are significantly higher in drug naive patients with SCZ compared to healthy controls.[145,147] It is important to note, however, that the upregulation of S100B by astrocytes and oligodendrocytes has also been noted in a number of neurodegenerative disorders,[148] S100B expression has been associated with other neural cell types[149] and its expression can be affected by confounding factors, such as obesity and diabetes.[149-151] As with many other implicated pathways, the involvement of glial reactivity and its contribution to the immune signature of SCZ awaits further validation in drug-naive, or minimally medicated first-episode patients with SCZ.

SCZ, Autoimmune Diseases and Autoantibodies

A positive association between several autoimmune diseases present in the endocrine, neurologic and vascular systems, and SCZ is well documented in the literature.[152] A variety of autoantibodies with cross-reactivity against specific brain regions and antigens linked to neurotransmission have also been described in the sera of patients with SCZ.[23,153] It is well established that N-methyl-D-aspartate (NMDAR) hypofunction and downstream dysfunctional cortical-subcortical circuitry exists as one of the most persuasive models for SCZ.[154,155] Healthy volunteers given NMDA antagonists such as ketamine display symptoms and cognitive deficits routinely observed in SCZ patients.[156-158] Studies showing an increase in the

concentration of antibodies directed against NMDARs, and other neurotransmission receptors[159,160] implicated in SCZ, provide an important link between immune abnormalities and altered neurotransmission. It has now been suggested that the NMDAR antibody interferes with glutamatergic signalling by selectively decreasing the number of NMDAR clusters in the postsynaptic density.[161] In fact, prominent psychiatric symptoms such as psychosis, catatonia-like symptoms and dyskinesias in patients with encephalitis[162,163] can be triggered by IgG serum and CSF antibodies that are directed against extracellular epitopes of the NR1a subunit of NMDARs.[164] Recent studies found that approximately 5-10% of SCZ cases were associated with serum and CSF autoantibodies to the NMDAR.[165-167] Importantly, the repertoire of antibody subtypes in SCZ has now been shown to differ from NMDAR encephalitis,[167] potentially revealing a novel method to reaffirm the diagnosis of SCZ and provide more effective immunomodulatory treatment strategies.

Adjunctive Immune Modulation Therapies

Despite potentially fatal side effects, clozapine remains the most effective antipsychotic drug used in the treatment of SCZ.[168] Immunologically mediated mechanisms have been attributed to the development of some of its more serious side effects, including agranulocytosis,[169] myocarditis[170] and serositis.[171] Data from both *in vivo* and *in vitro* studies suggest that clozapine exerts significant immunomodulatory actions on a number of cytokines, possibly resulting in a long-term normalisation of IL-6 levels.[172-174] It is conceivable that clozapine is so successful in treating the treatment resistant positive symptoms of SCZ, and to a lesser extent the negative symptoms, because of its immunomodulatory effects. However, due to its potentially harmful effects on neutrophil levels together with the limited efficacy of a large proportion of current antipsychotic treatments, new immune-focused therapeutic strategies have been investigated. One of the major disabilities affecting the quality of life of people with SCZ, and left largely untouched, and possibly exacerbated by current antipsychotics, is the set of negative symptoms. Negative symptoms include social withdrawal, self-neglect and apathy and their severity can act as a major predictor of patient functioning.[175-177] Several studies aimed at alleviating particularly the negative symptoms of SCZ have focussed on the anti-inflammatory, neuroprotective and antioxidant effects of a well-tolerated and widely available tetracycline antibiotic, minocycline.[178] Minocycline can cross the BBB and has been shown to exert neuroprotective effects on models of ischaemic injury and Parkinson's disease by reducing the infarct size and increasing survival of hippocampal neurons, respectively.[179-182] Randomised controlled trials of minocycline in patients with early-phase SCZ showed significant treatment effects on negative symptoms and in general outcome.[183,184] Minocycline may also elicit a marked acute antipsychotic effect in a subset of patients.[184,185] It is likely that prompt treatment of neuronal inflammation will lead to an improvement in the quality of life and potentially delay the progression of SCZ; however, it remains unclear as to whether the therapeutic effects of minocycline are mediated by neuroprotective and/or anti-inflammatory actions.

Steroids are effective treatments for a variety of autoimmune and inflammatory conditions, for example Systemic Lupus Erythematosis (SLE) and Wegners Granulomatosis, but can result in alterations in mood, dementia and psychosis.[186,187] Steroids are therefore a double edged sword, forcing researchers to turn to another class of molecules that counteract the effects of inflammatory mediators without inducing psychiatric effects. A recent meta-analysis on the use of non-steroidal anti-inflammatory drugs (NSAIDs) as useful therapeutic strategies in SCZ suggests a promising avenue for further investigation.[188] A very recent review of 26 double-blind randomised controlled trials looking at the efficacy of a number of anti-inflammatory agents on symptom severity in patients with SCZ found that aspirin had beneficial effects.[189] Together, these results provide further support for a neuroinflammatory (co)etiology and suggest that NSAIDs could be used as a relatively easy and early intervention therapy to minimise deficits and possibly even the neuro-structural and -functional abnormalities associated with the progression of SCZ. More studies using anti-inflammatory agents as augmentation therapies need to be carried out, especially those that may also impact on the metabolic syndrome, like statins.

SUMMARY AND OUTLOOK

Despite tremendous scientific and pharmacological advances, identification of the target pathology of SCZ remains a major challenge. Nevertheless, what remains abundantly clear after decades of research is that a single locus of dysfunction within the brains of SCZ patients cannot be responsible for the spectrum of symptoms that arise during the course of illness. The fact that antipsychotics provide only a partial answer together with a

leap in our understanding of the immune system has re-awakened an interest in one of the most persistent, enduring themes of research into the pathophysiological signature of SCZ. Substantial evidence from both human and animal studies suggests an association between increased levels of inflammatory cytokines, altered immune-related gene expression and SCZ, along with structural brain alterations associated with the disorder. Future clarification of cytokine and microglial signalling profiles, expression and distribution, all features of an over-active immune system, will help to elucidate how these factors are capable of giving rise to SCZ. Further understanding of gene—environment interactions will also accelerate the identification of novel genetic variants that are relevant to SCZ and help clarify how an inflammatory imbalance may precipitate the onset of psychiatric symptoms. Clinical trials involving larger patient numbers, standardised quantitative measures, validated genetic variance profiles and reliable immune markers will lead to a more comprehensive understanding of both the pro- and anti-inflammatory arms of the immune system and their involvement in SCZ.

REFERENCES

1. Tandon R, Keshavan MS, Nasrallah HA. *Schizophrenia, "just the facts" what we know in 2008. 2. Epidemiology and etiology. Schizophr Res 2008;102:1-18.*
2. Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S, *et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. Arch Gen Psychiatry 2007;64:19-28.*
3. Liddle PF. *The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. Br J Psychiatry 1987;151:145-151.*
4. Bellak L. *Schizophrenia: a review of the syndrome. New York:Logos Press;1958.*
5. Harrison PJ, Weinberger DR. *Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. Mol Psychiatry 2005;10:40-68; image 5.*
6. Jaaro-Peled H, Hayashi-Takagi A, Seshadri S, Kamiya A, Brandon NJ, Sawa A. *Neurodevelopmental mechanisms of schizophrenia: understanding disturbed postnatal brain maturation through neuregulin-1-ErbB4 and DISC1. Trends Neurosci 2009;32:485-495.*
7. Lewis DA, Levitt P. *Schizophrenia as a disorder of neurodevelopment. Annu Rev Neurosci 2002;25:409-432.*
8. Lewis DA, Lieberman JA. *Catching up on schizophrenia: natural history and neurobiology. Neuron 2000;28:325-334.*
9. Mueser KT, McGurk SR. *Schizophrenia. Lancet 2004;363: 2063-2072.*
10. Sawa A, Snyder SH. *Schizophrenia: diverse approaches to a complex disease. Science 2002;296:692-695.*
11. Weinberger DR. *Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry 1987;44:660-669.*
12. Carlsson A. *The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1988;1:179-186.*
13. Kim JS, Kornhuber HH, Schmid-Burgk W, Holzmüller B. *Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. Neurosci Lett 1980;20:379-382.*
14. Olney JW, Farber NB. *NMDA antagonists as neurotherapeutic drugs, psychotogens, neurotoxins, and research tools for studying schizophrenia. Neuropsychopharmacology 1995;13:335-345.*
15. Koran LM. *Gamma-Aminobutyric-acid deficiency in schizophrenia. Lancet 1976;2:1025.*
16. Lewis DA, Hashimoto T, Volk DW. *Cortical inhibitory neurons and schizophrenia. Nat Rev Neurosci 2005;6:312-324.*
17. Ingvar DH, Franzén G. *Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta Psychiatr Scand 1974;50:425-462.*
18. Wolkin A, Jaeger J, Brodie JD, Wolf AP, Fowler J, Rotrosen J, *et al. Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. Am J Psychiatry 1985;142: 564-571.*
19. Andreasen N, Nasrallah HA, Dunn V, Olson SC, Grove WM, Ehrhardt JC, *et al. Structural abnormalities in the frontal system in schizophrenia. A magnetic resonance imaging study. Arch Gen Psychiatry 1986;43:136-144.*
20. Murray RM, Lewis SW. *Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed) 1987;295:681-682.*
21. Zubin J, Spring B. *Vulnerability-a new view of schizophrenia. J Abnorm Psychol 1977;86:103-126.*
22. Lin A, Kenis G, Bignotti S, Tura GJ, De Jong R, Bosmans E, *et al. The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6. Schizophr Res 1998;32:9-15.*
23. Rothermundt M, Arolt V, Bayer TA. *Review of immunological and immunopathological findings in schizophrenia. Brain Behav Immun 2001;15:319-339.*
24. Fan X, Goff DC, Henderson DC. *Inflammation and schizophrenia. Expert Rev Neurother 2007;7:789-796.*
25. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. *Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry 2008;63: 801-808.*
26. Drexhage RC, Knijff EM, Padmos RC, Heul-Nieuwenhuijzen Lv, Beumer W, Versnel MA, *et al. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. Expert Rev Neurother 2010;10:59-76.*
27. Johnstone EC, Macmillan JF, Crow TJ. *The occurrence of organic disease of possible or probable aetiological significance in a population of 268 cases of first episode schizophrenia. Psychol Med 1987;17:371-379.*
28. Misra PC, Hay GG. *Encephalitis presenting as acute schizophrenia. Br Med J 1971;1:532-533.*
29. Weinstein EA, Linn L, Kahn RL. *Encephalitis with a clinical picture of schizophrenia. J Mt Sinai Hosp N Y 1955;21:341-354.*
30. Heidrich R, Wuenscher W. *Catatoniform state in the course of a leuko-encephalitis. Psychiatr Neurol Med Psychol (Leipz) 1961;13:241-247.*
31. Raskin DE, Frank SW. *Herpes encephalitis with catatonic stupor. Arch Gen Psychiatry 1974;31:544-546.*
32. Kim CH, Perlstein MA. *Encephalitis with catatonic schizophrenic symptoms. IMJ Ill Med J 1970;138:503-507.*

33. Brown AS, Susser ES. *In utero infection and adult schizophrenia. Ment Retard Dev Disabil Res Rev 2002;8:51-57.*
34. Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, *et al. Association of schizophrenia and autoimmune diseases: linkage of Danish national registers. Am J Psychiatry 2006;163:521-528.*
35. Müller N, Ackenheil M, Hofschuster E, Mempel W, Eckstein R. *Cellular immunity in schizophrenic patients before and during neuroleptic treatment. Psychiatry Res 1991;37:147-160.*
36. Smith RS. *The immune system is a key factor in the etiology of psychosocial disease. Med Hypotheses 1991; 34:49-57.*
37. Stevens JR. *Neuropathology of schizophrenia. Arch Gen Psychiatry 1982;39:1131-1139.*
38. Serhan CN, Savill J. *Resolution of inflammation: the beginning programs the end. Nat Immunol 2005;6:1191-1197.*
39. Majno G. *The healing hand: man and wound in the ancient world. Cambridge:Harvard University Press;1975.*
40. Steinke JW, Borish L. *3. Cytokines and chemokines. J Allergy Clin Immunol 2006;117(2 Suppl Mini-Primer): S441-S445.*
41. Curfs JH, Meis JF, Hoogkamp-Korstanje JA. *A primer on cytokines: sources, receptors, effects, and inducers. Clin Microbiol Rev 1997;10:742-780.*
42. Simard AR, Rivest S. *Do pathogen exposure and innate immunity cause brain diseases? Neurol Res 2005;27:717-725.*
43. Ferrari G, Toffano G, Skaper SD. *Epidermal growth factor exerts neuronotrophic effects on dopaminergic and GABAergic CNS neurons: comparison with basic fibroblast growth factor. J Neurosci Res 1991;30:493-497.*
44. Li Y, Liu L, Barger SW, Griffin WS. *Interleukin-1 mediates pathological effects of microglia on tau phosphorylation and on synaptophysin synthesis in cortical neurons through a p38-MAPK pathway. J Neurosci 2003;23:1605-1611.*
45. Namba H, Nagano T, Iwakura Y, Xiong H, Jourdi H, Takei N, *et al. Transforming growth factor alpha attenuates the functional expression of AMPA receptors in cortical GABAergic neurons. Mol Cell Neurosci 2006;31:628-641.*
46. Namba H, Takei N, Nawa H. *Transforming growth factor-alpha changes firing properties of developing neocortical GABAergic neurons by down-regulation of voltage-gated potassium currents. Neuroscience 2003;122: 637-646.*
47. Qin L, Wu X, Block ML, Liu Y, Breese GR, Hong JS, *et al. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia 2007;55:453-462.*
48. Kronfol Z, Remick DG. *Cytokines and the brain: implications for clinical psychiatry. Am J Psychiatry 2000; 157:683-694.*
49. Raison CL, Miller AH. *Is depression an inflammatory disorder? Curr Psychiatry Rep 2011;13:467-475.*
50. Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium. *Genome-wide association study identifies five new schizophrenia loci. Nat Genet 2011;43: 969-976.*
51. Li T, Li Z, Chen P, Zhao Q, Wang T, Huang K, *et al. Common variants in major histocompatibility complex region and TCF4 gene are significantly associated with schizophrenia in Han Chinese. Biol Psychiatry 2010;68: 671-673.*
52. Stefansson H, Ophoff RA, Steinberg S, Andreassen OA, Cichon S, Rujescu D, *et al. Common variants conferring risk of schizophrenia. Nature 2009;460:744-747.*
53. International Schizophrenia Consortium, Purcell SM, Wray NR, Stone JL, Visscher PM, O'Donovan MC, *et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. Nature 2009;460:748-752.*
54. Shiina T, Hosomichi K, Inoko H, Kulski JK. *The HLA genomic loci map: expression, interaction, diversity and disease. J Hum Genet 2009;54:15-39.*
55. van Heel DA, Franke L, Hunt KA, Gwilliam R, Zhernakova A, Inouye M, *et al. A genome-wide association study for celiac disease identifies risk variants in the region harboring IL2 and IL21. Nat Genet 2007;39: 827-829.*
56. International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), Harley JB, Alarcón-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, *et al. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet 2008;40:204-210.*
57. Hwang Y, Kim J, Shin JY, Kim JI, Seo JS, Webster MJ, *et al. Gene expression profiling by mRNA sequencing reveals increased expression of immune/inflammation-related genes in the hippocampus of individuals with schizophrenia. Transl Psychiatry 2013;3:e321.*
58. Allen NC, Bagade S, McQueen MB, Ioannidis JP, Kavvoura FK, Khoury MJ, *et al. Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. Nat Genet 2008;40: 827-834.*
59. Paul-Samojedny M, Owczarek A, Suchanek R, Kowalczyk M, Fila-Danilow A, Borkowska P, *et al. Association study of interferon gamma (IFN-γ) +874T/A gene polymorphism in patients with paranoid schizophrenia. J Mol Neurosci 2011;43:309-315.*
60. Ozbey U, Tug E, Kara M, Namli M. *The value of interleukin-12B (p40) gene promoter polymorphism in patients with schizophrenia in a region of East Turkey. Psychiatry Clin Neurosci 2008;62:307-312.*
61. Ozbey U, Tug E, Namli M. *Interleukin-10 gene promoter polymorphism in patients with schizophrenia in a region of East Turkey. World J Biol Psychiatry 2009;10:461-468.*
62. Xu M, He L. *Convergent evidence shows a positive association of interleukin-1 gene complex locus with susceptibility to schizophrenia in the Caucasian population. Schizophr Res 2010;120:131-142.*
63. Katila H, Hänninen K, Hurme M. *Polymorphisms of the interleukin-1 gene complex in schizophrenia. Mol Psychiatry 1999;4:179-181.*
64. Zanardini R, Bocchio-Chiavetto L, Scassellati C, Bonvicini C, Tura GB, Rossi G, *et al. Association between IL-1beta -511C/T and IL-1RA (86bp)n repeats polymorphisms and schizophrenia. J Psychiatr Res 2003;37:457-462.*
65. Shirts BH, Wood J, Yolken RH, Nimgaonkar VL. *Association study of IL10, IL1beta, and IL1RN and schizophrenia using tag SNPs from a comprehensive database: suggestive association with rs16944 at IL1beta. Schizophr Res 2006;88:235-244.*
66. Lencz T, Morgan TV, Athanasiou M, Dain B, Reed CR, Kane JM, *et al. Converging evidence for a pseudoautosomal cytokine receptor gene locus in schizophrenia. Mol Psychiatry 2007;12:572-580.*
67. Sun S, Wang F, Wei J, Cao LY, Wu GY, Lu L, *et al. Association between interleukin-3 receptor alpha polymorphism and schizophrenia in the Chinese population.*

Neurosci Lett 2008;440:35-37.
68. Sun S, Wei J, Li H, Jin S, Li P, Ju G, *et al. A family-based study of the IL3RA gene on susceptibility to schizophrenia in a Chinese Han population. Brain Res 2009;1268:13-16.*
69. Fillman SG, Cloonan N, Catts VS, Miller LC, Wong J, McCrossin T, *et al. Increased inflammatory markers identified in the dorsolateral prefrontal cortex of individuals with schizophrenia. Mol Psychiatry 2013;18:206-214.*
70. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. *Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011;70:663-671.*
71. Szuster-Ciesielska A, Słotwińska M, Stachura A, Marmurowska-Michałowska H, Kandefer-Szerszeń M. *Neuroleptics modulate cytokine and reactive oxygen species production in blood leukocytes of healthy volunteers. Arch Immunol Ther Exp (Warsz) 2004;52:59-67.*
72. Ghezzi P, Garattini S, Mennini T, Bertini R, Delgado Hernandez R, Benigni F, *et al. Mechanism of inhibition of tumor necrosis factor production by chlorpromazine and its derivatives in mice. Eur J Pharmacol 1996;317:369-376.*
73. Maes M, Meltzer HY, Bosmans E. *Immune-inflammatory markers in schizophrenia: comparison to normal controls and effects of clozapine. Acta Psychiatr Scand 1994;89: 346-351.*
74. Hinze-Selch D, Pollmächer T. *In vitro cytokine secretion in individuals with schizophrenia: results, confounding factors, and implications for further research. Brain Behav Immun 2001;15:282-318.*
75. Pollmächer T, Hinze-Selch D, Mullington J, Fenzel T, Holsboer F. *Smoking affects plasma-soluble interleukin-2 receptor levels in patients with schizophrenia. Arch Gen Psychiatry 1997;54:89-90.*
76. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, *et al. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010;67:446-457.*
77. Johnstone EC, Crow TJ, Frith CD, Husband J, Kreel L. *Cerebral ventricular size and cognitive impairment in chronic schizophrenia. Lancet 1976;2:924-926.*
78. Reveley AM, Reveley MA, Clifford CA, Murray RM. *Cerebral ventricular size in twins discordant for schizophrenia. Lancet 1982;1:540-541.*
79. Andreasen NC. *Brain imaging: applications in psychiatry. Science 1988;239:1381-1388.*
80. Andreasen NC, Ehrhardt JC, Swayze VW 2nd, Alliger RJ, Yuh WT, Cohen G, *et al. Magnetic resonance imaging of the brain in schizophrenia. The pathophysiologic significance of structural abnormalities. Arch Gen Psychiatry 1990;47:35-44.*
81. Andreasen NC, Swayze VW 2nd, Flaum M, Yates WR, Arndt S, McChesney C. *Ventricular enlargement in schizophrenia evaluated with computed tomographic scanning. Effects of gender, age, and stage of illness. Arch Gen Psychiatry 1990;47:1008-1015.*
82. Lawrie SM, Abukmeil SS. *Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry 1998; 172:110-120.*
83. Van Horn JD, McManus IC. *Ventricular enlargement in schizophrenia. A meta-analysis of studies of the ventricle: brain ratio (VBR). Br J Psychiatry 1992;160:687-697.*
84. Lawrie SM, Whalley H, Kestelman JN, Abukmeil SS, Byrne M, Hodges A, *et al. Magnetic resonance imaging of brain in people at high risk of developing schizophrenia. Lancet 1999;353:30-33.*
85. Erlenmeyer-Kimling L. *Neurobehavioral deficits in offspring of schizophrenic parents: liability indicators and predictors of illness. Am J Med Genet 2000;97:65-71.*
86. Niemi LT, Suvisaari JM, Tuulio-Henriksson A, Lönnqvist JK. *Childhood developmental abnormalities in schizophrenia: evidence from high-risk studies. Schizophr Res 2003; 60:239-258.*
87. Harris JM, Moorhead TW, Miller P, McIntosh AM, Bonnici HM, Owens DG, *et al. Increased prefrontal gyrification in a large high-risk cohort characterizes those who develop schizophrenia and reflects abnormal prefrontal development. Biol Psychiatry 2007;62:722-729.*
88. Job DE, Whalley HC, Johnstone EC, Lawrie SM. *Grey matter changes over time in high risk subjects developing schizophrenia. Neuroimage 2005;25:1023-1030.*
89. Johnstone EC, Abukmeil SS, Byrne M, Clafferty R, Grant E, Hodges A, *et al. Edinburgh high risk study-findings after four years: demographic, attainment and psychopathological issues. Schizophr Res 2000;46:1-15.*
90. McIntosh AM, Owens DC, Moorhead WJ, Whalley HC, Stanfield AC, Hall J, *et al. Longitudinal volume reductions in people at high genetic risk of schizophrenia as they develop psychosis. Biol Psychiatry 2011;69:953-958.*
91. Harrison PJ. *Brains at risk of schizophrenia. Lancet 1999; 353:3-4.*
92. Ellman LM, Deicken RF, Vinogradov S, Kremen WS, Poole JH, Kern DM, *et al. Structural brain alterations in schizophrenia following fetal exposure to the inflammatory cytokine interleukin-8. Schizophr Res 2010;121:46-54.*
93. Stefansson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S, *et al. Neuregulin 1 and susceptibility to schizophrenia. Am J Hum Genet 2002; 71:877-892.*
94. Corfas G, Roy K, Buxbaum JD. *Neuregulin 1-erbB signaling and the molecular/cellular basis of schizophrenia. Nat Neurosci 2004;7:575-580.*
95. Hall J, Whalley HC, Job DE, Baig BJ, McIntosh AM, Evans KL, *et al. A neuregulin 1 variant associated with abnormal cortical function and psychotic symptoms. Nat Neurosci 2006;9:1477-1478.*
96. Hänninen K, Katila H, Saarela M, Rontu R, Mattila KM, Fan M, *et al. Interleukin-1 beta gene polymorphism and its interactions with neuregulin-1 gene polymorphism are associated with schizophrenia. Eur Arch Psychiatry Clin Neurosci 2008;258:10-15.*
97. Fatjó-Vilas M, Pomarol-Clotet E, Salvador R, Monté GC, Gomar JJ, Sarró S, *et al. Effect of the interleukin-1 β gene on dorsolateral prefrontal cortex function in schizophrenia: a genetic neuroimaging study. Biol Psychiatry 2012;72: 758-765.*
98. Papiol S, Molina V, Rosa A, Sanz J, Palomo T, Fañanás L. *Effect of interleukin-1beta gene functional polymorphism on dorsolateral prefrontal cortex activity in schizophrenic patients. Am J Med Genet B Neuropsychiatr Genet 2007; 144B:1090-1093.*
99. Dammann O, Leviton A. *Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn. Pediatr Res 1997;42:1-8.*
100. Dammann O, Leviton A. *Role of the fetus in perinatal infection and neonatal brain damage. Curr Opin Pediatr 2000;12:99-104.*
101. Shatrov JG, Birch SC, Lam LT, Quinlivan JA, McIntyre S, Mendz GL. *Chorioamnionitis and cerebral palsy: a meta-analysis. Obstet Gynecol 2010;116:387-392.*
102. Roberts GW. *Schizophrenia: a neuropathological perspec-*

tive. Br J Psychiatry 1991;158:8-17.
103. Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Wagner RL, Yolken RH. *Maternal cytokine levels during pregnancy and adult psychosis. Brain Behav Immun 2001;15:411-420.*
104. Brown AS, Hooton J, Schaefer CA, Zhang H, Petkova E, Babulas V, *et al. Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. Am J Psychiatry 2004;161:889-895.*
105. Khandaker G, Zurynski Y, Buttery J, Marshall H, Richmond PC, Dale RC, *et al. Neurologic complications of influenza A(H1N1)pdm09: surveillance in 6 pediatric hospitals. Neurology 2012;79:1474-1481.*
106. Brown AS, Derkits EJ. *Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry 2010;167:261-280.*
107. Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, *et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. Arch Gen Psychiatry 2004;61:774-780.*
108. Fellerhoff B, Laumbacher B, Mueller N, Gu S, Wank R. *Associations between Chlamydophila infections, schizophrenia and risk of HLA-A10. Mol Psychiatry 2007;12: 264-272.*
109. Fellerhoff B, Laumbacher B, Wank R. *High risk of schizophrenia and other mental disorders associated with chlamydial infections: hypothesis to combine drug treatment and adoptive immunotherapy. Med Hypotheses 2005; 65:243-252.*
110. Hammond CJ, Hobbs JA. *Parvovirus B19 infection of brain: possible role of gender in determining mental illness and autoimmune thyroid disorders. Med Hypotheses 2007; 69:113-116.*
111. Dalman C, Allebeck P, Gunnell D, Harrison G, Kristensson K, Lewis G, *et al. Infections in the CNS during childhood and the risk of subsequent psychotic illness: a cohort study of more than one million Swedish subjects. Am J Psychiatry 2008;165:59-65.*
112. Arias I, Sorlozano A, Villegas E, de Dios Luna J, McKenney K, Cervilla J, *et al. Infectious agents associated with schizophrenia: a meta-analysis. Schizophr Res 2012;136:128-136.*
113. Yolken RH, Torrey EF. *Are some cases of psychosis caused by microbial agents? A review of the evidence. Mol Psychiatry 2008;13:470-479.*
114. Prasad KM, Shirts BH, Yolken RH, Keshavan MS, Nimgaonkar VL. *Brain morphological changes associated with exposure to HSV1 in first-episode schizophrenia. Mol Psychiatry 2007;12:105-113.*
115. Schretlen DJ, Vannorsdall TD, Winicki JM, Mushtaq Y, Hikida T, Sawa A, *et al. Neuroanatomic and cognitive abnormalities related to herpes simplex virus type 1 in schizophrenia. Schizophr Res 2010;118:224-231.*
116. Prasad KM, Eack SM, Goradia D, Pancholi KM, Keshavan MS, Yolken RH, *et al. Progressive gray matter loss and changes in cognitive functioning associated with exposure to herpes simplex virus 1 in schizophrenia: a longitudinal study. Am J Psychiatry 2011;168:822-830.*
117. Whitford TJ, Wood SJ, Yung A, Cocchi L, Berger G, Shenton ME, *et al. Structural abnormalities in the cuneus associated with Herpes Simplex Virus (type 1) infection in people at ultra high risk of developing psychosis. Schizophr Res 2012;135:175-180.*
118. Prasad KM, Bamne MN, Shirts BH, Goradia D, Mannali V, Pancholi KM, *et al. Grey matter changes associated with host genetic variation and exposure to Herpes Simplex Virus 1 (HSV1) in first episode schizophrenia. Schizophr Res 2010;118:232-239.*
119. Clarke MC, Tanskanen A, Huttunen M, Whittaker JC, Cannon M. *Evidence for an interaction between familial liability and prenatal exposure to infection in the causation of schizophrenia. Am J Psychiatry 2009;166:1025-1030.*
120. Meyer U, Feldon J. *Epidemiology-driven neurodevelopmental animal models of schizophrenia. Prog Neurobiol 2010;90:285-326.*
121. Meyer U, Feldon J, Yee BK. *A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. Schizophr Bull 2009;35:959-972.*
122. Patterson PH. *Immune involvement in schizophrenia and autism: etiology, pathology and animal models. Behav Brain Res 2009;204:313-321.*
123. Macêdo DS, Araújo DP, Sampaio LR, *Vasconcelos SM, Sales PM, Sousa FC, et al. Animal models of prenatal immune challenge and their contribution to the study of schizophrenia: a systematic review. Braz J Med Biol Res 2012;45:179-186.*
124. Ibi D, Nagai T, Nakajima A, Mizoguchi H, Kawase T, Tsuboi D, *et al. Astroglial IFITM3 mediates neuronal impairments following neonatal immune challenge in mice. Glia 2013;61:679-693.*
125. Horváth S, Mirnics K. Immune system disturbances in schizophrenia. *Biol Psychiatry 2013. [Epub ahead of print]*
126. Brass AL, Huang IC, Benita Y, John SP, Krishnan MN, Feeley EM, *et al. The IFITM proteins mediate cellular resistance to influenza A H1N1 virus, West Nile virus, and dengue virus. Cell 2009;139:1243-1254.*
127. Ransohoff RM, Perry VH. *Microglial physiology: unique stimuli, specialized responses. Annu Rev Immunol 2009;27: 119-145.*
128. Block ML, Zecca L, Hong JS. *Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat Rev Neurosci 2007;8:57-69.*
129. Bernstein HG, Steiner J, Bogerts B. *Glial cells in schizophrenia: pathophysiological significance and possible consequences for therapy. Expert Rev Neurother 2009;9: 1059-1071.*
130. Monji A, Kato T, Kanba S. *Cytokines and schizophrenia: Microglia hypothesis of schizophrenia. Psychiatry Clin Neurosci 2009;63:257-265.*
131. Bayer TA, Buslei R, Havas L, Falkai P. *Evidence for activation of microglia in patients with psychiatric illnesses. Neurosci Lett 1999;271:126-128.*
132. Radewicz K, Garey LJ, Gentleman SM, Reynolds R. *Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. J Neuropathol Exp Neurol 2000;59:137-150.*
133. Garey L. *When cortical development goes wrong: schizophrenia as a neurodevelopmental disease of microcircuits. J Anat 2010;217:324-333.*
134. Wierzba-Bobrowicz T, Lewandowska E, Lechowicz W, Stepień T, Pasennik E. *Quantitative analysis of activated microglia, ramified and damage of processes in the frontal and temporal lobes of chronic schizophrenics. Folia Neuropathol 2005;43:81-89.*
135. van Berckel BN, Bossong MG, Boellaard R, Kloet R, Schuitemaker A, Caspers E, *et al. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. Biol Psychiatry 2008; 64:820-822.*
136. Doorduin J, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA, Klein HC. *Neuroinflammation in schizophre-*

nia-related psychosis: a PET study. J Nucl Med 2009;50: 1801-1807.
137. Togo T, Akiyama H, Kondo H, Ikeda K, Kato M, Iseki E, *et al. Expression of CD40 in the brain of Alzheimer's disease and other neurological diseases. Brain Res 2000;885:117-121.*
138. Falke E, Han LY, Arnold SE. *Absence of neurodegeneration in the thalamus and caudate of elderly patients with schizophrenia. Psychiatry Res 2000;93:103-110.*
139. Arnold SE, Trojanowski JQ, Gur RE, Blackwell P, Han LY, Choi C. *Absence of neurodegeneration and neural injury in the cerebral cortex in a sample of elderly patients with schizophrenia. Arch Gen Psychiatry 1998;55:225-232.*
140. Kurumaji A, Wakai T, Toru M. *Decreases in peripheral-type benzodiazepine receptors in postmortem brains of chronic schizophrenics. J Neural Transm 1997;104:1361-1370.*
141. Steiner J, Mawrin C, Ziegeler A, Bielau H, Ullrich O, Bernstein HG, *et al. Distribution of HLA-DR-positive microglia in schizophrenia reflects impaired cerebral lateralization. Acta Neuropathol 2006;112:305-316.*
142. Dong Y, Benveniste EN. *Immune function of astrocytes. Glia 2001;36:180-190.*
143. Donato R. *Intracellular and extracellular roles of S100 proteins. Microsc Res Tech 2003;60:540-551.*
144. Heizmann CW, Ackermann GE, Galichet A. *Pathologies involving the S100 proteins and RAGE. Subcell Biochem 2007;45:93-138.*
145. Rothermundt M, Ponath G, Glaser T, Hetzel G, Arolt V. *S100B serum levels and long-term improvement of negative symptoms in patients with schizophrenia. Neuropsychopharmacology 2004;29:1004-1011.*
146. Sorci G, Bianchi R, Riuzzi F, Tubaro C, Arcuri C, Giambanco I, *et al. S100B protein, a damage-associated molecular pattern protein in the brain and heart, and beyond. Cardiovasc Psychiatry Neurol 2010;2010. pii: 656481.*
147. Rothermundt M, Missler U, Arolt V, Peters M, Leadbeater J, Wiesmann M, *et al. Increased S100B blood levels in unmedicated and treated schizophrenic patients are correlated with negative symptomatology. Mol Psychiatry 2001;6:445-449.*
148. Steiner J, Bogerts B, Schroeter ML, Bernstein HG. *S100B protein in neurodegenerative disorders. Clin Chem Lab Med 2011;49:409-424.*
149. Steiner J, Bernstein HG, Bielau H, Berndt A, Brisch R, Mawrin C, *et al. Evidence for a wide extra-astrocytic distribution of S100B in human brain. BMC Neurosci 2007;8:2.*
150. Steiner J, Myint AM, Schiltz K, Westphal S, Bernstein HG, Walter M, *et al. S100B serum levels in schizophrenia are presumably related to visceral obesity and insulin resistance. Cardiovasc Psychiatry Neurol 2010;2010:480707.*
151. Gonçalves CA, Leite MC, Guerra MC. *Adipocytes as an important source of serum S100B and possible roles of this protein in adipose tissue. Cardiovasc Psychiatry Neurol 2010;2010:790431.*
152. Chen SJ, Chao YL, Chen CY, Chang CM, Wu EC, Wu CS, *et al. Prevalence of autoimmune diseases in in-patients with schizophrenia: nationwide population-based study. Br J Psychiatry 2012;200:374-380.*
153. Strous RD, Shoenfeld Y. *Schizophrenia, autoimmunity and immune system dysregulation: a comprehensive model updated and revisited. J Autoimmun 2006;27:71-80.*
154. Stephan KE, Friston KJ, Frith CD. *Dysconnection in schizophrenia: from abnormal synaptic plasticity to failures of self-monitoring. Schizophr Bull 2009;35:509-527.*
155. Javitt DC. *Glutamate and schizophrenia: phencyclidine, N-methyl-D-aspartate receptors, and dopamine-glutamate interactions. Int Rev Neurobiol 2007;78:69-108.*
156. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, *et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 1994;51:199-214.*
157. Javitt DC, Zukin SR. *Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry 1991;148:1301-1308.*
158. Kantrowitz JT, Javitt DC. *Thinking glutamatergically: changing concepts of schizophrenia based upon changing neurochemical models. Clin Schizophr Relat Psychoses 2010;4: 189-200.*
159. Tanaka S, Matsunaga H, Kimura M, Tatsumi Ki, Hidaka Y, Takano T, *et al. Autoantibodies against four kinds of neurotransmitter receptors in psychiatric disorders. J Neuroimmunol 2003;141:155-164.*
160. Borda T, Perez Rivera R, Joensen L, Gomez RM, Sterin-Borda L. *Antibodies against cerebral M1 cholinergic muscarinic receptor from schizophrenic patients: molecular interaction. J Immunol 2002;168:3667-3674.*
161. Hughes EG, Peng X, Gleichman AJ, Lai M, Zhou L, Tsou R, *et al. Cellular and synaptic mechanisms of anti-NMDA receptor encephalitis. J Neurosci 2010;30:5866-5875.*
162. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, *et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091-1098.*
163. Braakman HM, Moers-Hornikx VM, Arts BM, Hupperts RM, Nicolai J. *Pearls & Oy-sters: electroconvulsive therapy in anti-NMDA receptor encephalitis. Neurology 2010;75:e44-e46.*
164. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, *et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.*
165. Tsutsui K, Kanbayashi T, Tanaka K, Boku S, Ito W, Tokunaga J, *et al. Anti-NMDA-receptor antibody detected in encephalitis, schizophrenia, and narcolepsy with psychotic features. BMC Psychiatry 2012;12:37.*
166. Zandi MS, Irani SR, Lang B, Waters P, Jones PB, McKenna P, *et al. Disease-relevant autoantibodies in first episode schizophrenia. J Neurol 2011;258:686-688.*
167. Steiner J, Walter M, Glanz W, Sarnyai Z, Bernstein HG, Vielhaber S, *et al. Increased prevalence of diverse N-methyl-D-aspartate glutamate receptor antibodies in patients with an initial diagnosis of schizophrenia: specific relevance of IgG NR1a antibodies for distinction from N-methyl-D-aspartate glutamate receptor encephalitis. JAMA Psychiatry 2013;70:271-278.*
168. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373: 31-41.
169. Whiskey E, Taylor D. *Restarting clozapine after neutropenia: evaluating the possibilities and practicalities. CNS Drugs 2007;21:25-35.*
170. Merrill DB, Dec GW, Goff DC. *Adverse cardiac effects associated with clozapine. J Clin Psychopharmacol 2005; 25:32-41.*
171. Mouaffak F, Gaillard R, Burgess E, Zaki H, Olié JP, Krebs

MO. *Clozapine-induced serositis: review of its clinical features, pathophysiology and management strategies. Clin Neuropharmacol 2009;32:219-223.*
172. Leykin I, Mayer R, Shinitzky M. *Short and long-term immunosuppressive effects of clozapine and haloperidol. Immunopharmacology 1997;37:75-86.*
173. Song C, Lin Ah, Kenis G, Bosmans E, Maes M. *Immunosuppressive effects of clozapine and haloperidol: enhanced production of the interleukin-1 receptor antagonist. Schizophr Res 2000;42:157-164.*
174. Himmerich H, Schönherr J, Fulda S, Sheldrick AJ, Bauer K, Sack U. *Impact of antipsychotics on cytokine production in-vitro. J Psychiatr Res 2011;45:1358-1365.*
175. Milev P, Ho BC, Arndt S, Andreasen NC. *Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: a longitudinal first-episode study with 7-year follow-up. Am J Psychiatry 2005;162:495-506.*
176. Narvaez JM, Twamley EW, McKibbin CL, Heaton RK, Patterson TL. *Subjective and objective quality of life in schizophrenia. Schizophr Res 2008;98:201-208.*
177. Tek C, Kirkpatrick B, Buchanan RW. *A five-year followup study of deficit and nondeficit schizophrenia. Schizophr Res 2001;49:253-260.*
178. Dean OM, Data-Franco J, Giorlando F, Berk M. *Minocycline: therapeutic potential in psychiatry. CNS Drugs 2012;26:391-401.*
179. Yrjänheikki J, Tikka T, Keinänen R, Goldsteins G, Chan PH, Koistinaho J. *A tetracycline derivative, minocycline, reduces inflammation and protects against focal cerebral ischemia with a wide therapeutic window. Proc Natl Acad Sci U S A 1999;96:13496-13500.*
180. Du Y, Ma Z, Lin S, Dodel RC, Gao F, Bales KR, *et al. Minocycline prevents nigrostriatal dopaminergic neurodegeneration in the MPTP model of Parkinson's disease. Proc Natl Acad Sci U S A 2001;98:14669-14674.*
181. Amin AR, Attur MG, Thakker GD, Patel PD, Vyas PR, Patel RN, *et al. A novel mechanism of action of tetracyclines: effects on nitric oxide synthases. Proc Natl Acad Sci U S A 1996;93:14014-14019.*
182. Yong VW, Wells J, Giuliani F, Casha S, Power C, Metz LM. *The promise of minocycline in neurology. Lancet Neurol 2004;3:744-751.*
183. Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, *et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. J Clin Psychiatry 2010;71:138-149.*
184. Chaudhry IB, Hallak J, Husain N, Minhas F, Stirling J, Richardson P, *et al. Minocycline benefits negative symptoms in early schizophrenia: a randomised double-blind placebo-controlled clinical trial in patients on standard treatment. J Psychopharmacol 2012;26:1185-1193.*
185. Miyaoka T, Yasukawa R, Yasuda H, Hayashida M, Inagaki T, Horiguchi J. *Minocycline as adjunctive therapy for schizophrenia: an open-label study. Clin Neuropharmacol 2008;31:287-292.*
186. Lewis DA, Smith RE. *Steroid-induced psychiatric syndromes. A report of 14 cases and a review of the literature. J Affect Disord 1983;5:319-332.*
187. Ling MH, Perry PJ, Tsuang MT. *Side effects of corticosteroid therapy. Psychiatric aspects. Arch Gen Psychiatry 1981;38:471-477.*
188. Sommer IE, de Witte L, Begemann M, Kahn RS. *Nonsteroidal anti-inflammatory drugs in schizophrenia: ready for practice or a good start? A meta-analysis. J Clin Psychiatry 2012;73:414-419.*
189. Sommer IE, van Westrhenen R, Begemann MJ, de Witte LD, Leucht S, Kahn RS. *Efficacy of anti-inflammatory agents to improve symptoms in patients with schizophrenia: an update. Schizophr Bull 2013. [Epub ahead of print]*